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A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: The Belgrade Atrial Fibrillation Study ☆

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ABSTRACT

Background: To investigate baseline characteristics and long-term prognosis of carefully characterized asymptomatic and symptomatic patients with atrial fibrillation (AF) in a 'real-world' cohort of first-diagnosed non-valvular AF over a 10-year follow-up period.

Methods and results: We conducted an observational, non-interventional, and single-centre registry-based study of consecutive first-diagnosed AF patients. Of 1100 patients (mean age 52.7 ± 12.2 years and mean follow-up 9.9 ± 6.1 years), 146 (13.3%) had asymptomatic AF.

Persistent or permanent AF, slower ventricular rate during AF (<100/min), CHA_2DS_2–VASc score of 0, history of diabetes mellitus and male gender were independent baseline risk factors for asymptomatic AF presentation (all $p < 0.01$) with a good predictive ability of the multivariable model (c-statistic 0.86, $p < 0.001$).

Kaplan–Meier 10-year estimates of survival free of progression of AF (log-rank test = 33.4, $p < 0.001$) and ischemic stroke (log-rank test = 6.2, $p = 0.013$) were significantly worse for patients with asymptomatic AF compared to those with symptomatic arrhythmia. In the multivariable Cox regression analysis, intermittent asymptomatic AF was significantly associated with progression to permanent AF (Hazard Ratio 1.6; 95% CI, 1.1–2.2; $p = 0.009$).

Conclusions: In a 'real-world' setting, patients with asymptomatic presentation of their first-diagnosed AF could have different risk profile and long-term outcomes compared to those with symptomatic AF. Whether more intensive monitoring and comprehensive AF management including AF ablation at early stage following the incident episode of AF and increased quality of oral anticoagulation could alter the long-term prognosis of these patients requires further investigation.

1. Introduction

Atrial fibrillation (AF) is commonly symptomatic [1–4]. Treatment often reduces symptomatic recurrences but many patients continue to have silent AF episodes [5,6]. Furthermore, AF may be diagnosed by screening for other reasons [7] or during diagnostic evaluation of cryptogenic stroke [8].

Many patients with permanent pacemakers or implantable cardioverter–defibrillators (ICDs) have recurrent device-detected atrial tachyarrhythmias, with increased risk of clinical events [9,10]. Asymptomatic, device-detected atrial tachyarrhythmias were documented in 35% of such patients with no history of prior AF (and hence, no oral anticoagulation). Only 16% of patients subsequently developed clinically overt AF, but asymptomatic atrial tachyarrhythmias were associated with a 2.5-fold increase in the risk of stroke [11].

The true prevalence and prognostic significance of silent AF have been difficult to assess in unselected cohorts [1–11]. Patients with asymptomatic AF have been reported to have less cardiac comorbidities [4,12], but the risk of stroke was similar compared with symptomatic AF in a randomized clinical trial [4]. Data on clinical features and long term impact of asymptomatic AF in 'real world' cohorts with long term follow-up are limited.

Our objective was to investigate baseline characteristics and long-term prognosis of carefully characterized asymptomatic and symptomatic

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patients with first-diagnosed non-valvular AF in a 'real-world' cohort (that is, a cohort from everyday clinical practice, and not from a randomized setting) with a 10-year follow-up. We tested the hypothesis that there was no significant difference in baseline characteristics and long-term outcomes between asymptomatic and symptomatic patients in this cohort.

2. Methods

We conducted an observational investigation of AF patients in the Belgrade Atrial Fibrillation Study, which was a non-interventional, prospective, and single-centre registry of patients with non-valvular AF seen in the Clinical Center of Serbia between 1992 and 2007. The study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board stated that the approval was not necessary due to the observational study design. All patients gave informed consent to be included into the registry, which would be used for various AF-related analyses upon its completion.

Consecutive patients with first-diagnosed, non-valvular AF were included in this analysis. A detailed review of each patient's medical records was performed to exclude previous AF. Asymptomatic AF was defined as AF documented by 12-lead electrocardiogram (ECG) during regular visit, in the absence of any new symptoms such as palpitations, tachycardia, fatigue, malaise, shortness of breath on exertion, dyspnoea, chest pain, syncope or pre-syncope, or worsening of pre-existent symptoms related to other illness. In patients without pre-existent medical conditions, AF was diagnosed accidentally during medical examination for other reasons (for example, annual examinations of employees, medical examination for driver's licence), and was labelled as first-diagnosed asymptomatic AF only if there was an evidence of sinus rhythm in the previous 12 months and the patient denied any recent change in the self-perception of his/her physical condition. Patients with apparently first-diagnosed AF and prior stroke or transient ischemic attack (TIA) were excluded from this analysis due to a possibility of previous 'subclinical' AF. Patients with acute causes of AF (e.g. acute myocardial infarction [MI], recent cardiac surgery, etc.), valvular heart disease, prosthetic valves or known malignancy were also excluded.

Detailed diagnostic evaluation was performed at baseline and at regular annual follow-up visits. History, physical examination, 12-lead ECG, blood pressure measurement, blood and urine analysis, chest radiography and transthoracic echocardiography (TTE) were performed routinely; other diagnostic procedures were used if needed. Between the pre-scheduled follow-up visits, control visits were performed as needed.

Cardiac and non-cardiac diseases were noted in the presence of a detailed medical record on diagnosis and treatment or a self-reported history of the disease, or when standard diagnostic criteria were fulfilled. Hypertension was diagnosed if the patient had a physician confirmed diagnosis and was taking antihypertensive therapy, or with an untreated blood pressure of >150/90 mm Hg. CAD was suspected in the presence of chest pain syndrome (typical anginal pain or atypical chest pain) or angina equivalent, and further assessed by echo-stress testing (as needed) and confirmed by coronary angiography (significant coronary artery disease [CAD] was defined as stenosis of ≥70% in at least one major epicardial coronary artery, or ≥50% in the left main coronary artery). MI was diagnosed using standard criteria: typical chest pain, cardiac enzyme abnormalities and typical ECG abnormalities. At baseline, two thromboembolic risk scores were calculated: the $CHADS_2$ (1 point each for congestive heart failure [HF], hypertension, age > 75 years and diabetes, and 2 points for prior stroke/TIA) and CHA_2DS_2-VASc score (1 point each for congestive HF/left ventricular systolic dysfunction, hypertension, diabetes, peripheral vascular disease [including prior MI or complex aortic plaque], age 65–74 years and female gender, and 2 points for prior stroke/TIA or age ≥ 75 years).

Subsequently, baseline AF was classified as paroxysmal, persistent or permanent [13]. The prevalent approach in our centre was to make every reasonable effort to achieve rhythm control using beta-blockers, class IC or III drugs in a 'stepwise' fashion: beta-blockers or propafenone was tried first, followed by flecainide or sotalol and, finally, amiodarone. Patients with left ventricular systolic dysfunction received amiodarone (or amiodarone plus beta blocker) as a first-line option. Rate control was applied if electrocardioversion had failed or long-term pharmacotherapy had been exhausted. During follow-up, catheter

Table 1
Baseline characteristics of patients with first-diagnosed non-valvular atrial fibrillation.

Variable N (%)	All patients 1100 (100%)	Asymptomatic AF 146 (13.3%)	Symptomatic AF 954 (86.7%)	Odds Ratio (95% CI) with asymptomatic AF	p
Age (years)	52.7 ± 12.2	53.1 ± 13.1	52.6 ± 12.1	–	0.614
Follow-up	9.9 ± 6.1	10.1 ± 6.9	9.9 ± 5.9	–	0.728
Male gender	711 (64.6)	122 (83.6)	589 (61.7)	3.2 (2.0–5.0)	<0.001
Paroxysmal AF	665 (60.5)	39 (26.7)	626 (65.6)	0.2 (0.1–0.3)	<0.001
Persistent AF	225 (20.5)	40 (27.4)	185 (19.4)	1.6 (1.1–2.3)	0.026
Permanent AF	210 (19.0)	67 (45.9)	143 (15.0)	4.8 (3.3–7.0)	<0.001
AF ≥ 100 bpm	930 (84.5)	54 (37.0)	876 (91.8)	0.05 (0.03–0.08)	<0.001
History of					
Any cardiac disease	658 (59.8)	82 (56.2)	576 (60.4)	0.8 (0.6–1.2)	0.334
Hypertension	552 (50.2)	71 (48.6)	481 (50.4)	0.9 (0.7–1.3)	0.687
CAD/MI	53 (4.8)	7 (4.8)	46 (4.8)	1.0 (0.4–2.3)	0.989
Any non-cardiac disease	217 (19.7)	33 (22.6)	184 (19.3)	1.2 (0.8–1.9)	0.349
Diabetes mellitus	76 (6.9)	17 (11.6)	59 (6.2)	2.0 (1.1–3.5)	0.017
COPD	33 (3.0)	7 (4.8)	26 (2.7)	1.8 (0.8–4.2)	0.178
Hiatus hernia	37 (3.4)	2 (1.4)	35 (3.7)	0.4 (0.1–1.5)	0.168
LA > 40 mm	424 (38.5)	81 (55.5)	343 (36.0)	2.2 (1.6–3.2)	<0.001
LVEF ≤ 45%	83 (7.5)	12 (8.2)	71 (7.4)	1.1 (0.6–2.1)	0.741
Treatment of rhythm disorder					
No treatment	179 (16.3)	18 (12.3)	161 (16.9)	0.7 (0.4–1.2)	0.168
Drugs slowing AV conduction	613 (55.7)	79 (54.1)	534 (56.0)	0.9 (0.7–1.3)	0.673
Class IA/IC or sotalol	156 (14.2)	16 (11.0)	140 (14.7)	0.7 (0.4–1.2)	0.233
Amiodarone	152 (13.8)	33 (22.6)	119 (12.5)	2.0 (1.3–3.2)	0.001
Thromboprophylaxis					
None	304 (27.6)	17 (11.6)	287 (30.1)	0.3 (0.2–0.5)	<0.001
Aspirin	534 (48.5)	70 (47.9)	464 (48.6)	1.0 (0.7–1.4)	0.876
Oral anticoagulant	262 (23.8)	59 (40.4)	203 (21.3)	2.5 (1.7–3.6)	<0.001
$CHADS_2$ score					
0	509 (46.3)	69 (47.3)	440 (46.1)	1.0 (0.7–1.5)	0.797
1	474 (43.1)	56 (38.4)	418 (43.8)	0.8 (0.6–1.1)	0.215
≥2	117 (10.6)	21 (14.4)	96 (10.1)	1.5 (0.9–2.5)	0.117
CHA_2DS_2–VASc score					
0	329 (29.9)	56 (38.4)	273 (28.6)	1.6 (1.1–2.2)	0.017
1	375 (34.1)	42 (28.8)	333 (34.9)	0.8 (0.5–1.1)	0.146
≥2	396 (36.0)	48 (32.9)	348 (36.5)	0.9 (0.6–1.2)	0.399

Values are presented as n (%) or mean ± SD and range.
AF, atrial fibrillation; CAD/MI, coronary artery disease/myocardial infarction; COPD, chronic obstructive pulmonary disease; LA, left atrium; LVEF, left ventricular ejection fraction; Drugs slowing AV (atrioventricular) conduction — verapamil, diltiazem, beta-blockers, digitalis; Class IA drugs — quinidine, disopyramide; Class IC drugs — propafenone, flecainide.
The $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus — 1 point each, and previous stroke or TIA — 2 points); the CHA_2DS_2–VASc score (Congestive heart failure or left ventricular systolic dysfunction, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years and Sex category (female gender)).