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Progression From Paroxysmal to Persistent Atrial Fibrillation

Clinical Correlates and Prognosis

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Objectives We investigated clinical correlates of atrial fibrillation (AF) progression and evaluated the prognosis of patients demonstrating AF progression in a large population.

Background Progression of paroxysmal AF to more sustained forms is frequently seen. However, not all patients will progress to persistent AF.

Methods We included 1,219 patients with paroxysmal AF who participated in the Euro Heart Survey on AF and had a known rhythm status at follow-up. Patients who experienced AF progression after 1 year of follow-up were identified.

Results Progression of AF occurred in 178 (15%) patients. Multivariate analysis showed that heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and hypertension were the only independent predictors of AF progression. Using the regression coefficient as a benchmark, we calculated the HATCH score. Nearly 50% of the patients with a HATCH score >5 progressed to persistent AF compared with only 6% of the patients with a HATCH score of 0. During follow-up, patients with AF progression were more often admitted to the hospital and had more major adverse cardiovascular events.

Conclusions A substantial number of patients progress to sustained AF within 1 year. The clinical outcome of these patients regarding hospital admissions and major adverse cardiovascular events was worse compared with patients demonstrating no AF progression. Factors known to cause atrial structural remodeling (age and underlying heart disease) were independent predictors of AF progression. The HATCH score may help to identify patients who are likely to progress to sustained forms of AF in the near future. (J Am Coll Cardiol 2010;55:725–31) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. The arrhythmia is associated with increased morbidity and mortality, mainly as a result of 2 complications: stroke and heart failure (1).

In clinical practice, one should distinguish between the clinical AF type (paroxysmal AF, episodes of the arrhythmia that terminate spontaneously) and persistent AF (episodes that are sustained longer than 7 days and are not self-terminating) (2). The latter will affect the individual treatment strategy for each patient. Important differences were found between the clinical subsets of AF (3). Underlying heart disease occurs more frequently in patients with sustained AF. Patients with paroxysmal AF are more often treated with antiarrhythmic drugs, whereas patients with chronic AF receive more rate control therapy. In the CARAF (Canadian Registry of Atrial Fibrillation) study, investigators evaluated determinants of AF progression (4). The investigators found that underlying heart disease and age were independently associated with progression of AF. The Euro Heart Survey (EHS) on AF presents a unique overview of AF management in a large group of patients in several European countries. Nieuwlaat et al. (5) previously reported the influence of underlying heart disease on the progression of AF in the EHS. However, in this univariate analysis, no correction for possible confounders was performed, and the contribution of each factor to AF progression was not studied.

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Abbreviations and Acronyms

AF = atrial fibrillation

AUC = area under the curve

COPD = chronic obstructive pulmonary disease

TIA = transient ischemic attack

The present study is the largest study to investigate the clinical correlates of arrhythmia progression in patients with paroxysmal AF. In addition, we evaluated the prognosis of patients with AF progression and validated a risk stratification rule to assess the probability of AF progression.

Methods

A detailed description of the methods, data collection, validation, and the first results of the EHS on AF were presented by Nieuwlaat et al. (6). In 2003 and 2004, 5,333 AF patients were enrolled in this survey. These patients were enrolled at 182 hospitals in 35 different member countries of the European Society of Cardiology. Inclusion criteria were age older than 18 years and AF on an electrocardiogram or Holter recording in the previous 12 months or at the time of inclusion. Enrollment of consecutive patients took place at several sites within the cardiology departments.

AF was classified into 5 categories. The clinical AF type was first detected AF in 978 patients, paroxysmal AF in 1,517 patients, persistent AF in 1,167 patients, permanent AF in 1,541 patients, and unknown type of AF in 130 patients. In the present study, only the records for patients with paroxysmal AF and first detected AF in whom sinus rhythm restored spontaneously or after pharmacological treatment during admission were evaluated, leaving a study population of 1,219 patients with a known rhythm status at 1-year follow-up. We did not include patients who underwent electrical cardioversion to sinus rhythm because one cannot be sure that those patients have self-terminating AF. In addition, we did not take persistent AF as a separate entity to evaluate progression to permanent AF because the classification permanent AF is physician driven and does not depend on the pathophysiology or clinical characteristics of the arrhythmia and therefore precludes proper assessment of progression (2).

In the EHS on AF, data were collected from medical records and medical information systems or entered by the attending physician. Progression of AF was defined as follows: paroxysmal AF at baseline becoming persistent or permanent AF at 1-year follow-up or first detected AF at baseline with spontaneous conversion to sinus rhythm during admission becoming persistent or permanent AF at 1-year follow-up. We also determined the $CHADS_2$ score (7). This acronym stands for congestive heart failure, hypertension, age (75 years and older), diabetes mellitus, and a history of stroke/transient ischemic attack (TIA) (2 points). This scoring system allows instant classification of the relative thromboembolic risk in patients with AF and is incorporated in the latest guidelines on the management of AF.

Statistical analysis. Data analysis was performed with SPSS statistical software (version 15.0, SPSS Inc., Chicago, Illinois). Continuous variables are reported as mean ± SD and categorical variables as observed number of patients (percentage). When comparing patients with AF progression and no AF progression regarding baseline characteristics, treatment, or outcome, we used an independent *t* test for continuous variables and the Fisher exact test for categorical variables. The p values resulting from these analyses are reported in Tables 1, 2, and 3. All baseline characteristics showing a significant univariate relationship with AF progression at follow-up were included in a logistic regression model (heart failure in history, chronic obstructive pulmonary disease [COPD] in history, left atrial size on echocardiogram, age, regular physical activity, hypertension, coronary artery disease, valve disease, previous stroke or TIA, renal failure). We did not include the variables lone AF or $CHADS_2$ score in the model because they were derived from other variables included in the model. Model reduction was performed by stepwise excluding variables from the model with a p value <0.10. All variables that were independently associated with AF progression were tested for interactions. To develop a convenient score, the regression coefficients of the final logistic regression model were used to estimate the contribution of each variable to the risk estimation of AF progression. This resulted in the attribution of 1 or 2 points for each variable included in the score.

The predictive accuracy of the known predictors of AF progression and the HATCH score was reported using a receiver-operator characteristic curve. To compare the discriminative power of the HATCH score (acronym stands for hypertension, age [75 years and older], transient ischemic attack or stroke (2 points), chronic obstructive pulmonary disease and heart failure (2 points); this scoring system allows instant classification of the risk of progression to persistent or permanent AF in patients with paroxysmal AF) and the $CHADS_2$ score, we applied the Delong, Delong, Clarke-Pearson method using Analyse-it 2.20 statistical software (Leeds, United Kingdom). All tests performed were 2 sided. Overall, a p value of <0.05 was considered to be statistically significant.

Results

The age of the 1,219 patients included in the present study was 64 ± 13 years. Progression of AF to more sustained forms occurred in 178 patients (15%). Table 1 shows the baseline characteristics of patients with and without AF progression. Patients who experienced AF progression were older and performed less regular physical activity. In addition, these patients had more underlying heart disease. Hypertension, coronary artery disease, valve disease, heart failure, COPD, stroke or TIA, and renal failure occurred more frequently in patients with AF progression. This is reflected by the higher mean $CHADS_2$ score (1.9 ± 1.3 vs.

Table 1 Baseline Characteristics

	All Patients	No AF Progression	AF Progression	p Value
n	1,219	1,041 (85%)	178 (15%)	
Age (yrs)	64 ± 13	63 ± 13	68 ± 11	<0.001
Female	524 (43%)	439 (42%)	85 (49%)	0.165
Body mass index (kg/m^2)	27 ± 4	27 ± 4	28 ± 5	0.246
Symptoms (admission)	913 (75%)	773 (74%)	140 (79%)	0.261
Regular physical activity	415 (34%)	370 (36%)	45 (25%)	0.010
Echocardiogram and electrocardiogram characteristics				
Left atrial size on echo (mm)	43 ± 8	43 ± 8	45 ± 8	<0.001
Ventricular rate (when sinus rhythm)	70 ± 15	70 ± 15	72 ± 19	0.195
Ventricular rate (when AF)	109 ± 30	109 ± 31	110 ± 30	0.712
Type of AF				
First detected	165 (14%)	140 (13%)	25 (14%)	
Paroxysmal	1,054 (86%)	901 (87%)	153 (86%)	
Underlying disease				
Hypertension	752 (62%)	626 (60%)	126 (71%)	0.007
Coronary artery disease	392 (32%)	321 (31%)	71 (40%)	0.024
Diabetes mellitus	182 (15%)	148 (14%)	34 (19%)	0.110
Valve disease	233 (19%)	188 (18%)	45 (25%)	0.030
Heart failure	247 (21%)	181 (18%)	66 (38%)	<0.001
Chronic obstructive pulmonary disease	137 (11%)	104 (10%)	33 (19%)	0.002
Hyperthyroidism	60 (5%)	52 (5%)	8 (5%)	0.853
History of stroke or TIA	105 (9%)	77 (8%)	28 (16%)	0.001
Malignancy	56 (5%)	47 (5%)	9 (5%)	0.699
Peripheral vascular disease	74 (6%)	58 (6%)	16 (9%)	0.089
Renal failure	56 (5%)	41 (4%)	15 (9%)	0.018
Lone AF	203 (17%)	189 (19%)	14 (8%)	<0.001
$CHADS_2$ score	1.3 ± 1.2	1.2 ± 1.1	1.9 ± 1.3	<0.001

Values are presented as n, n (%), or mean ± SD.
AF = atrial fibrillation; TIA = transient ischemic attack.

1.2 ± 1.1, $p < 0.001$) and lower percentage of lone AF (8% vs. 19%, $p < 0.001$) in patients with AF progression compared with patients whose AF remained paroxysmal after 1 year. No significant difference was found between the percentage of patients with diabetes demonstrating AF progression and patients who remained in sinus rhythm. On the echocardiogram obtained at baseline, patients with AF progression had a larger left atrium.

Medication use at baseline is presented in Table 2. Understandably, all drugs associated with heart failure were

Table 2 Medication Use at Baseline

	All Patients	No AF Progression	AF Progression	p Value
n	1,219	1,041 (85%)	178 (15%)	
Oral anticoagulation	594 (50%)	490 (49%)	104 (60%)	0.007
Aspirin	437 (37%)	376 (37%)	61 (35%)	0.611
Beta-blocker	495 (42%)	418 (41%)	77 (44%)	0.506
Diltiazem	36 (3%)	29 (3%)	7 (4%)	0.468
Verapamil	60 (5%)	48 (5%)	12 (7%)	0.257
Digitalis	136 (11%)	108 (11%)	28 (16%)	0.039
Any antiarrhythmic drug	627 (52%)	541 (52%)	86 (49%)	0.415
Flecainide	89 (7%)	80 (8%)	9 (5%)	0.274
Disopyramide	6 (1%)	6 (1%)	0	0.601
Propafenone	111 (9%)	101 (10%)	10 (6%)	0.090
Sotalol	145 (12%)	128 (12%)	17 (10%)	0.379
Amiodarone	288 (24%)	237 (23%)	51 (29%)	0.086
Angiotensin-converting enzyme inhibitor	518 (44%)	411 (41%)	107 (62%)	<0.001
Angiotensin II receptor blocker	142 (12%)	130 (13%)	12 (7%)	0.023
Diuretics	428 (36%)	339 (34%)	89 (51%)	<0.001

Values are presented as n, n (%), or mean ± SD.
AF = atrial fibrillation.

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Table 3 Characteristics at 1-Year Follow-up

	All Patients	No AF Progression	AF Progression	p Value
n	1,219	1,041 (85%)	178 (15%)	
Symptoms	366 (32%)	280 (29%)	86 (52%)	<0.001
Death	22 (2%)	16 (2%)	6 (3%)	0.118
Type of AF				
First detected	107 (9%)	107 (10%)	0	
Paroxysmal	860 (71%)	860 (83%)	0	
Persistent	81 (7%)	0	81 (46%)	
Permanent	97 (8%)	0	97 (54%)	
Considered cured	74 (5%)	74 (7%)	0	
Hospital admissions during 1 yr				
Cardiovascular admissions	523 (53%)	419 (50%)	104 (71%)	<0.001
Pharmacological cardioversion	255 (23%)	217 (22%)	38 (24%)	0.534
Number of pharmacological cardioversions	0.4 ± 1.3	0.4 ± 1.3	0.5 ± 1.0	0.847
Electrical cardioversion	161 (15%)	122 (13%)	39 (26%)	<0.001
Number of electrical cardioversions	0.2 ± 0.7	0.2 ± 0.7	0.4 ± 0.8	0.009
Catheter ablation	61 (5%)	57 (6%)	4 (2%)	0.065
Major adverse cardiovascular events				
Coronary artery disease	72 (6%)	57 (6%)	15 (8%)	0.168
Myocardial infarction	17 (1%)	12 (1%)	5 (3%)	0.091
Unstable angina	44 (4%)	34 (3%)	10 (6%)	0.130
Ischemic stroke or TIA	31 (3%)	20 (2%)	11 (6%)	0.003
Ischemic stroke	20 (2%)	12 (1%)	8 (5%)	0.005
TIA	11 (1%)	8 (1%)	3 (2%)	0.212
Combined survival/stroke	40 (3%)	27 (3%)	13 (7%)	0.005

Values are presented as n, n (%), or mean ± SD.
Abbreviations as in Table 1.

used more frequently in patients with AF progression: digitalis, angiotensin-converting enzyme inhibitors, and diuretics. Furthermore, patients experiencing worsening of their AF used more oral anticoagulation, which likely is the result of a higher mean $CHADS_2$ score in this group. Patients with AF progression used angiotensin II receptor blockers (7% vs. 13%, p = 0.023) less frequently. Beta-blockers were prescribed in 56% of patients with heart failure and in 65% of patients with coronary artery disease.

During follow-up, in patients with AF progression, either persistent (46%) or permanent (54%) AF developed (Table 3). The patients with progression were more often symptomatic compared with patients without AF progression. Patients without AF progression had either first detected AF (10%) or paroxysmal AF (83%), and nearly 7% of the patients were considered cured by their physician. Finally, patients who progressed to more sustained forms of AF underwent more electrical cardioversions, were more often admitted to the hospital for a cardiovascular problem, and had more often a stroke or TIA during the 1 year of follow-up. We found no significant differences in pharmacological cardioversions between both groups.

The multivariate logistic regression regarding factors associated with AF progression after 1 year of follow-up is presented in Table 4. A history of heart failure, hypertension, COPD, and stroke or TIA and age older than 75 years were the only independent factors associated with AF progression. No significant interactions were found between these variables. Using the regression coefficient as a benchmark, we determined the relative contribution of each factor to the prediction of AF progression. This resulted in the HATCH score rule: 1 × (hypertension) + 1 × (age >75 years) + 2 × (stroke or TIA) + 1 × (COPD) + 2 × (heart failure).

Table 4 Independent Predictors of AF Progression Resulting From Multivariate Logistic Regression Analysis

	OR	95% CI	Regression Coefficient	p Value	Score
History of heart failure	2.22	1.54–3.22	0.80	<0.001	2
Hypertension	1.52	1.05–2.20	0.42	0.024	1
Chronic obstructive pulmonary disease	1.51	0.95–2.39	0.41	0.088	1
History of stroke or TIA	2.02	1.24–3.31	0.71	0.007	2
Age >75 yrs	1.57	1.07–2.30	0.45	0.024	1

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Because of its plausible preventive effect on AF progression, we repeated the logistic regression including antiarrhythmic drugs. However, antiarrhythmic drugs were not present in the final logistic regression model resulting from this analysis. The final model contained the same variables as the initial analysis excluding antiarrhythmic drugs (data not shown). We also excluded first-detected AF patients who underwent a pharmacological cardioversion in a separate analysis (data not shown) because these patients could have a more advanced electrophysiological substrate than pure paroxysmal AF patients. However, this did not alter the results significantly.

Nearly 50% of the patients with paroxysmal AF and a HATCH score of 6 or 7 had AF progression after 1 year compared with only 6% of the patients with a HATCH score of 0. The percentages of AF progression in patients with a HATCH score of 0 through 7 are presented in Figure 1. With increasing HATCH score, the proportion of patients with AF progression during follow-up increases.

The receiver-operator characteristic curve to discriminate individuals who will or will not have AF progression during follow-up based on their HATCH score is shown in Figure 2. The area under the curve (AUC) is 0.675 (95% confidence interval: 0.632 to 0.718, $p < 0.001$). The predictive value of the HATCH score is higher than all other independent predictors of AF progression individually: heart failure (AUC = 0.599), hypertension (AUC = 0.564), COPD (AUC = 0.542), stroke or TIA (AUC = 0.545), and age (AUC = 0.561). The AUC of the HATCH score was slightly higher compared with the $CHADS_2$ score (difference: 0.02 (95% confidence interval: 0.00 to 0.04); $p = 0.0576$).

We classified patients into 4 groups based on their HATCH score. The percentages of AF progression for each group are presented in Figure 3. This figure demonstrates that with increasing score, the percentage of AF progression during follow-up increases as well.

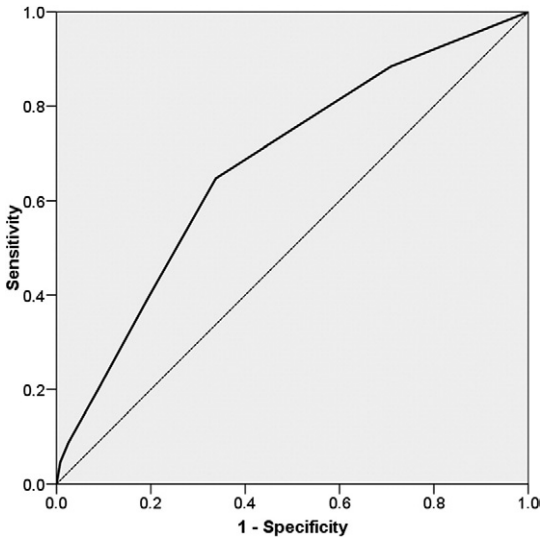

Figure 2 **Predictive Ability of the HATCH Score**

The receiver-operator characteristic curve for the prediction of clinical atrial fibrillation type progression using the HATCH score.

Discussion

The present study is the largest study evaluating clinical correlates of AF progression. It provides a unique insight into the characteristics and prognosis of patients with progression from paroxysmal to more sustained forms of

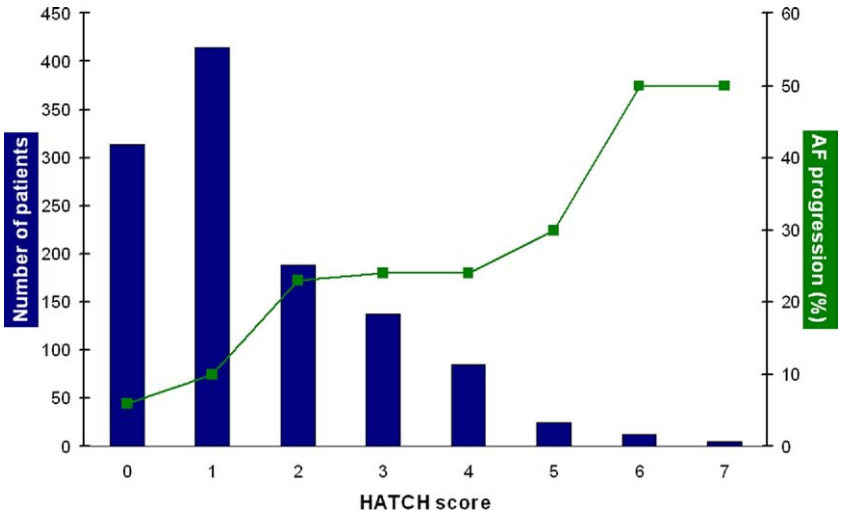

Figure 1 **Prevalence of the Different HATCH Scores and Incidence of Progression**

The number of patients for each HATCH score is represented by the **blue bars**. The percentage of atrial fibrillation (AF) progression after 1 year of follow-up per HATCH score is represented by the **green line**.

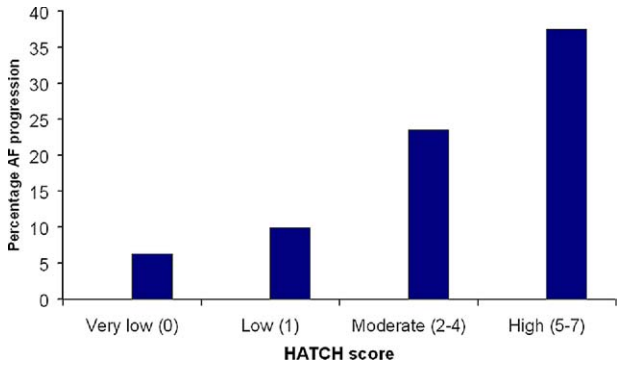

Figure 3 **Incidence of AF Progression**

The 1-year incidence of atrial fibrillation (AF) progression per HATCH score. The HATCH score is divided into 4 categories that could be clinically relevant.

AF. Nearly 15% of the patients with paroxysmal AF included in this study progressed to persistent or permanent AF after 1 year of follow-up, despite the fact that more effort was made to obtain sinus rhythm in this group. In addition, patients with progression had more adverse cardiovascular events and were more often admitted in the hospital. Heart failure, previous stroke or TIA, COPD, hypertension, and age were independent predictors of AF progression. Considering the nature of these factors and in view of the fact that they are associated with future cardiovascular events, one may conjecture that structural rather than electrical remodeling of the atria is involved in AF progression. Underlying diseases might cause chronic stretch and atrial dilation, which seem to be important stimuli for chronic atrial structural remodeling (cellular hypertrophy, fibroblast proliferation, and tissue fibrosis), which enables maintenance of AF (8). It is likely that structural atrial remodeling leading to atrial pathology enables the development of cardiovascular events, which might explain the relatively high stroke rate among the patients with AF progression in our survey. In addition, recent studies showed that patients with a higher AF burden, which is the case in patients demonstrating AF progression, are more prone to have a stroke (9).

Based on the predictors of AF progression, we developed a risk stratification rule to estimate the probability of AF progression in patients with paroxysmal AF: the HATCH score. This score enables the detection of patients in whom more sustained forms of AF are likely to develop in the near future. Previous studies showed that the presence of underlying heart disease is associated with poor outcome of rhythm control therapy (10). However, these patients are more likely to have AF progression. In the same way, our data suggest that the potential preventive effect of antiarrhythmic drugs on AF progression was outperformed by the promoting effect of underlying heart disease and age, as represented by the HATCH parameters. Therefore, it seems very important to identify patients that are likely to progress to persistent AF beforehand to avoid needless rhythm control therapy. This holds even more because AF progression may be associated with major events that are easily enhanced by rhythm control drugs known for their potential to induce proarrhythmia, heart failure, and atrioventricular block. In our study, relatively low numbers of beta-blockers were prescribed in patients with heart failure and coronary artery disease. We hypothesized that this is probably the result of the use antiarrhythmic drugs in our patients. Many antiarrhythmic drugs such as amiodarone, sotalol, and propafenone have beta-blocking properties. Bradycardia might result when these antiarrhythmic drugs are prescribed together with a beta-blocker. Our results suggest that if a high HATCH score is found, clinicians should focus on rate control and upstream therapy rather than rhythm control therapy. Several studies investigating AF progression have been published in the past (5,11–13). The rate of AF progression described in these studies varied between 8% (4) and 22% (14) after 1 year of follow-up, depending on the rhythm-monitoring methods used. Various factors were associated with AF progression: valvular disease, alcohol consumption, age, left atrial dimension and amount of atrial enlargement over time, stroke, and heart failure. However, correction for possible confounders was not always performed, and the currently available risk stratification parameters resulting from these studies have limited the predictive value in individual patients. Our findings suggest that combining several independent predictors of AF progression into a balanced rule outperforms all the previously known predictors for the development of sustained AF.

Clinical implications. The HATCH score in daily practice could guide the physician in the clinical decision-making process. First, patients with a high HATCH score should be monitored more frequently because they are prone to the development of cardiovascular events. In addition, one could hypothesize that the HATCH score may be used for early selection of patients for rhythm control therapy in an effort to prevent disease progression. Conversely, potentially harmful drugs and interventions including cardioversion and ablation may be avoided in patients with a high HATCH score. Obviously, further studies are needed to confirm these hypotheses and show the clinical value of the HATCH score when implemented in clinical practice.

Study limitations. We performed a subgroup analysis of the EHS. As a result, our data should be interpreted with care. Follow-up regarding rhythm status was unavailable for approximately 31% of the patients with first detected or paroxysmal AF at baseline. Patients with unknown rhythm status had more often underlying heart disease and a higher HATCH score (1.8 vs. 1.5) compared with patients with a known rhythm status at follow-up (additional data not shown). This may have led to an underestimation of the incidence of AF progression. Conversely, this does not, in our view, reduce the predictive capacity of the HATCH score.

Considering the relatively low use of beta-blockers, ACE inhibitors, and angiotensin-receptor blockers, the patients

included in the present analysis may have been undertreated, especially the patients concomitantly having coronary artery disease and heart failure (15). Future studies may show that progression factors other than the HATCH score are important in AF patients fully managed according to all the guidelines pertinent to their various underlying diseases. The definition of AF progression that we selected is arbitrary. In clinical practice, it is extremely difficult to robustly determine the progression from persistent to permanent AF because a firm end point is lacking. However, we believe that our definition reflects the pathophysiological stage of AF severity. This is supported by the direct or indirect relationship between AF progression as defined and clinical outcomes such as hospital admissions and major adverse cardiovascular events.

The predictive value of the HATCH score was not flawless. In addition, the score should be validated in another population of patients with AF before it can be applied in clinical practice.

Conclusions

This is the largest study exploring the characteristics and outcome of patients with AF progression. A substantial number of patients progress to sustained AF within 1 year. The clinical outcome of these patients with regard to hospital admissions and major adverse cardiovascular events was worse compared with patients demonstrating no AF progression. Heart failure, previous stroke or TIA, COPD, hypertension, and age were independent predictors of AF progression. Based on these parameters, we developed the HATCH score, which enhances detection of patients in whom more sustained forms of AF are likely to develop in the near future.

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Key Words: atrial fibrillation ■ epidemiology ■ prediction ■ progression ■ prognosis.