CHEST

Original Research

CARDIOVASCULAR DISEASE

A 12-Year Follow-up Study of Patients With Newly Diagnosed Lone Atrial Fibrillation

Implications of Arrhythmia Progression on Prognosis: The Belgrade Atrial Fibrillation Study

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Background: **Lone atrial fibrillation (AF) has been suggested to have a favorable long-term prognosis. Significant interest has been directed at factors predicting arrhythmia progression, and the HATCH score (hypertension, age ≥ 75 years, transient ischemic attack or stroke [2 points], COPD, and heart failure [2 points]) recently has been proposed as a predictive score for AF progression. We investigated long-term outcomes in a large cohort of newly diagnosed lone AF and whether progression from paroxysmal to permanent AF confers an adverse impact on outcomes, including stroke and thromboembolism.**

Methods: **The study was an observational cohort of 346 patients with newly diagnosed lone AF with a mean follow-up of 12.1 ± 7.3 years.**

Results: **Baseline paroxysmal AF was confirmed in 242 patients, and of these, 65 (26.9%) subsequently experienced progression to permanent AF. Older age and development of congestive heart failure during follow-up were the multivariate predictors of AF progression (both $P < .01$), which was documented in 19.8% of patients with a HATCH score of 0 vs 63.2% with a score of 2 ($P < .001$), although the predictive validity of the HATCH score per se was modest (C statistic, 0.6). The annual rate of thromboembolism and heart failure during follow-up were low (0.4% each), and five patients (1.4%) died. AF progression, development of cardiac diseases, and older age were multivariate predictors of adverse outcomes, including thromboembolism (all $P < .05$). Baseline $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack) score was not predictive for thromboembolism (C statistic, 0.50; 95% CI, 0.31-0.69).**

Conclusions: **This 12-year follow-up study provides confirmatory evidence of a generally favorable prognosis of lone AF, but adverse outcomes (including stroke and thromboembolism) are significantly influenced by age and the (new) development of underlying heart disease. Arrhythmia progression in lone AF is a marker of increased risk for adverse cardiovascular events.**

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Abbreviations: ACEi = angiotensin II-converting enzyme inhibitor; AF = atrial fibrillation; CAD = coronary artery disease; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack; CHF = congestive heart failure; HATCH = hypertension, age ≥ 75 years, transient ischemic attack or stroke, COPD, and heart failure; HR = hazard ratio; OAC = oral anticoagulant; TIA = transient ischemic attack; TTE = transthoracic echocardiography

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which increases with increasing age and associated comorbidities.[1-3] Nevertheless, 1.6% to 30% of patients with AF aged ≤ 60 years have no evidence of associated cardiopulmonary or other comorbid disease and are referred to as having "lone AF."[4,5] Lone AF is more prevalent among patients with paroxysmal AF, whereas permanent AF is seen more frequently in elderly patients with comorbidities.[5,6] Although AF generally has been associated with increased mortality and morbidity, lone

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AF has been considered to have a favorable prognosis.[6-9] However, this perception is based on relatively

small study populations with variable follow-up duration.[5,10-15]

Significant interest also has been directed to factors predicting the progression of paroxysmal to permanent AF. Recently, the HATCH score, which is an acronym for hypertension, age ≥ 75 years, transient ischemic attack (TIA) or stroke (2 points), COPD, and heart failure (2 points), was proposed as a simple clinical tool to identify patients who are likely to progress to permanent AF.[16]

The aim of the present study was to determine the rate, predictors, and long-term risk of lone AF progression from a paroxysmal to permanent arrhythmia as well as the risks of stroke/thromboembolism, congestive heart failure (CHF), and mortality in a population of 346 patients with newly diagnosed lone AF and 12-year mean follow-up. We also tested the hypothesis that arrhythmia progression confers an adverse impact on outcomes.

Materials and Methods

We conducted an observational, longitudinal cohort study of patients with newly diagnosed lone AF in the Belgrade Atrial Fibrillation Study, which was a prospectively completed registry of patients with AF seen in the Clinical Center of Serbia between 1992 and 2007. This is the main cardiology center for specialist arrhythmia services serving the population of Belgrade. All patients gave informed consent. The study complies with the Declaration of Helsinki. The institutional review board stated that approval was not necessary due to the observational design of the study.

Detailed diagnostic evaluation was implemented to exclude all known acute causes of AF, underlying heart diseases, and noncardiac disorders. History, physical examination, 12-lead ECG, BP measurement, blood and urine analyses, chest radiography, and transthoracic echocardiography (TTE) were performed routinely; stress testing, coronary angiography, and other diagnostic procedures were used as needed. Hypertension was diagnosed if BP was > 140/85 mm Hg on three or more visits; such patients and those with treated hypertension, atrial flutter, or ventricular preexcitation also were excluded. TTE was obtained at baseline, before each cardioversion, and as needed during follow-up. The $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack) score was calculated based on giving 1 point each for CHF, hypertension, age > 75 years, and diabetes mellitus and 2 points for prior stroke or TIA.[4]

Baseline AF was classified as paroxysmal, persistent, or permanent according to the definition of AF types in the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines following review of detailed medical records for each patient.[4] Lone AF was diagnosed in the absence of any other clinical, ECG, or structural abnormality, except for AF and mild left atrial anteroposterior diameter dilatation of < 45 mm.

Treatment

Management was at the discretion of the responsible cardiologist, but the basic approach during the whole study was to make every reasonable effort to achieve rhythm control. Rate control was applied at any point of the study if (1) electrocardioversion had failed, (2) AF had persisted for > 1 year and left atrial anteroposterior diameter increased > 55 mm during follow-up, (3) long-term pharmacotherapy had been exhausted or caused complications, or (4) frequent persistent AF episodes were noted within 1 year despite active treatment.

In paroxysmal AF, no medication, a "pill in the pocket," or long-term pharmacotherapy were applied according to clinical judgment. In persistent AF, pharmacological cardioversion was attempted using IV propafenone, amiodarone, or oral quinidine sulfate. In some cases, sinus rhythm (SR) was restored during amiodarone pretreatment before elective electrocardioversion. External direct current shock was applied as a first choice or when pharmacological cardioversion had failed. Maintenance of SR included intermittent or long-term use of β-blocker class IA, IC, or III drugs, although β-blockers and rate-limiting calcium antagonists often were coprescribed to ensure rate control in case of recurrent AF. In permanent AF, rate control was attempted, aiming for a target heart rate of < 100 beats/min while resting and ≤ 120 beats/min during usual activities as documented by 24-h Holter monitoring (where necessary), with either drugs (digitalis, verapamil, diltiazem, β-blockers) or radiofrequency catheter ablation of the atrioventricular node with permanent pacemaker implantation. For the prevention of thromboembolism, aspirin, oral anticoagulants (OACs), or both were prescribed according to guideline recommendations that corresponded to the given study period.

Outcome Parameters and Follow-up

Progression of AF was defined as paroxysmal AF at baseline, which had become permanent AF during follow-up. Progression to permanent AF was recorded when rhythm control had failed (eg, unsuccessful electrocardioversion or based on clinical judgment). Stroke and TIA were diagnosed by a neurologist (records from neurology wards of local hospitals or neurology clinics also were included as evidence of central embolism). Systemic thromboembolism was diagnosed by a vascular surgeon, whereas CHF was defined by clinical symptoms, physical examination, and pulmonary congestion on chest radiography. The cause of death was obtained from medical records (hospital records, death certificates, or autopsy reports).

Total follow-up was ≥ 5 years or until death. Patients were included if the date of newly diagnosed AF was no later than January 2003, and follow-up continued until January 2008 or death. Patients with complete medical records on their previous lone AF also were included, but no later than January 2007, thus allowing at least 1-year prospective follow-up. Follow-up visits

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were performed at least annually, and AF hospitalizations were scheduled according to clinical judgment.

Statistical Analyses

Following a test of statistical normality, continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are reported as counts with percentages. The Student *t* test was used for comparison of age among clinical types of AF. Differences in categorical variables were tested by χ^2 test. Kaplan-Meier estimates and Cox proportional hazard regression analyses were used to study the relationships between independent variables and outcome parameters.

The development of cardiac disorders and diabetes were entered in the analysis of outcome parameters only when they occurred before the analyzed outcome event. All results of multivariable analyses are adjusted for differences among clinical types of AF at diagnosis. The C statistic, a measure of the area under the receiver operating characteristic curve, quantified the predictive validity of the HATCH and $CHADS_2$ scores and tested the hypothesis that these schemes perform significantly better than chance (indicated by a C statistic ≥ 0.5). The C statistic quantifies discriminant ability, whereas the hazard ratio (HR) quantifies the increased relative risk of AF progression or thromboembolic events with the HATCH and $CHADS_2$ scores, respectively. A $P < .05$ was considered statistically significant. Statistical analysis was performed using the SPSS, version 17.0 (SPSS Inc) software package.

Results

Of 1,086 patients with newly diagnosed AF, 346 (31.9%) met inclusion criteria for lone AF. Table 1 shows baseline characteristics and differences among clinical types of AF. Mean total follow-up was 12.1 ± 7.3 years (median, 10.0 years; range, 5-40 years). Mean prospective follow-up was 6.3 ± 4.6 years (median, 5 years; range, 1-16 years). Approximately one-third of patients developed cardiovascular risk factors during follow-up, most frequently hypertension (25%). The rate of development of coronary artery disease (CAD) was low (Table 1). Outcome parameters and treatments are summarized in Table 1 and Table 2, respectively.

Progression to Permanent AF

At diagnosis, 242 patients (69.9%) had paroxysmal AF, and 65 of 242 (26.9%) subsequently progressed to permanent AF (Fig 1). Mean age at time of progression was 56.6 ± 9.2 years (range, 38-74 years), and mean time from the first AF was 11.9 ± 7.5 years (range, 1-34 years). A 10-year cumulative rate of progression was 19.1% (95% CI, 12.8%-25.4%) (Fig 2A).

Overall, progression to permanent AF was documented in 107 of 319 patients (33.5%) who had either paroxysmal or persistent AF at baseline (Fig 1). Mean age at time of progression was 54.6 ± 10.6 years (range, 24-74 years), and mean time from the first AF was 9.9 ± 7.3 years (range, 0.5-34 years). A 10-year cumulative rate of progression was 26.1% (95% CI, 20.2%-32.0%) (Fig 2C).

Older age at diagnosis and development of CHF were predictors of AF progression (all $P < .01$), and development of hypertension was significantly but inversely related to AF progression (Table 3). Patients with hypertension were more frequently prescribed angiotensin II-converting enzyme inhibitors (ACEi)

Table 1—*Study Population According to Baseline AF Types*

	All Patients (N = 346; 100%)	Paroxysmal AF (n = 242; 69.9%)	Persistent AF (n = 77; 22.3%)	Permanent AF (n = 27; 7.8%)	*P* Value
Baseline characteristics[a]					
Age, y	43.2 ± 9.9	42.9 ± 9.6	43.4 ± 11.0	45.0 ± 10.3	.591
Age range, y	18-60	19-60	18-60	18-60	
Male sex	263 (76.0)	173 (71.5)	71 (92.2)	19 (70.4)	.001
Asymptomatic AF	40 (11.6)	13 (5.4)	16 (20.8)	11 (40.7)	< .001
LA ≤ 40 mm	296 (85.5)	221 (91.3)	60 (77.9)	15 (55.6)	< .001
Events recorded during follow-up[b]					
Development of condition					
Any cardiac disease	120 (34.7)	83 (34.3)	28 (36.4)	9 (33.3)	.935
Hypertension	85 (24.6)	58 (24.0)	20 (26.0)	7 (25.9)	.925
CAD	8 (2.3)	7 (2.9)	1 (1.3)	0 (0.0)	.509
Diabetes mellitus	36 (10.4)	25 (10.3)	7 (9.1)	4 (14.8)	.702
Outcome parameters[c]					
Progression to permanent AF	107 (33.5)	65 (26.9)	42 (54.5)	NA	< .001
TE events	14 (4.0)	12 (5.0)	1 (1.3)	1 (1.3)	.363
CHF	14 (4.0)	7 (2.9)	6 (7.8)	1 (3.7)	.164
Death	5 (1.4)	5 (2.1)	0 (0.0)	0 (0.0)	.336

Data are presented as mean ± SD or No. (%), unless otherwise indicated. AF = atrial fibrillation, CAD = coronary artery disease; CHF = congestive heart failure; LA = left atrium; NA = not applicable; TE = thromboembolic.

[a]Characteristics at presentation.

[b]Development of cardiac diseases during follow-up.

[c]Outcome parameters.

Table 2—*Treatment According to Baseline AF Types*

	All Patients (N = 346; 100%)	Paroxysmal AF (n = 242; 69.9%)	Persistent AF (n = 77; 22.3%)	Permanent AF (n = 27; 7.8%)	*P* Value
Baseline[a]					
No antiarrhythmics	93 (26.9)	85 (35.1)	5 (6.5)	3 (11.1)	< .001
Digitalis, β-blockers, or Ca antagonists	159 (46.0)	128 (52.9)	8 (10.4)	23 (85.1)	< .001
Class IA	39 (11.3)	11 (4.5)	28 (36.4)	0 (0.0)	.006
Class IC	30 (8.7)	12 (5.0)	17 (22.1)	1 (3.7)	.001
Class III	25 (7.2)	6 (2.5)	19 (24.7)	0 (0.0)	.009
Prevention of TE events	177 (51.2)	89 (36.8)	64 (83.1)	24 (88.9)	< .001
Antiplatelet therapy	132 (38.1)	89 (40.5)	26 (33.8)	17 (63.0)	< .001
Oral anticoagulants	45 (13.0)	0 (0.0)	38 (49.4)	7 (25.9)	< .001
During the study[b,c]					
Digitalis	134 (38.7)	80 (33.1)	36 (46.8)	18 (66.7)	.001
Ca antagonists	189 (54.6)	133 (55.0)	35 (45.5)	21 (77.8)	.015
β-Blockers	195 (56.4)	147 (60.7)	32 (41.6)	16 (59.3)	.012
Quinidine	57 (16.5)	31 (12.8)	26 (33.8)	0 (0.0)	< .001
Disopyramide	44 (12.7)	34 (14.0)	9 (11.7)	1 (3.7)	.296
Propafenone	145 (41.9)	113 (46.7)	30 (39.0)	2 (7.4)	< .001
Flecainide	8 (2.3)	7 (2.9)	1 (1.3)	0 (0.0)	.509
Sotalol	38 (11.0)	33 (13.6)	4 (5.2)	1 (3.7)	.054
Amiodarone	184 (53.2)	125 (51.7)	50 (64.9)	9 (33.3)	.012
Prevention of TE events	285 (82.4)	182 (75.2)	76 (98.7)	27 (100)	< .001
Antiplatelet therapy	258 (74.6)	172 (71.1)	66 (85.7)	20 (74.1)	.029
Oral anticoagulants	186 (53.9)	103 (42.6)	65 (84.4)	18 (66.7)	< .001
ACEi	79 (22.8)	56 (23.1)	15 (19.5)	8 (29.6)	.546

Data are presented as No. (%). ACEi = angiotensin II-converting enzyme inhibitor. See Table 1 legend for expansion of other abbreviations.
[a]At baseline.
[b]During the study period.
[c]At any point of the study during a variable time interval, not necessarily throughout the whole study.

than those who remained normotensive (60 of 78 [76.9%] vs 11 of 241 [4.6%], $P < .001$). In the univariate analysis, use of ACEi during the study was inversely related to progression to more sustained AF (HR, 0.7; 95% CI, 0.5-1.0; $P = .0338$), with a nonsignificant trend for progression to permanent AF (HR, 0.7; 95% CI, 0.4-1.0; $P = .08$). There was no difference in the use of β-blockers, propafenone, or amiodarone between patients with hypertension and those who remained normotensive (β-blockers, 49 of 78 [62.8%] vs 130 of 241 [53.9%]; propafenone, 40 of 78 [51.3%] vs 103 of 241 [42.7%]; amiodarone, 50 of 78 [64.1%] vs 125 of 241 [51.9%]; all $P > .05$).

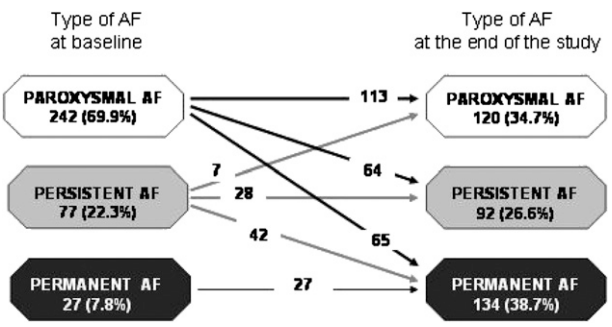

FIGURE 1. Distribution of paroxysmal, persistent, and permanent AF at baseline and at the end of follow-up. AF = atrial fibrillation.

Arrhythmia Progression Based on the HATCH Score

In the subset of 242 patients with baseline paroxysmal AF, 167 (69.0%) had a HATCH score of 0 (very low), 56 (23.1%) had a score of 1 (low), and 19 (7.9%) had a score of 2 (moderate). Progression to permanent AF was recorded in 33 of 167 (19.8%; 95% CI, 13.7%-25.9%), 20 of 56 (35.7%; 95% CI, 22.8%-48.7%), and 12 of 19 (63.2%; 95% CI, 39.3%-87.0%) patients, respectively ($P < .001$) (C statistic, 0.64; 95% CI, 0.55-0.72; $P = .001$) (Fig 2B).

Overall, of 319 patients with either paroxysmal or persistent AF, 215 (67.4%) had a HATCH score of 0, 78 (24.5%) had a score of 1, and 26 (8.2%) had a score of 2. Progression to permanent AF was recorded in 52 of 215 (26.5%; 95% CI, 20.6%-32.5%), 33 of 78 (42.3%; 95% CI, 31.1%-53.5%), and 17 of 26 (65.4%; 95% CI, 45.8%-85.0%) patients, respectively ($P < .001$) (C statistic, 0.61; 95% CI, 0.55-0.68; $P = .001$) (Fig 2D).

Thromboembolic Events

Thromboembolism was documented in 14 patients (4.0%), of whom nine had ischemic stroke. At the time of thromboembolism, mean age was 59.1 ± 10.3 years (range, 39-78 years), and mean time from the first AF was 11.5 ± 7.6 years (range, 1-27 years). Seven patients had paroxysmal AF, two persistent

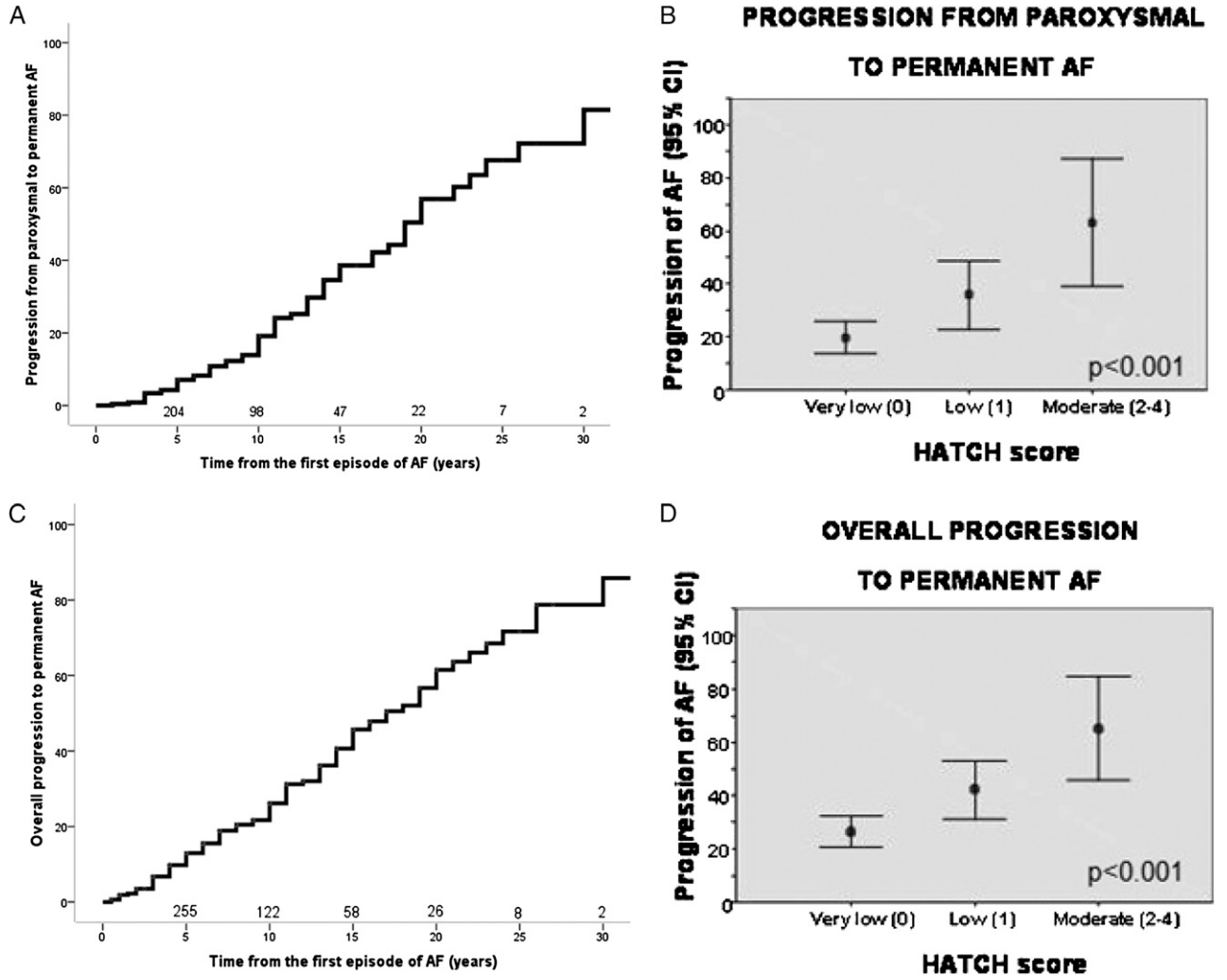

FIGURE 2. Progression of AF. A, Kaplan-Meier estimates of progression from paroxysmal to permanent AF. B, According to HATCH score (point estimates with 95% CIs). C, Kaplan-Meier estimates of progression from both paroxysmal and persistent AF to permanent AF. D, According to HATCH score. HATCH = hypertension, age ≥ 75 years, transient ischemic attack or stroke (2 points), COPD, and heart failure (2 points). See Figure 1 legend for expansion of other abbreviation.

AF, and five permanent AF; six patients (42.8%) developed one or more thromboembolic risk factors (five patients hypertension, one CAD, two diabetes, and none CHF); eight patients (57.1%) were taking aspirin; and six patients had no antithrombotic therapy. A 10-year survival free of thromboembolism was 97.3% (95% CI, 95.3%-99.3%) (e-Figure 1A). After initiation of OAC, no patient had recurrent thromboembolism.

Progression from paroxysmal to permanent AF was significantly related to thromboembolism in the univariate analysis (HR, 3.4; 95% CI, 1.2-10.0; $P = .0259$) as was older age at diagnosis of AF and the development of hypertension, CAD, and diabetes mellitus (all $P < .05$) (Table 4). When these variables were entered into a multivariate analysis, development of hypertension (HR, 24.4; 95% CI, 7.8-76.4; $P < .0001$) and CAD (HR, 22.0; 95% CI, 2.7-182.2; $P = .0041$) were identified as multivariate predictors of thromboembolism.

At baseline, mean $CHADS_2$ score of the whole cohort was 0. At the point of an adverse event, the mean $CHADS_2$ had increased to 0.42 (95% CI, 0.35-0.49). Neither baseline $CHADS_2$ score (C statistic, 0.50; 95% CI, 0.31-0.69; $P = 1.000$) nor $CHADS_2$ score at the time of a thromboembolic event (C statistic, 0.51; 95% CI, 0.30-0.72; $P = .922$) were predictive for thromboembolism.

Development of CHF

During follow-up, 14 patients (4.0%) developed CHF at a mean age of 54.9 ± 10.9 years (range, 38-71 years) and a mean time from the first AF of 10.0 ± 7.0 years (range, 0-26 years). A 10-year survival free of CHF was 95.9% (95% CI, 93.3% to 98.4%), (e-Figure 1C). Before the development of

Table 3—*Univariate and Multivariate Predictors of Progression to Permanent AF*

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Progression from paroxysmal to permanent AF						
Age at diagnosis, decades	1.5	1.2-2.0	.0034	1.1	1.0-1.1	.0008
Development of CHF	10.6	3.7-30.2	< .0001	6.2	2.1-18.6	.0012
Development of hypertension	0.3	0.2-0.7	.0013	0.4	0.2-0.8	.0147
Overall progression from paroxysmal or persistent to permanent AF						
Age at diagnosis, decades	1.4	1.2-1.8	.001	1.4	1.1-1.7	.003
Development of CHF	3.3	1.7-6.4	< .001	2.9	1.5-5.5	.002
Development of hypertension	0.6	0.4-0.9	.009	0.6	0.4-0.9	.019

Univariate Cox proportional hazard regression analyses with independent variables as follows: age at diagnosis of AF; sex; left atrial diameter; and development of any cardiac disease, hypertension, CAD, CHF, or diabetes during follow-up. Only variables with $P \leq .05$ are shown (and entered into a multivariate model), adjusted for sex, baseline differences among initial AF types, and treatment at baseline and during follow-up. See Table 1 legend for expansion of abbreviations.

CHF, progression to permanent AF was diagnosed in five patients, hypertension in three, CAD in two, thromboembolism in one, and diabetes in three. Progression to permanent AF was significantly related to development of CHF in the univariate analysis (HR, 23.2; 95% CI, 4.8-46.8; $P < .0001$) as was the development of CAD and diabetes mellitus (all $P < .05$) (Table 4). When these variables were entered into a multivariate analysis, overall progression to permanent AF was identified as a multivariate predictor of CHF (HR, 60.3; 95% CI, 19.1-190.6; $P < .0001$).

Overall Survival

The 10-year survival of patients in our study was 99.6% (95% CI, 98.8%-100.0%), (e-Figure 1D). Mean age at the time of death was 66.4 ± 6.6 years (range, 56-74 years), and mean time from the first AF was 18.0 ± 8.2 years (range, 7-27 years). Five patients (1.4%) died, and death was noncardiovascular in four (two died of malignancy, one after noncardiac surgery, and one accidentally).

Discussion

To our knowledge, the present study examines one of the largest prospective cohorts of newly diagnosed lone AF. After a median 10-year follow-up, our results confirm previous findings of a generally favorable long-term prognosis of lone AF in terms of mortality, thromboembolism, and CHF, with a similar rate of progression to permanent AF as in other lone AF studies.[5,10-13,17] Moreover, the present study has documented significant negative implications of progression to permanent AF in relation to long-term outcomes of patients with lone AF.

The reported prevalence of lone AF varies between 1.6% and 30.0%, which is strongly influenced by the diagnostic criteria used in any particular study and, therefore, the true prevalence of lone AF is arguably unknown.[18,19] In the present study, the criteria for lone AF were very strictly applied,[4] and the high proportion of lone AF (31.9%) also could be explained by the characteristics of the screened AF population (essentially, relatively young patients with first-diagnosed nonvalvular AF and the low prevalence of underlying cardiac diseases). However, there are numerous new risk factors for AF, including obesity, metabolic syndrome, sleep apnea, increased alcohol consumption, endurance sport practice, subclinical atherosclerosis, smoking, and so forth, that could impose some difficulties on the precise clinical diagnosis of a truly lone AF and may significantly influence its prevalence.[18,20]

Progression to permanent AF ranged from 4.7% to 34% in other lone AF studies[5,10-13] and was documented in 33.5% of patients in the present study. Of note, one study even reported no AF progression, but the follow-up was not clearly defined.[17] Compared to patients with AF with underlying structural heart disease,[21] risk factors for progression to permanent AF in patients with lone AF are less well defined, given that the anatomic substrate for sustained AF should, by definition, be absent in lone AF. Indeed, age was the sole multivariate predictor of progression to permanent AF in one study on lone AF.[10] Besides age, we found CHF to be an independent predictor of AF progression. In this context, CHF could be viewed as an ultimate common expression of various structural myocardial alterations caused by either the development of an underlying heart disease during follow-up, AF itself, or both. Indeed, atrial fibrosis and isolated atrial myocardial perfusion abnormalities with impairment of coronary flow reserve have been documented in patients with lone AF along with numerous ultrastructural alterations, including dedifferentiation of cardiomyocytes, pronounced apoptosis, and increased accumulation of various proteins in

Table 4—*Univariate Predictors of TE Events and CHF During Follow-up*

Variable	HR	95% CI	*P* Value
Univariate predictors of TE events during follow-up[a]			
Age at diagnosis, decades	1.9	1.1-3.5	.0302
Progression of paroxysmal to permanent AF	3.4	1.2-10.0	.0259
Overall progression to permanent AF	15.6	4.3-59.2	< .0001
Development of hypertension	21.8	7.1-66.5	< .0001
Development of CAD	14.1	1.8-112.5	.0125
Development of diabetes mellitus	11.8	2.5-55.4	.0018
Univariate predictors of CHF during follow-up[b]			
Newly diagnosed persistent AF	3.2	1.1-9.6	.0368
Progression of paroxysmal to permanent AF	60.3	19.1-190.6	< .0001
Overall progression to permanent AF	23.2	4.8-46.8	< .0001
Development of CAD	5.4	1.2-24.9	.0294
Development of diabetes mellitus	16.1	4.3-60.5	< .0001

Only variables with $P \leq .05$ are shown. See Table 1 legend for expansion of abbreviations.

[a]Univariate Cox proportional hazard regression analysis with independent variables as follows: age at diagnosis of AF; sex; left atrial diameter; development of any cardiac disease, hypertension, CAD, CHF, or diabetes during follow-up; baseline AF type; progression to more sustained AF; progression of paroxysmal to persistent AF; and progression of paroxysmal to permanent AF.

[b]Univariate Cox proportional hazard regression analysis with same independent variables as in footnote a, excluding development of CHF.

the extracellular matrix, that have been attributed solely to AF and not to an underlying pathological process.[22-24] Moreover, an important role of ectopic discharges from the pulmonary veins and posterior left atrium in both the initiation and the maintenance of AF has been documented.[25] Overall, our findings reflect the interactions of AF triggers, perpetuators, and substrate, where increasing duration of AF combined with atrial electric, contractile, and structural remodeling create a fertile environment for AF make it more difficult to treat; however, it remains unclear whether structural remodeling precedes AF, is AF induced, or is simply a feature of aging or underlying disease.[24-27]

The recently proposed HATCH score, which was tested previously in an unselected paroxysmal AF patient population,[16] has been shown to have a weak predictive value for arrhythmia progression (C statistics, ~0.61-0.64) among the present population of patients with lone AF. The C statistics in the present study are broadly similar to the original derivation study (0.675) from the EuroHeart survey on AF,[16] but our study shows how age and the development of CHF or hypertension influences arrhythmia progression among patients with lone AF. Indeed, an unexpected protective effect of hypertension on AF progression in the present study could be explained by the more frequent use of ACEi,[28] possibly more attention paid by medical practitioners, and more dedicated compliance of hypertensive patients with AF to medication or a healthy lifestyle. There were no differences in the prescription of β-blockers, propafenone, or amiodarone (which could influence the arrhythmia progression) compared with normotensive patients with AF.

The annual rate of thromboembolic events was ≤1% in other lone AF studies.[5,11,13,17] Similar to these findings, the rate of thromboembolism was low in the present study (~0.4% annually), and the occurrence of thromboembolic events was related to well-defined risk factors that developed during the follow-up, including age, hypertension, CAD, and diabetes.[10,11,15,29] However, nearly 60% of thromboembolic events occurred in the absence of risk factors other than AF, and the $CHADS_2$ stroke risk stratification schema was not helpful in this population of patients with AF. Moreover, nearly 50% of the patients with thromboembolism in the present study were not taking any thromboprophylaxis at the time of a thromboembolic event. These observations further emphasize the importance of careful assessment of AF-related thromboembolic risk, with the need for stroke risk stratification schema to be able to identify truly low-risk patients, as recently proposed[28,30]; indeed, the $CHADS_2$ schema may be inadequate to identify patients with AF who are truly low risk for stroke and thromboembolism.[31,32] Of note, there was no significant relationship between thromboembolism and baseline AF type in the present study, consistent with the growing evidence of similar stroke risk in paroxysmal, persistent, and permanent AF.[31] However, subsequent AF progression was an independent predictor of thromboembolism in our study. This finding could be explained by the association between progression of AF and greater endocardial damage/dysfunction, the latter being important in thrombogenesis.[33]

When evaluating the AF-CHF relationship, caution must be exercised in implying a cause-and-effect relation between the two conditions: Either AF or

CHF may actually be the later manifestation of a common pathophysiological process.[7,8,34] Consistent with other studies,[10,34] the development of CHF in the present study was significantly related to development of cardiac diseases and diabetes. Moreover, progression to permanent AF was significantly related to subsequent CHF in the patients in our study.

Consistent with previous studies, we found an excellent overall survival of patients with lone AF, with low rates of all-cause and cardiovascular mortality similar to other AF studies.[5,10,35,36] Our results also suggest that overall survival is not affected by newly diagnosed permanent AF,[10] although subsequent progression to permanent AF (especially from paroxysmal AF) was an independent predictor of complications. This raises the possibility that progression of paroxysmal to permanent AF (despite active treatment) may serve as a clinical indicator of a subpopulation of patients with lone AF, which is "not so lone" given that such progression may be an early marker of target organ damage and the herald of future adverse events. The progression of AF may help in further risk stratification of young patients with lone AF to nonprogressors with predominantly electrophysiological disturbances and an excellent long-term prognosis compared with the progressors (in whom certain pathological substrate exists, possibly not clinically evident, as yet) with increased risk of cardiovascular events.

The present study has limitations inherent to its observational nature and registry-based setting. Data on exact AF burden (frequency of paroxysms and persistent AF duration before cardioversion), the duration of hypertension, CHF, and diabetes and detailed information on treatment with antiarrhythmics, ACEi, statins, aspirin, and OAC during follow-up (especially dose and drug changes over time) are lacking; ideally, time-dependent Cox regression analysis with these variables should have been performed. Similarly, precise data on echocardiographic changes in left atrial size and left ventricular ejection fraction over time were lacking, and, therefore, TTE parameters were not included in the statistical analyses. Because of incomplete data on development of peripheral vascular disease during follow-up, the recently proposed CHA_2DS_2VASc (CHF/left ventricular dysfunction; hypertension, age ≥ 75 years, diabetes mellitus, stroke/TIA/thromboembolism, vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plague], age 65-74 years, sex category [ie, female]) thromboembolic risk score [28,30] could not be tested in the present study. Finally, our findings should be interpreted with regard to the relatively small numbers of certain outcomes (in particular, stroke, CHF, and death), which precluded any further analysis beyond a descriptive one, whereas CIs for the predictors of thromboembolism and CHF were wide.

Conclusions

The present study provides convincing evidence of a generally favorable prognosis of patients with lone AF. However, long-term outcome in such patients is significantly influenced by aging and the development of underlying heart disease. Because there is no cure for aging per se, thorough screening, prevention, and treatment of associated comorbidities should be among the most important issues in the management of patients with lone AF. Moreover, progression to permanent AF despite active treatment in a subpopulation of young, otherwise apparently healthy patients with lone AF may serve as an additional risk stratification clinical tool to identify those with early or subclinical cardiac structural alterations and an increased risk for adverse cardiovascular events.

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Dr Potpara: contributed to the hypothesis, data collection and analyses, data interpretation, and drafting of the manuscript.
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Dr Marinkovic: contributed to the data interpretation and drafting of the manuscript.
Dr Ostojic: contributed to the data interpretation and drafting of the manuscript.
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