Prediction of Congestive Heart Failure in Patients with Non Valvular Atrial Fibrillation

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Abstract

Objective Patients with atrial fibrillation (AF) have an increased risk of congestive heart failure (CHF) as well as ischemic stroke. The aim of this study was to investigate the clinical predictors of CHF in patients with non-valvular AF (NVAF).

Methods Three hundred and forty-seven patients (derivation cohort) with NVAF were retrospectively evaluated between 2004 and 2005. The associations between potential risk factors and CHF were tested using a Cox proportional hazards analysis, and a risk score for predicting CHF was created. The model was then validated in 161 patients (validation cohort) enrolled between 2008 and 2010. During the follow-up period, 41 patients in the derivation cohort developed CHF requiring hospitalization due to New York Heart Association (NYHA) class III or IV disease. Four independent risk factors were identified, each of which was assigned a number of points as follows: Age ≥ 72 years (1 point), heart rate ≥ 80 bpm (1 point), hypertension (1 point), and a previous history of congestive heart failure (2 points). The patients were grouped into one of three risk categories according to the calculated risk score (ARC₂H score): low risk (0 points), intermediate risk (1-3 points) and high risk (4-5 points).

Result In the derivation cohort, the annual rates of CHF in these risk categories were 0%, 2.5% and 18% per year respectively. In the validation cohort, the corresponding rates were 0.8%, 8% and 35% per year respectively.

Conclusion A simple clinical risk score, the ARC₂H score, was developed to predict CHF in patients with NVAF and validated in an independent cohort.

Key words: atrial fibrillation, ARC₂H score, congestive heart failure

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is well recognized that stroke and congestive heart failure (CHF) are the two most important clinical comorbid conditions associated with AF. It has been reported that the annual rate of stroke in AF patients ranges from less than 2% to more than 10% per year (1-6) depending on the risk of stroke (7). On the other hand, the incidence of CHF among AF patients varies from 1.7% to more than 10% per year (8-10), depending on the patient's background clinical condition.

Although a previous report suggested that CHF has an adverse impact on the prognosis of patients with AF independent of other cardiovascular diagnoses and risk factors (9), other reports have suggested that AF is not associated with worse mortality in patients with advanced heart failure (11, 12). These discordant results suggest that the risk of CHF differ among AF patient with different clinical backgrounds. Therefore, it is especially important to assess the risk of CHF and optimally manage patients with AF who are at a high likelihood of developing CHF.

The CHADS₂ score has been established to be a simple and reproducible risk score for predicting stroke in patients with AF (13). Although AF patients have an increased risk

Table 1. Clinical Characteristics of the Derivative Cohort

	CHF (n=41)	Non-CHF (n=306)	p value
Age, years	73.9 ± 8.9	71.1 ± 9.1	0.038
Female gender, n (%)	19 (46)	102 (29)	0.025
Body mass index, kg/m ²	22.6 ± 3.1	23.9 ± 4.1	0.193
Heart rate, beats/min	85.7 ± 18.4	79.4 ± 17.6	0.018
Hypertension, n (%)	30 (73)	156 (50)	0.021
Hyperlipidemia, n (%)	10 (24)	80 (26)	0.222
Diabetes mellitus, n (%)	10 (24)	70 (23)	0.393
Smoking, n (%)	18 (43)	104 (33)	0.108
History of IHD, n (%)	5 (12)	18 (6)	0.194
History of stroke, n (%)	5 (12)	31 (10)	0.562
History of CHF, n (%)	30 (73)	59 (20)	<0.0001

CHF: congestive heart failure, IHD: ischemic heart disease

of CHF, no risk score for predicting CHF in patients with AF has been established. Therefore, the purpose of this study was to investigate predictors of CHF in patients with AF and to propose a clinical score for predicting CHF in patients with non valvular AF (NVAF).

Materials and Methods

Study population

Between October 2004 and December 2005, 592 (3.2%) patients with AF were identified and included from a retrospective database of 18,568 consecutive patients who underwent 12-lead electrocardiogram (ECG) examination at our hospital. Patients with paroxysmal AF, pacemaker implantation or valvular AF were excluded. In addition, patients were also excluded if their clinical outcomes could not be evaluated. Ultimately, 347 patients (derivation cohort: 121 women, mean age 71±9 years, range: 18 to 93 years) with (NVAF) were enrolled. The patients were divided into two groups: patients who developed CHF requiring hospitalization due to New York Heart Association (NYHA) class III or IV disease (CHF group, n=41) and those who did not develop CHF (non-CHF group, n=306) during the follow-up period (median: 42 months). CHF was defined according to the Framingham Heart Study criteria (14). To identify predictors of CHF, clinical characteristics, laboratory data and medications were compared between the two groups. Based on the results obtained from the derivation cohort, a clinical risk score to predict CHF was constructed. The constructed model was then validated in a validation cohort. A total of 486 consecutive outpatients with newly diagnosed NVAF who visited our hospital between 2008 and 2010 were identified. Patients with paroxysmal AF or pacemaker implantation were excluded. Ultimately, 161 patients (validation cohort: 51 women, mean age: 71±2 years, range: 36 to 98 years, mean follow-up: 24 months) were enrolled.

Criteria for persistent atrial fibrillation

AF was defined according to the ACC/AHA/ESC guide-

Table 2. Medications of the Derivative Cohort

	CHF (n=41)	Non-CHF (n=306)	p value
ACE-I / ARB, n (%)	20 (48)	124 (41)	0.314
CCB, n (%)	16 (39)	90 (29)	0.210
Beta-blockers, n (%)	10 (24)	54 (18)	0.296
Digitalis, n (%)	18 (43)	130 (42)	0.427
Warfarin, n (%)	22 (53)	179 (58)	0.556
Statins, n (%)	6 (14)	40 (13)	0.182

ACE-I: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor blockers, CCB: calcium channel blockers

Table 3. Univariable and Multivariable Predictors of CHF

	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
History of CHF	6.29 (3.65-10.8)	<0.0001	6.44 (3.62-11.5)	<0.0001
Heart rate, bpm	1.12 (1.02-1.34)	0.020	1.03 (1.00-1.06)	0.035
Age, years	1.86 (1.16-2.99)	<0.01	1.92 (1.13-3.29)	0.016
Hypertension	2.69 (1.65-4.40)	<0.01	2.30 (1.34-3.90)	0.023
Female	1.87 (1.03-3.42)	0.042	0.68 (0.37-1.23)	0.205

CHF: congestive heart failure, HR: hazard ratio, CI: confidence interval
bpm: beats per minutes

lines (12). The presence of AF was confirmed based on the results of two consecutive 12-lead ECG examinations performed at least seven days apart. All study patients were diagnosed as presenting with AF for at least one year or more at the time of study entry and exhibited AF that persisted throughout the follow-up period. Heart rate [HR, beat/min (bpm)] at rest was defined as the average of 10 consecutive beats during resting 12-lead ECG.

The study protocol was approved by the Institutional Review Committee on Human Research at our institution.

Statistical analysis

The data are expressed as the mean ± SD. The two groups were compared using unpaired Student's *t*-test and chi-square test. A Cox proportional hazard analysis was used to identify the independent risk factors for CHF in the derivation cohort. A receiver operator characteristic (ROC) curve analysis was used to determine the cut-off values of age and HR. All statistical analyses were performed using the SAS software program, version 8.2 (SAS Institute, Cary, NC, USA).

Results

During the follow-up period (median: 42 months), 41 (12%) patients in the derivation cohort developed CHF requiring hospitalization.

Table 1 summarizes the baseline clinical characteristics of the two groups in the derivation cohort. Age and HR were significantly higher in the CHF group than in the non-CHF group. A female gender, hypertension, history of CHF and history of open heart surgery were more frequently observed in the CHF group than in the non-CHF group. The medica-

Figure 1. Relationship between the ARC₂H score and incidence of CHF in patients with the derivation cohort. As the ARC₂H score increased, incidence of CHF increased.

Figure 3. Relationship between the ARC₂H score and incidence of CHF in patients with the validation cohort. As the ARC₂H score was increased, the incidence of was CHF increased.

tions are summarized in Table 2. There were no significant differences in medications between the two groups.

The univariable predictors of CHF were a history of CHF, age, female gender, hypertension and HR. According to the multivariable Cox proportional hazard analysis, age, hypertension, HR and a history of CHF were independent predictors of CHF (Table 3). A cut-off value of an age ≥ 72 years was identified in the ROC curve analysis. Similarly, according to the ROC curve analysis, HR ≥ 80 bpm was identified as a cut-off value predicting CHF.

Risk score for predicting CHF in patients with NVAf

Based on the results obtained in the derivation cohort, we constructed a clinical risk score, the “ARC₂H” (Age, HR, history of CHF and Hypertension) score, to predict CHF in patients with NVAf. The ARC₂H score was calculated by assigning 1 point each for the presence of hypertension, an age ≥ 72 years and HR ≥ 80 bpm and 2 points to a history of CHF because a history of CHF added significant independent predictive power to the other clinical risk factors. Fig. 1 shows the relationship between the ARC₂H score and the rate of CHF per year in the derivation cohort. The rate of CHF increased as the ARC₂H score increased. The patients

Figure 2. Kaplan-Meier plot of the CHF-free survival curves in each risk category of the derivation cohort. CHF-free survival rate was significantly lower in high risk category group than in intermediate and low risk category groups.

Table 4. Clinical Characteristics and Medication of the Validation Cohort

	n=161
Age, years	71.2 $\pm$ 2.0
Female gender, n (%)	51 (31)
Body mass index, kg/m ²	23.6 $\pm$ 2.1
Heart rate, bpm	80.1 $\pm$ 17.7
Hypertension, n (%)	87 (54)
Hyperlipidemia, n (%)	87 (54)
Diabetes mellitus, n (%)	32 (20)
Smoking, n (%)	20 (13)
History of IHD, n (%)	9 (6)
History of stroke, n (%)	18 (11)
History of CHF, n (%)	24 (23)
Medications, n (%)	
ACE-I / ARB, n (%)	93 (58)
CCB, n (%)	57 (35)
Beta-blockers, n (%)	59 (37)
Digitalis, n (%)	45 (28)
Warfarin, n (%)	142 (88)
Statins, n (%)	21 (13)

CHF, congestive heart failure, IHD: ischemic heart disease, ACE-I: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor blockers, CCB: calcium channel blockers, bpm: beats per minutes

were then grouped into one of the three risk categories: low risk (0 points), intermediate risk (1 to 3 points) and high risk (4 to 5 points). In the derivation cohort, the annual rates of CHF in the risk categories were 0% (low risk), 2.5% (intermediate risk), and 18% (high risk) per year, respectively. Fig. 2 shows a Kaplan-Meier plot of the CHF-free survival curves for each risk category in the derivation cohort. The patients in the high-risk category had a significantly lower CHF-free survival rate.

Table 4 summarizes the clinical characteristics and medications of the validation cohort. Digitalis was less frequently used in the validation cohort than in the derivation cohort. On the other hand, beta-blockers and warfarin were more

Figure 4. A: Relationship between the CHADS₂ score and incidence of stroke in study patients. Annual rate of stroke was strongly related to the stroke risk categories. B: Relationship between the CHADS₂ score and incidence of CHF in study patients. Annual rate of CHF did not differ between the stroke risk categories.

Figure 5. Relationship between the ARC₂H score and incidence of stroke in study patients. Annual risk of stroke did not differ between the risk categories stratified by the ARC₂H score.

frequently prescribed in the validation cohort than in the derivation cohort.

Fig. 3 shows the annual rate of CHF in the validation group. Similar to that observed in the derivation group, the rate of CHF increased as the ARC₂H score increased. In the validation cohort, the annual rates of CHF in the risk categories were 0.8% (low risk), 8% (intermediate risk) and 35% (high risk) per year, respectively.

Both the derivation and validation cohorts were grouped according to the stroke risk categories (low risk, intermediate risk and high risk) stratified by the CHADS₂ score. As expected, the annual rate of stroke was strongly related to the stroke risk categories (Fig. 4A). On the other hand, the annual rate of CHF did not differ between the stroke risk categories (Fig. 4B). Conversely, annual risk of stroke did not differ between the risk categories stratified by the ARC₂H score (Fig. 5).

The derivation cohort was further divided into two groups according to the presence or absence of a previous history of CHF. Among the patients with a history of CHF, the independent predictors of CHF were hypertension (OR=3.43, 95%CI: 1.19-9.82, $p=0.022$) and HR (OR=1.03, 95%CI: 1.00-1.06, $p=0.045$). On the other hand, only hypertension (OR=2.08, 95%CI: 1.10-3.94, $p=0.024$) and age (OR=1.05, 95% CI: 1.01-1.09, $p=0.015$) were independent predictors of CHF in the NVAf patients without a history of CHF.

Discussion

Our present study showed that age, hypertension, HR and a previous history of CHF were independent predictors of CHF in patients with NVAf. The ARC₂H score derived from these independent predictors may be used as a simple and useful clinical score to assess the risk of CHF in patients with NVAf.

It has been reported that a previous history of CHF is an independent predictor of future CHF (13). Our results showing that a history of CHF added significant independent predictive power to the other clinical risk factors are concordant with the findings of previous reports. On the other hand, the predictive role of baseline HR has not yet been established. Although the current ACC/AHA/ESC guidelines recommend a target HR of 60 to 80 bpm at rest in AF patients who receive rate control (15), the relationship between HR and the risk of CHF in AF patients remains controversial. Groenveld et al. reported that there are no significant differences in cardiovascular mortality or morbidity between AF patients with a HR of ≥ 80 bpm or HR < 80 bpm (16). On the other hand, Reinstra et al. reported that a lower HR (< 80 bpm) is associated with a poorer prognosis (17). Similarly, Castagnon et al. reported that the resting heart rate is only an important predictor of the outcome in patients with stable chronic heart failure without AF (18). More recently, Van Gelder et al. reported that there are no significant differences in cardiovascular mortality or morbidity between patients treated with strict rate control (HR < 80 bpm) and lenient rate control (HR < 110 bpm) strategies (19). Therefore, it remains unknown if strict rate control will prevent CHF and improve the prognosis in our study population.

It is well known that hypertension and age are independent risk factors for both AF and CHF (8, 14). Therefore, our results showing that age and hypertension are independent predictors of CHF are also concordant with the findings of these previous reports (8, 14).

It has been reported that elderly women are predominantly observed among patients with heart failure with a preserved ejection fraction (20-22). This phenomenon may be related to gender differences in the age-related deteriora-

tion of the diastolic function (23). In the present study, a female gender was a univariable predictor of CHF but not an independent predictor of CHF in the multivariable analysis. Differences in the study population and the small sample size of this study may explain the lack of association between gender and CHF. The rate of hospitalization for CHF was slightly different between the derivation and validation cohorts in our study. The left ventricular ejection fraction (LVEF) was significantly lower in the validation cohort than in the derivation cohort (LVEF; $54 \pm 11.9\%$ vs. 60 ± 10.8 , $p < 0.036$). Therefore, it is possible that differences in the baseline cardiac function affected the difference in the hospitalization rate observed between the derivation and validation groups.

Although the CHADS₂ score (13) is a predictor of stroke, it was not related to the incidence of CHF in our study population. Conversely, the ARC₂H score was not related to the incidence of stroke. Therefore, the ARC₂H score and the CHADS₂ score may be used to assess the risk of either CHF or stroke independently in patients with NVAf. A previous study reported that the echo Doppler derived index of the left ventricular filling pressure, E/e', predicts mortality and hospitalization due to CHF (24). Therefore, a clinical score may be used as a screening tool to select NVAf patients who should be referred for echocardiography examinations.

Suzuki et al. reported that the H2ARDD (heart diseases=2 points, anemia=1 point, renal dysfunction=1 point, diabetes=1 point and diuretic use=1 point; range 0 to 6 points) score predicts CHF in patients with AF (25). In our study, there were no significant differences in the rates of renal dysfunction, diuretic use, anemia or diabetes between the CHF and non-CHF groups. This difference between their study and our study may in be explained in part by the differences in the study populations. Their study included patients with valvular heart disease, while our study enrolled patients with NVAf. In addition, their cannot be denied until they perform a validation study.

In AF patients, antithrombotic therapy using warfarin or dabigatran has been established as a standard therapy for the preventing of strokes in patients with an $\geq$ intermediate stroke risk according to the CHADS₂ score (26, 27). On the other hand, specific medications to lower the risk of CHF have not yet been established. Previous studies have reported that angiotensin-converting-enzyme inhibitors, beta-blockers and angiotensin II receptor blockers may improve the outcomes of patients with CHF with or without a preserved left ventricular ejection fraction (28-31).

Recently, it was reported that irbesartan, an angiotensin II receptor blocker, may decrease the rate of hospitalization due to heart failure in patients with AF (32). Therefore, the impact of medical interventions on the risk of CHF requires further investigation.

Clinical implications

AF is an important clinical condition due to both its strong relationship with stroke and its function as a cause of

CHF. The ARC₂H score simply predicts the risk of CHF, as does the CHADS₂ score predict the risk of stroke, in patients with AF. Although echocardiographic indices as well as biomarkers, such as the level of BNP, can be used to further stratify AF patients with a higher risk for CHF, these indices were not included in our present study. The most important clinical implication of this study is that we can predict the risk of CHF using a medical interview and vital signs only, even in the outpatient clinic. Performing risk stratification of patients with NVAf using the ARC₂H score is useful for identifying high-risk patients who require aggressive medical therapy.

Study limitations

First, although consecutive patients were enrolled, this study may be weakened by the fact that it was a small, retrospective, single-center study. Therefore, the results must be confirmed in a large, prospective, multicenter studies. Second, the median follow-up period was only 42 months in the derivation group. This relatively short follow-up duration may have resulted in the underestimation of the true number of CHF events. Third, patients with paroxysmal AF were excluded. Therefore, our results cannot be generalized to all patients with AF. Finally, the impact of medical treatments on modifying the risk of CHF remains unknown and should be investigated further.

Conclusion

Age, heart rate, hypertension and a history of CHF are independently associated with CHF in patients with NVAf. The ARC₂H score may be used as a simple clinical score for predicting CHF in patients with NVAf.

The authors state that they have no Conflict of Interest (COI).

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