CJC Open 3 (2021) 1482–1489

Original Article

Incidence and Predictors of Heart Failure in Patients With Atrial Fibrillation

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ABSTRACT

Background: Heart failure (HF) is a frequent cause of hospitalization and death in patients with atrial fibrillation (AF). Identifying AF patients at risk of HF hospitalization could help select individuals for intensive follow-up and treatment.

Methods: We pooled data from 3 randomized trials (ACTIVE-A, RE-LY, AVERROES) of AF patients, for derivation and internal validation of a risk score for first HF hospitalization. Secondary endpoints were cardiovascular death and a composite of HF hospitalizations and cardiovascular death.

Results: In 23,503 patients, the mean age was 71.3 years, and 62% were male. Over a mean follow-up of 2.0 years, 875 patients (3.7%) experienced their first HF hospitalization, and 1037 patients (4.4%)

RÉSUMÉ

Introduction : L'insuffisance cardiaque (IC) est une cause fréquente d'hospitalisation et de décès chez les patients atteints de fibrillation auriculaire (FA). Le repérage des patients atteints de FA exposés au risque d'hospitalisation liée à l'IC pourrait faciliter la sélection des individus pour un suivi et un traitement intensifs.

Méthodes : Nous avons regroupé les données de trois essais contrôlés (ACTIVE-A, RE-LY, AVERROES) de patients atteints de FA pour obtenir la dérivation et la validation interne d'un score de risque lors de la première hospitalisation liée à l'IC. Les critères secondaires étaient les décès dus aux maladies cardiovasculaires et le critère composite d'hospitalisations liées à l'IC et de décès dus aux maladies cardiovasculaires.

Atrial fibrillation (AF) is a major risk factor for stroke, heart failure (HF), and death.[1-4] AF and HF share common risk factors and can perpetuate each other's progression; their coexistence is associated with a higher incidence of mortality, compared to that for each individual condition.[1,2,5] Among individuals with AF, HF is a common cause of not only hospitalization but also death.[3] Although current data to support strategies of HF prevention in individuals with AF are limited, early identification of AF patients at high risk of developing HF could facilitate the evaluation of HF prevention in this population. Intensified follow-up, referral to specialized centres, rhythm management, and risk factor management all may improve the prognosis of patients with AF.[6-11]

Stroke prevention is one of the central goals in patients with AF. In comparison, HF prevention receives considerably less attention in clinical care, guidelines, and research. At present, we lack good tools to predict incident HF among patients with AF, and HF prevention is not currently a major clinical focus in this population.[12-14] Although a risk score

Received for publication July 13, 2021. Accepted July 27, 2021.

Ethics Statement: All studies were approved by the ethics committee at each participating site, and all patients provided written informed consent before enrollment.

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See page 1488 for disclosure information.

https://doi.org/10.1016/j.cjco.2021.07.016

died from cardiovascular causes. Incidence rates per 100 patient-years were 1.85 for HF hospitalizations, 2.15 for cardiovascular death, and 3.71 for the composite. Independent predictors for HF hospitalizations included the following: increased age, weight, heart rate and serum creatinine level, lower height and systolic blood pressure, diabetes, vascular disease, valvular disease, heart rhythm, left ventricular hypertrophy, and intraventricular conduction delay. The C-statistic (95% confidence intervals by bootstrap simulations) was 0.717 (0.705-0.732). At 2 years of follow-up, the incidence rate of the primary outcome increased across risk-score quintiles: 0.49, 0.87, 1.29, 2.44, and 4.51 per 100 patient-years, respectively. Patients in the highest quintile had an absolute risk of 6.8% for the primary endpoint at 2 years.

Conclusions: In a large AF population, new-onset HF was common. A combination of characteristics can identify high-risk patients for whom strategies to prevent HF should be considered.

Résultats : L'âge moyen des 23 503 patients, dont 62 % étaient des hommes, était de 71,3 ans. Durant un suivi moyen de 2,0 ans, 875 patients (3,7 %) ont subi leur première hospitalisation liée à l'IC, et 1 037 patients (4,4 %) sont morts de maladies cardiovasculaires. Les taux d'incidence par 100 patients-années étaient de 1,85 pour les hospitalisations liées à l'IC, de 2,15 pour les décès dus aux maladies cardiovasculaires et de 3,71 pour le critère composite. Les prédicteurs indépendants des hospitalisations liées à l'IC étaient les suivants : l'âge avancé, le poids, la fréquence cardiaque et la concentration sérique de la créatinine, la taille inférieure et la pression artérielle systolique, le diabète, les maladies vasculaires, la valvulopathie, le rythme cardiaque, l'hypertrophie ventriculaire gauche et le retard de conduction intraventriculaire. La statistique C (intervalles de confiance à 95 % obtenus par simulations d'auto-amorçage) était de 0,717 (0,705-0,732). Après deux ans de suivi, le taux d'incidence du critère d'évaluation principal augmentait de façon respective dans tous les quintiles de scores de risque : 0,49, 0,87, 1,29, 2,44 et 4,51 par 100 patients-années. Les patients dans le quintile supérieur avaient un risque absolu du critère d'évaluation principal de 6,8 % après deux ans.

Conclusions : Dans une vaste population atteinte de FA, l'IC d'apparition récente était fréquente. La combinaison des caractéristiques peut permettre de déterminer les patients exposés à un risque élevé chez lesquels des stratégies de prévention de l'IC devraient être envisagées.

derived from the Framingham Heart Study showed good risk discrimination, it was limited by a lack of generalizability to contemporary AF populations and performed poorly in the elderly.[14] An easily available and generalizable risk score for incident HF in AF patients would enable clinicians to easily identify high-risk patients and implement early intervention strategies to potentially prevent HF. Moreover, it would lay the foundation to test primary preventive strategies in randomized trials. Beyond improving patients' prognosis and quality of life, healthcare costs could be reduced, as could HF hospitalizations.[15]

In the current study, we aimed to investigate risk factors for incident HF hospitalization in patients with AF and derive a clinically useful risk score to identify high-risk patients.

Methods

Patient population

The present analysis pooled data from 3 large randomized trials of antithrombotic treatment in patients with AF: the **A**trial **F**ibrillation **C**lopidogrel **T**rial With **I**rbesartan for Prevention of **V**ascular **E**vents—**A**spirin (ACTIVE-A),[16] the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY),[17] and the **A**pixaban **Ver**sus Acetylsalicylic Acid to P**r**event Str**o**k**e**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES)[18] studies. In brief, ACTIVE-A enrolled 14,260 patients, with a mean [standard deviation (SD)] follow-up time of 2.4 (1.4) years for the evaluation of clopidogrel plus aspirin for the prevention of stroke and other vascular events in AF patients. Patients were required to have AF at enrollment or at least 2 episodes of AF in the previous 6 months and at least one additional risk factor for stroke (age $\geq$ 75 years; treated hypertension; previous stroke, transient ischemic attack, or non—central nervous system systemic embolism; left ventricular ejection fraction (LVEF) $<$ 45%; peripheral vascular disease; age of 55-74 years and diabetes mellitus or coronary artery disease). The RE-LY study enrolled 18,113 patients with a mean (SD) follow-up time of 2.0 (0.6) years for the comparison of dabigatran and warfarin in patients with AF documented on electrocardiography (ECG) within 6 months of enrollment and at least one additional risk factor (previous stroke or transient ischemic attack; LVEF $\leq$40%; New York Heart Association class $\geq$ II within 6 months before screening; age $\geq$ 75 years or an age of 65-74 years plus diabetes mellitus, hypertension, or coronary artery disease). The AVERROES study had a mean (SD) follow-up time of 1.1 (0.5) years; it enrolled 5599 patients not suitable for vitamin K antagonist therapy, who were aged $\geq$ 50 years, with AF documented within 6 months before or at enrollment for the comparison of apixaban and aspirin with at least one additional risk factor for stroke (prior stroke or transient ischemic attack; age $\geq$ 75 years; treated hypertension or diabetes mellitus, HF (New York Heart Association class $\geq$ 2 at the time of enrollment), LVEF $\leq$ 35%; peripheral-artery disease). All studies were approved by the ethics committee at each participating site, and all patients provided written informed consent before enrollment. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Of the 37,972 patients in the pooled cohort, we excluded 3127 (8.2%) patients due to missing variables. We then excluded 11,342 (29.9%) patients with a history of prior HF, leaving 23,503 (61.9%) patients for analysis (Supplemental Fig. S1).

Outcomes

The primary outcome for this analysis was the first hospitalization for HF. Secondary outcomes were cardiovascular (CV) death and a composite of first hospitalization for HF and CV death. Hospitalization and death events were defined according to the primary reason for hospitalization or death, respectively. We did not further differentiate between HF with reduced vs preserved LVEF. All reported outcomes were identified by local investigators and adjudicated by a committee whose members were blinded to treatment allocation.

Statistical analysis

Baseline characteristics were stratified by study. Continuous variables are presented as mean (SD), and categorical variables are shown as frequency (percentage). Event rates were calculated per 100 patient-years of follow-up. Detailed information on the model building and validation is provided in Supplemental Appendix S1. For modelling of a combined risk score model for the primary outcome, we first built a basic Cox proportional hazards model adjusted for age, sex, study cohort, and use of antiarrhythmic drugs (basic model). We then added prespecified risk factors separately to the basic model. Risk factors were selected based on previous reports, availability in clinical care, and biological plausibility.[12-14] These included weight, height, smoking (ever, never), AF-type (paroxysmal, persistent, permanent), systolic blood pressure (BP), resting heart rate, creatinine clearance level, LVEF $\leq$ 35%, diabetes, vascular disease (prior myocardial infarction, history of coronary artery bypass, other evidence of coronary artery disease or peripheral artery disease), known valvular heart disease (aortic stenosis/regurgitation, mitral stenosis/regurgitation and/or valve replacement/repair judged as relevant by the local investigators), heart rhythm on the baseline ECG (AF, sinus rhythm or other, including atrial flutter and pacemaker rhythms), signs of left ventricular hypertrophy (LVH) on the baseline ECG, as assessed by the local investigator, and intraventricular conduction delay (QRS $\geq$ 120 ms) on the baseline ECG. The final multivariable model was selected on the basis of significant associations of individual risk factors in the basic models, the lowest Akaike information criterion, and a likelihood ratio test. Multicollinearity was defined as a variance inflation factor $>$ 4; no variables met this definition. The proportional hazards assumption was tested by adding an interaction term between survival time and the individual risk factors to the models, and by assessing Schoenfeld residuals (Supplemental Tables S6 and S7; Supplemental Figs. S2-S12). No violations were detected. Risk prediction was performed for the mean follow-up time over all 3 studies.

After derivation, the final model was validated internally using bootstrap resampling with replacement, and 100 simulations. We also obtained the optimism-corrected C-statistics and calculated the 95% confidence intervals (CIs) for the C-statistics by 100 bootstrap replications. Quintiles of risk categories were calculated, and a user-friendly risk score was built based on the final model for individual risk calculation. Kaplan–Meier survival curves were plotted stratified by risk quintiles. Sensitivity analyses included a competing risks analysis for the primary endpoint, considering all-cause death as a competing event. Similar analyses were done for CV death and the composite outcome. Subgroup analyses of the final model were performed excluding patients with a LVEF $\leq$ 35%. We also calculated the C-statistics with similar bootstrap validation for 2 established HF risk scores derived in community-based studies—the **A**therosclerosis **R**isk **i**n **C**ommunities (ARIC) HF prediction score[19] and the Framingham HF risk score[20]—to evaluate their performance in a population with AF.

A 2-sided P value $<$ 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using SAS 9.4 (Cary, NC) or R 4.0 (Vienna, Austria).

Results

Detailed information on the baseline characteristics are shown in Table 1. In the pooled study cohort, mean (SD) age was 71.3 (8.9) years, and 14,582 (62.0%) patients were male. AF was classified as paroxysmal, persistent, or permanent in 31.2%, 23.6%, and 45.2% of the patients, respectively, and 71.4% were in AF at the time of enrollment. Comorbidities included arterial hypertension in 83.6%, diabetes in 20.1%, vascular disease in 24.7%, and relevant valvular disease in 22.0% of the patients.

Over a mean (SD) follow-up time of 2.0 (1.1) years, 875 patients (3.7%) were hospitalized for HF the first time, translating into an incidence rate of 1.85 per 100 patient-years. Incidence rates per 100 patient-years for the primary endpoint stratified by AF type were 1.31 for paroxysmal AF, 1.60 for persistent AF, and 2.35 for permanent AF. CV death occurred in 1037 patients (4.4%), and 1755 patients (7.5%) experienced the composite outcome. Corresponding incidence rates per 100 patient-years were 2.15 for CV death and 3.71 for the composite outcome, respectively. Detailed information about event rates over time is given in Supplemental Table S1.

The final, multivariable model for the prediction of first HF hospitalization included the following risk factors: male gender, age, weight, height, heart rate, systolic BP, renal function, diabetes, vascular disease, valvular disease, rhythm on the ECG, signs of LVH on the ECG, and intraventricular conduction delay on the ECG. The individual hazard ratios are shown in Table 2. The 3 strongest predictors [hazard ratio (95% CI)] were diabetes [1.81 (1.56; 2.09), $P < 0.001$], vascular disease [1.70 (1.47; 1.96), $P < 0.001$), and signs of LVH on the ECG [1.54 (1.28; 1.85), $P < 0.001$). The C-statistic of the final model for a 2-year risk prediction for the primary outcome was 0.717. The 95% CIs of the C-statistics, as assessed by 100 bootstrap simulations, were 0.705-0.732. The net reclassification index (95% CI) from the basic to the final model was 0.584 (0.531; 0.637) (Supplemental Table S2). The optimism-corrected C-statistic based on 100 bootstraps with stepdown selection of predictors was 0.708 for the final model. When we applied the model to a 5-year risk prediction, the C-statistic (95% CI) was similar at 0.717 (0.706; 0.733), with an optimism-corrected C-statistic of 0.710.

Detailed information on events and event rates at 2 years of follow-up for the overall study cohort and stratified by risk quintiles based on the developed risk score is shown in Table 3. Over increasing risk quintiles, incidence rates per 100 patient-years for the primary outcome were 0.49, 0.87, 1.29, 2.44, and 4.51 from the lowest to the highest category,

Table 1. Baseline characteristics stratified by study cohort

Characteristic	Overall	ACTIVE	RE-LY	AVERROES
N	23,503	9420	11,027	3056
Sex (male)	14,582 (62.0)	5893 (62.6)	6820 (61.9)	1869 (61.2)
Age, y, mean (SD)	71.3 (8.9)	70.2 (9.8)	72.7 (7.6)	69.9 (9.4)
Weight, kg, mean (SD)	81.8 (18.6)	82.4 (18.4)	81.7 (18.7)	79.8 (19.1)
Height, cm, mean (SD)	168.8 (10.7)	169.1 (10.5)	169.0 (10.8)	167.5 (10.8)
Heart rate, bpm, mean (SD)	73.2 (14.6)	74.0 (14.3)	72.6 (14.8)	73.3 (14.6)
Systolic blood pressure, mm Hg, mean (SD)	134.1 (17.9)	136.0 (18.7)	132.8 (17.4)	133.1 (16.6)
Ever smoking	11,980 (51.0)	4975 (52.8)	5649 (51.2)	1356 (44.4)
Alcohol drinker	8319 (35.4)	3382 (35.9)	4020 (36.5)	917 (30.0)
AF type				
Paroxysmal	7328 (31.2)	2199 (23.3)	4155 (37.7)	974 (31.9)
Persistent	5544 (23.6)	1434 (15.2)	3448 (31.3)	662 (21.7)
Permanent	10,631 (45.2)	5787 (61.4)	3424 (31.1)	1420 (46.5)
CHADS2 score				
0	753 (3.2)	333 (3.5)	408 (3.7)	12 (0.4)
1	10,364 (44.1)	4524 (48.0)	4176 (37.9)	1664 (54.5)
2	7662 (32.6)	3049 (32.4)	3740 (33.9)	873 (28.6)
3	2906 (12.4)	886 (9.4)	1705 (15.5)	315 (10.3)
4	1542 (6.6)	527 (5.6)	857 (7.8)	158 (5.2)
5	276 (1.2)	101 (1.1)	141 (1.3)	34 (1.1)
6	0 (-)	0 (-)	0 (-)	0 (-)
LVEF, %				
> 35	19,637 (83.6)	9286 (98.6)	7333 (66.5)	3018 (98.8)
≤ 35	3866 (16.5)	134 (1.4)	3694 (33.5)	38 (1.2)
Creatinine clearance, ml/min				
> 80	7129 (30.3)	2845 (30.2)	3333 (30.2)	951 (31.1)
50–80	10,713 (45.6)	3457 (36.7)	5531 (50.2)	1725 (56.5)
30–49	3789 (16.1)	1338 (14.2)	2097 (19.0)	354 (11.6)
< 30	1872 (8.0)	1780 (18.9)	66 (0.6)	26 (0.9)
Medical history				
Stroke/TIA	4155 (17.7)	1289 (13.7)	2451 (22.2)	415 (13.6)
Hypertension	19,639 (83.6)	8040 (85.4)	8879 (80.5)	2720 (89.0)
Diabetes mellitus	4718 (20.1)	1757 (18.7)	2357 (21.4)	604 (19.8)
Vascular disease	5794 (24.7)	2536 (26.9)	3180 (28.8)	78 (2.6)
Valvular disease	5172 (22.0)	2415 (25.6)	2118 (19.2)	639 (20.9)
Aortic stenosis*	579 (11.2)	224 (9.3)	277 (13.1)	78 (12.2)
Aortic insufficiency*	1170 (22.6)	552 (22.9)	459 (21.7)	159 (24.9)
Mitral stenosis*	161 (3.1)	17 (0.7)	96 (4.5)	48 (7.5)
Mitral insufficiency*	4011 (77.6)	1931 (80.0)	1602 (75.6)	478 (74.8)
Other*	1714 (33.1)	919 (38.1)	795 (37.5)	0 (-)
Rhythm in ECG				
Atrial fibrillation	16,784 (71.4)	7025 (74.6)	7738 (70.2)	2021 (66.1)
Sinus rhythm	5769 (24.6)	1935 (20.5)	2897 (26.3)	937 (30.7)
Other	950 (4.0)	460 (4.9)	392 (3.6)	98 (3.2)
LVH in ECG	2644 (11.3)	1102 (11.7)	1149 (10.4)	393 (12.9)
Intraventricular conduction delay in ECG	2635 (11.2)	1210 (12.9)	1145 (10.4)	280 (9.2)
Medication				
ACE inhibitor or ARB	14,277 (60.8)	5679 (60.3)	6817 (61.8)	1781 (58.3)
Calcium channel blocker	7804 (33.2)	2907 (30.9)	3940 (35.7)	957 (31.3)
Beta-blocker	13,227 (56.3)	4924 (52.3)	6683 (60.6)	1620 (53.0)
Amiodarone	2334 (9.9)	1027 (10.9)	1019 (9.2)	288 (9.4)
Digoxin	5901 (25.1)	2682 (28.5)	2542 (23.1)	677 (22.2)
Aspirin	10,585 (45.0)	5235 (55.6)	4389 (39.8)	961 (31.5)
Clopidogrel	825 (3.5)	218 (2.3)	594 (5.4)	13 (0.4)
Vitamin K antagonist	10,794 (45.9)	3887 (41.3)	6904 (62.6)	3 (0.1)
DOAC	8856 (62.9)	0 (-)	7354 (66.7)	1502 (49.2)
Statin	9069 (38.6)	2989 (31.7)	5002 (45.4)	1078 (35.3)

Values are n (%), unless otherwise indicated.

ACE, angiotensin-converting enzyme; ACTIVE-A, **A**trial **F**ibrillation **C**lopidogrel **T**rial With **I**rbesartan for Prevention of **V**ascular **E**vents—**A**spirin; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AVERROES, **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**oke**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; bpm, beats per minute; CHADS2, congestive heart failure, hypertension, age ≥75, diabetes, stroke; DOAC, direct oral anticoagulant; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RE-LY, **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y**; SD, standard deviation; TIA, transient ischemic attack.

*The categories are not mutually exclusive and used the number of valvular disease cases as the denominator.

Table 2. Final risk-factor model for first heart failure hospitalizations

Risk factor	HR (95% CI)	*P*
Male sex	0.95 (0.80; 1.14)	0.60
Age, per 5 years	1.24 (1.19; 1.31)	< 0.001
Weight, per 1 kg	1.01 (1.01; 1.02)	< 0.001
Height, per 10 cm	0.81 (0.74; 0.88)	< 0.001
Heart rate, per 10 bpm	1.13 (1.08; 1.18)	< 0.001
Systolic blood pressure, per 10 mm Hg	0.95 (0.91; 0.98)	0.004
Creatinine clearance, ml/min		
< 30	1.25 (0.96; 1.63)	0.10
≤ 30 to 50	1.47 (1.15; 1.87)	0.002
≤ 50 to 80	1.17 (0.96; 1.42)	0.13
> 80	1.00	
Diabetes	1.81 (1.56; 2.09)	< 0.001
Vascular disease	1.70 (1.47; 1.96)	< 0.001
Valvular disease	1.32 (1.14; 1.53)	< 0.001
Rhythm in ECG		
Atrial fibrillation	1.33 (1.09; 1.63)	0.006
Other	1.36 (0.97; 1.93)	0.08
Sinus rhythm	1.00	
Left ventricular hypertrophy in ECG	1.54 (1.28; 1.85)	< 0.001
Intraventricular conduction delay in ECG	1.40 (1.17; 1.67)	< 0.001

All estimated HRs (95% CIs) were mutually adjusted for all other risk factors, for antiarrhythmic drug use, and study cohort.

bpm, beats per minute; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio.

respectively (Fig. 1). In the highest risk quintile, 6.8% of the patients were hospitalized for HF, 6.3% died from a CV cause, and 11.9% experienced the composite outcome.

Sensitivity analyses for the hazard ratios of the final model with all-cause death as a competing event provided similar results (Supplemental Table S3). Using the final model for the secondary endpoints provided similar predictor variables (Supplemental Table S4). However, some predictor variables that were included in the score for the primary outcome did not predict the secondary outcomes. CV death was not predicted by systolic BP, valvular disease, and intraventricular conduction on the ECG, but it was predicted by male sex and higher weight, in contrast to the primary outcome. The composite outcome was not predicted by weight and systolic BP. Subgroup analyses of the final model excluding patients with a LVEF ≤ 35% showed C-statistics (95% CI by 100 bootstrap simulations) of 0.719 (0.704; 0.739) for a 2-year risk prediction, and 0.718 (0.708; 0.741) for 5-year risk prediction. The C-statistics (95% CI by 100 bootstrap simulations) of the ARIC HF prediction score and the Framingham HF risk score for the primary endpoint were 0.702 (0.690; 0.718) and 0.696 (0.682; 0.711) for a 2-year risk prediction, and 0.704 (0.692; 0.717) and 0.697 (0.683; 0.710) for a 5-year risk prediction, respectively. The net reclassification indices (95% CI) from the ARIC HF prediction score and the Framingham HF risk score to the final model were 0.197 (0.144; 0.249) and 0.153 (0.109; 0.197) for the 2-year risk prediction, respectively (Supplemental Table S5).

Discussion

First hospitalization for HF occurred frequently in this large population of clinically stable AF patients without a prior history of HF. Our risk score provided good discrimination. Patients in the highest risk category had a risk of HF hospitalization that may justify primary preventive measures. The score comprised variables that are readily available in clinical practice. We suggest that the risk score be named the "REACT-HF" risk score, based on the derivation studies (the **RE**-LY, **A**VERROES, and A**CT**IVE-A trials).

Compared to stroke, HF is not only a much more frequent adverse event but also one of the most frequent causes of death and the major driver of healthcare costs in contemporary AF populations.[3,15] In contrast to the well-established primary prevention for stroke, there is no successfully proven primary prevention strategy for HF that has been tested in a randomized trial. The keys for a shift from secondary to primary prevention is an easily available method to identify individuals at high risk for HF who may benefit from changes in management in a cost-effective manner, and the availability of beneficial interventions. A previously published risk score for incident HF in AF patients from the Framingham Heart Study aimed to provide such a tool.[14] Although the risk score performed well in discriminating between low-risk and high-risk patients, it was limited by its derivation in a relatively small sample, with data acquired over the past 50 years, which therefore included non-contemporary AF treatments, treatments with poorer performance in the elderly, and no external or internal validation.[14] Thus, the applicability and generalizability to contemporary AF populations were limited, which may be one reason the risk score did not find its way into clinical practice. We also tested HF risk scores derived from community-based studies in our current analyses.[19,20] Their C-statistics were lower, but still reasonable compared to those in our final risk model, a result that may be explained by the partial overlap with our predictor variables. However, we believe a score specific to an AF population is warranted, given the importance of HF among AF patients.

Our current risk score overcomes most of the limitations of prior HF risk scores in AF patients by the derivation and internal validation in a large, contemporary AF population with good discrimination and a wider generalizability. For ease of use, we provide an intuitive risk calculator in Supplemental Appendix S2. In addition, the current risk score may be the foundation for randomized controlled trials investigating primary preventive treatment strategies prospectively in high-risk patients.

Interventions that may be tested in randomized clinical trials and may be used in clinical practice include lifestyle management, and medical and interventional treatment, ideally combined in a comprehensive approach.[6,7,9-11] Several modifiable risk factors in our score offer treatment options. These include heart rate control, reduction of AF burden, improvement of blood glucose control, and risk factor management for vascular disease and LVH. In a multilevel treatment approach, aggressive lifestyle risk factor management needs to be the foundation of primary HF prevention in AF patients. Weight loss reduced temporal AF burden by more than half, with concomitant reduction in blood pressure and insulin homeostasis in patients with symptomatic AF.[6] Moreover, comprehensive lifestyle interventions, including smoking cessation, a reduction in alcohol consumption, controlled weight loss, optimal blood pressure control, glucose homeostasis, and therapy of sleep apnea, further led to both improvement of long-term success rates of catheter ablation

Table 3. Event rates at 2 years of follow-up

Study population	N	HF hospitalization	Event rate / 100 py	Cardiovascular death	Event rate / 100 py	Combined endpoint	Event rate / 100 py
Overall	23,503	698 (3.0)	1.87	727 (3.1)	1.92	1339 (5.7)	3.59
Risk quintile							
1	4700	38 (0.8)	0.49	55 (1.2)	0.71	91 (1.9)	1.17
2	4701	66 (1.4)	0.87	94 (2.0)	1.22	153 (3.3)	2.01
3	4701	97 (2.1)	1.29	108 (2.3)	1.42	197 (4.2)	2.62
4	4701	179 (3.8)	2.44	174 (3.7)	2.33	337 (7.2)	4.59
5	4700	318 (6.8)	4.51	296 (6.3)	4.04	561 (11.9)	7.96

Values are n (%), unless otherwise indicated. Quintiles of risk categories derived from the final model for 2-year prediction.
HF, heart failure; py, patient-years.

and positive remodelling of left atrial and left ventricular size.[21,22] The next key component is optimal medical management, including drugs that have shown benefits in HF populations. For example, blockade of the renin–angiotensin system in AF patients led to a substantial decrease in HF and reduced the risk for myocardial infarction.[23,24] Targeting other pathways, sodium–glucose cotransporter-2 (SGLT-2) inhibitors may offer further potential in HF risk reduction in addition to improving glycemic control along with lifestyle interventions.[25] In addition to medical management, catheter ablation may decrease the incidence of HF by reducing AF burden. The largest trial investigating AF ablation so far showed a nearly 20% reduction in a composite endpoint of death and CV hospitalizations in a population free of prior HF in 85% of all patients.[7] These results are supported by substantial risk reductions by catheter ablation in AF patients with known HF.[8] For bringing together these different treatment approaches, emphasis should be placed on specialized AF clinics that have access to a greater variety of treatment options compared to less-specialized centers.[9,10] However, the components of our risk score may not all necessarily be causal, and their modification might not translate fully into decreased risk for HF.

Strengths of our study include the contemporary, large, and well-defined sample size, and the adjudication of outcomes by a blinded committee. This study should be considered in light of several limitations. First, effective usage of our risk score mandates application in the right patient population. All 3 studies used for the risk score derivation enrolled clinically stable patients with at least one additional risk factor for stroke, mainly from North America and Europe.[16-18] Although this comprises a large population of AF patients, for which our risk score is suitable, it is of unknown generalizability to other populations, including patients who have AF alone or are at low risk for stroke. Risk factors might differ in clinically unstable patients presenting to the emergency department, and in AF patients in low- and middle-income countries.[3]

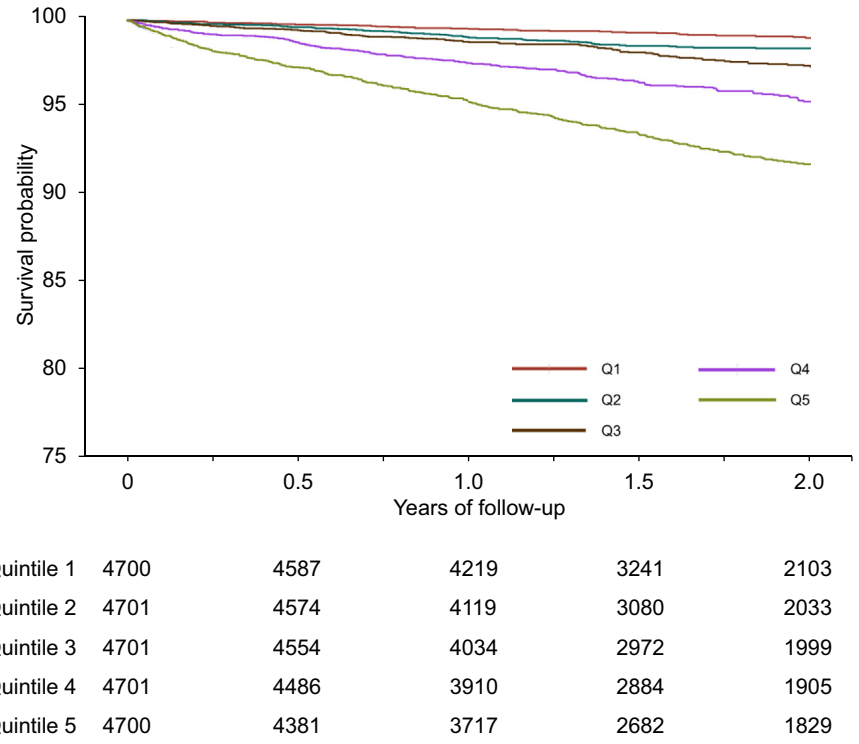

Figure 1. Survival curves for first heart failure hospitalization. Values for quintiles are number of participants. Q, quintile.

Second, the current study is a post hoc analysis, with the known accompanying limitations. Third, external validation of the risk score is needed to improve generalizability. Ideally, validation is performed in an unselected AF population, as for example in the Swiss-AF cohort study.[26] Fourth, the mean follow-up period was limited to 2 years, and thus the long-term risk for HF may have been underestimated in our study, although the risk score also showed good C-statistics for a 5-year risk prediction. Fifth, use of biomarkers, such as N-terminal pro-hormone brain natriuretic peptide, might have improved the diagnostic accuracy of our risk score, but these were not available in the investigated study populations. Sixth, inclusion of patients with asymptomatic LVEF $\leq$ 35% might mean that some patients had undiagnosed, prior HF. Although our subgroup analyses excluding patients with a LVEF $\leq$ 35% yielded similar results, bias still might have been introduced.

In conclusion, we developed a new risk score—the REACT-HF risk score—for HF hospitalizations in AF patients free of prior HF at baseline. Patients in the highest risk category based on our score had a substantial risk for HF hospitalization. Increased attention on primary prevention efforts might prevent incident HF and adverse outcomes.

Funding Sources

P.K. is supported by the University of Basel, the Mach-Gaensslen Foundation, and the Bangerter-Rhyner Foundation. L.J. is supported by governmental funding within the Swedish National Health Services, the Swedish Society of Medicine, the Swedish Heart and Lung Foundation, the Swedish Heart and Lung Association, the Swedish Society of Cardiology, and the Bergqvist Foundation. D.C. holds a McMaster University Department of Medicine Mid-Career Research Award. W.F.M. is supported by fellowship awards from the Canadian Stroke Prevention Intervention Network and the Canadian Institutes of Health Research.

Disclosures

J.H.S. reports research grants and speaking fees from BMS/Pfizer and Servier. The other authors have no conflicts of interest to disclose.

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Supplementary Material

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