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Clinical Research Study

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Abstract

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Background. Atrial fibrillation is often asymptomatic but outcomes need further characterization. **Aims.** To investigate clinical presentation, management and outcomes in asymptomatic and symptomatic atrial fibrillation patients prospectively enrolled in the EurObservational Research Programme – Atrial Fibrillation (EORP-AF) Pilot General Registry.

Results. A total of 3119 patients were enrolled, and 1237 (39.7%) were asymptomatic (EHRA score I). Among symptomatic patients, 963 (51.2%) had mild symptoms (EHRA score II) while 919 (48.8%) had severe or disabling symptoms (EHRA III-IV). Permanent atrial fibrillation was threefold more common in asymptomatic than in symptomatic patients.

On multivariate analysis, male gender (OR 1.630, 95% CI 1.384-1.921), older age (OR 1.019, 95% CI 1.012-1.026), previous myocardial infarction (OR 1.681, 95% CI 1.350-2.093), and limited physical activity (OR 1.757, 95% CI 1.495-2.064) were significantly associated with asymptomatic (EHRA I) atrial fibrillation.

Fully asymptomatic atrial fibrillation (absence of current and previous symptoms) was present in 520 patients (16.7%), and was independently associated with male gender, age and previous myocardial infarction. Appropriate guideline-based prescription of oral anticoagulants was lower in these patients, while aspirin was more frequently prescribed.

In asymptomatic patients, mortality at 1 year was more than two-fold higher compared to symptomatic patients (9.4 vs. 4.2%, $p < 0.0001$), and was independently associated with older age and comorbidities, including chronic kidney disease and chronic heart failure.

Conclusions. Asymptomatic atrial fibrillation is common in daily cardiology practice, being associated with elderly age and more co-morbidities, as well as high thromboembolic risks. A higher 1-year mortality was found in asymptomatic compared to symptomatic patients.

Key words Atrial fibrillation; Bleeding, Mortality; Registry; Stroke.

Atrial fibrillation is often asymptomatic and there is growing interest in its clinical presentation, management and outcomes.(1-4). Atrial fibrillation is often detected in asymptomatic patients, and the arrhythmia may become asymptomatic over time or after treatment (5). Indeed, silent atrial fibrillation episodes are common and can be detected during clinical screening for various reasons, continuous rhythm monitoring through an implanted device or during the diagnostic work up of patients presenting with cryptogenic stroke (6-9). The burden of stroke across Europe remains important (10) and detection of an underlying atrial fibrillation, either symptomatic or asymptomatic, has important implications not only in the perspective of individual patients but also in the perspective of public health systems (4, 11-13). The clinical presentation, associated co-morbidities and clinical management of atrial fibrillation patients may change over time, according to increasing awareness on the potential risks associated with atrial fibrillation, changes in population demography, evolution of treatments and more widespread implementation of evidence based guidelines (4, 14, 15). Therefore, a contemporary report of the current clinical presentation, management and outcomes in prospectively enrolled consecutive asymptomatic and symptomatic atrial fibrillation patients managed by European cardiologists is timely, especially since new management guidelines were published by the European Society of Cardiology (ESC) in 2010, followed by a focused update in 2012 (16, 17).

The objective of this article is to investigate clinical presentation, management and outcomes in asymptomatic and symptomatic atrial fibrillation patients prospectively enrolled in the EurObservational Research Programme – Atrial Fibrillation (EORP-AF) Pilot General Registry (18-20). We tested the hypothesis that asymptomatic patients with atrial fibrillation would have a worse prognosis compared to symptomatic patients, as the latter may receive better management given their symptomatic presentation.

Methods

The methods and baseline data from the EORP-AF Pilot General Registry have previously been published (18). Patients' enrollment started in early 2012. One-year follow-up phase ('pilot phase' or Phase 1) data were focused on the initial 3119 patients recruited into this database, collected from 9 countries, as a valid representative of ESC member countries (21).

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In brief, the registry population comprised consecutive in- and out-patients presenting with atrial fibrillation to cardiologists, enrolled in 67 centres in 9 countries (18). Consecutive patients were screened at the time of their presentation to a cardiologist (hospital or medical centre), and potential patients were approached to obtain written informed consent according to local rules. Enrolment required ECG-confirmed diagnosis of atrial fibrillation, with a qualifying episode of atrial fibrillation documented in the 12 months prior to enrolment. Stroke risk was categorized using the Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes, Stroke [Doubled] (CHADS₂) score and the Congestive heart failure, Hypertension, Age ≥ 75 [Doubled], Diabetes, Stroke [Doubled]- Vascular disease, Age 65-74, and Sex category [female] (CHA₂DS₂-VASc) score (14, 16), whilst bleeding risk was categorized using the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/ alcohol concomitantly (HAS-BLED) score (14, 16). Patients were followed up to 1 year after enrollment (21).

In this registry, a simple symptom score, proposed by the European Heart Rhythm Association (EHRA) (EHRA score) (16) was prospectively applied in order to quantify atrial fibrillation-related symptoms and clearly distinguish fully asymptomatic patients from patients with variable degrees of impairment in daily activity.

Specific data were collected on the degree of physical activities reported by the patients. A limited physical activity was defined as no exercise or exercise for < 3 hours/week for < 2 years or exercise < 3 hours/week for ≥ 2 years.

Statistical analyses

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean \pm SD and/or as median and Interquartile Range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal-Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a Chi-square test or a Fisher's exact test if any expected cell count was less than five.

Plots of the Kaplan-Meier curves for time to all-cause death in relation to EHRA symptoms subgroup were performed. The survival distributors between EHRA I and EHRA II-V subgroups have been compared

using the log-rank test. All the variables at entry which were statistically significant at univariate analysis and variables considered of relevant clinical interest were included in the multivariable model (logistic regression) to identify the variables independently associated with asymptomatic AF or with fully asymptomatic AF. Moreover, a multivariable model (logistic regression) was considered to identify the independent predictors of all-cause death, the composite of death or stroke/TIA/peripheral embolism at 1-year of follow-up.

A two-sided p value of <0.05 was considered as statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 3119 patients were enrolled, and at study entry 1237 (39.7%) were asymptomatic (EHRA score I). Among the 1882 patients who were symptomatic, 963 (51.2%) had mild symptoms (EHRA score II) while 919 (48.8%) had severe or disabling symptoms (EHRA III-IV) [Table 1]. Compared to symptomatic atrial fibrillation at enrollment, asymptomatic atrial fibrillation was more commonly seen in specialized centers (72.6 vs. 59.4%, $p<0.0001$) and in an outpatient clinic or private cardiology practice (39.8 vs. 23.4%, $p<0.0001$).

Clinical characteristics

Asymptomatic atrial fibrillation patients were older, more commonly males and with a higher proportion of concomitant diseases, including prior myocardial infarction and coronary revascularization (percutaneous transluminal coronary angioplasty/ coronary artery bypass graft. /) [Table 1]. A history of thromboembolic complications and stroke were more common amongst asymptomatic patients.

The type of atrial fibrillation differed significantly ($p<0.0001$) between patients with symptomatic and asymptomatic atrial fibrillation at enrollment. As shown in Figure 1, permanent atrial fibrillation was threefold more common in asymptomatic atrial fibrillation, while persistent atrial fibrillation was two-fold more common in symptomatic patients.

In patients with asymptomatic atrial fibrillation, as compared with symptomatic atrial fibrillation, the reason for admission/consultation was significantly different ($p<0.0001$), being less commonly the

arrhythmia itself (43.2 vs. 71.3%), but more commonly heart failure (19.4 vs. 14.0%), myocardial infarction (7.1 vs. 2.3%) or valvular heart disease (6.3 vs. 1.9%).

In asymptomatic atrial fibrillation heart rate at the ECG during atrial fibrillation was lower than in symptomatic atrial fibrillation, while on echocardiography left atrial size was larger and left ventricular hypertrophy less common [Table S1 supplementary material]. Risk scores for thromboembolic risk (CHA₂DS₂ and CHA₂DS₂-VASc), as well as bleeding risk (HAS-BLED) were higher in patients with asymptomatic atrial fibrillation [Table 1].

On multivariate analysis, male gender (OR 1.630, 95% CI 1.384-1.921), older age (OR 1.019, 95% CI 1.012-1.026), previous myocardial infarction (OR 1.681, 95% CI 1.350-2.093), and limited physical activity (OR 1.757, 95% CI 1.495-2.064) were significantly associated with asymptomatic (EHRA I) atrial fibrillation.

Prescribed interventions and medications

As expected, pharmacological and electrical cardioversion, antiarrhythmic drugs and left atrial ablation were less commonly employed in asymptomatic as compared to symptomatic atrial fibrillation patients [Table S2 supplementary material]. Rhythm control was more frequently applied to symptomatic patients, while simple observation was more commonly used in asymptomatic atrial fibrillation ($p < 0.0001$ for the difference in management strategy) [Figure 2].

When oral anticoagulants were indicated (ie, CHA₂DS₂-VASc ≥ 2 or cardioversion planned) oral anticoagulants were prescribed after admission/consultation in 81-83% of cases, independent from the presence/absence of atrial fibrillation symptoms [Figure 2]. Non-vitamin K antagonist oral anticoagulants were more commonly prescribed in symptomatic patients.

Fully asymptomatic atrial fibrillation

The group of 1237 patients presenting at study entry with asymptomatic atrial fibrillation has been split into a subgroup of 520 'fully asymptomatic' patients (ie. who previously never experienced atrial fibrillation symptoms) and a subgroup of 717 patients with 'asymptomatic atrial fibrillation at study entry but with previous atrial fibrillation symptoms' [Table 2].

Comparing these two subgroups, no differences were found with regard to observation in centers specialized in electrophysiology vs. non specialized centers, while the setting of observation differed significantly

($p=0.0076$), with fully asymptomatic atrial fibrillation patients less frequently seen in an outpatient clinic

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(27.7 vs. 35.1%).

The clinical characteristics of enrolled fully asymptomatic patients are shown in Table 2. Median age as well as the proportion of elderly patients were higher in fully asymptomatic patients. In a more general view, considering the full cohort of patients, the relationship between age and symptoms appeared to be U-shaped since median age was the highest in fully asymptomatic atrial fibrillation and the lowest in EHRA II [Table 3]

Less than one third of fully asymptomatic atrial fibrillation patients were female, a lower rate than in asymptomatic patients with previous symptoms. In fully asymptomatic atrial fibrillation patients, a history of myocardial infarction and percutaneous transluminal coronary angioplasty/ coronary artery bypass graft, chronic heart failure, chronic obstructive pulmonary disease, history of thromboembolic complications and stroke were more common than in fully asymptomatic atrial fibrillation patients.

The type of atrial fibrillation differed significantly ($p<0.0001$) between patients with fully symptomatic and asymptomatic atrial fibrillation at enrollment but with previous symptoms. As shown in Figure 1, first-detected atrial fibrillation accounted for 41.1% of fully asymptomatic atrial fibrillation, while paroxysmal atrial fibrillation was less common. In patients with fully asymptomatic atrial fibrillation, the reason for admission/consultation was significantly different ($p<0.0001$), being less commonly the arrhythmia itself (35.4 vs. 49.0%).

Risk scores for thromboembolism (CHA_2DS_2 and $\text{CHA}_2\text{DS}_2\text{-VASc}$) and bleeding (HAS-BLED) were higher in fully asymptomatic atrial fibrillation patients. Electrical cardioversion, antiarrhythmic drugs and left atrial ablation were less commonly employed in fully asymptomatic atrial fibrillation patients, with rate control more frequently applied to fully asymptomatic patients [Figure 2 and Table S3 and S4 supplementary material].

When oral anticoagulants were indicated, according to guidelines (ie, $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ or cardioversion planned) oral anticoagulants were prescribed in a significantly lower proportion of fully asymptomatic patients, whilst aspirin was more frequently prescribed. Conversely, the proportion of use of vitamin K antagonists and non-vitamin K antagonist oral anticoagulants did not differ [Figure 2].

On multivariate analysis (adjusting for male gender, age, previous myocardial infarction, CHA₂DS₂-VASc score, CHADS₂ score, HAS-BLED score, limited physical activity and heart rate during atrial fibrillation) male gender (OR 1.658, 95% CI 1.286-2.138), older age (OR 1.036, 95% CI 1.025-1.048), and previous myocardial infarction (OR 1.630 (95% CI 1.215-2.188) were significantly associated with fully asymptomatic atrial fibrillation.

Follow-up

Mean follow-up was 366.4±31.8 days. One-year follow-up was available for 2642 of enrolled patients (10 patients were dead at discharge and 467 patients, i.e. 15%, were lost to follow-up).

Asymptomatic atrial fibrillation (EHRA I) was associated with a significantly higher occurrence of death as compared with symptomatic atrial fibrillation, while the occurrence of cardiovascular hospitalizations was significantly lower [Table 4]. Also the composite end point of stroke/transient ischemic attacks/peripheral embolism or death had a significantly higher occurrence in asymptomatic atrial fibrillation patients. Kaplan-Meier curves for survival for asymptomatic (EHRA I) and symptomatic (EHRA II-IV) atrial fibrillation patients are shown in Figure 3.

On multivariate analysis, older age (OR 1.062, 95% CI 1.041-1.083), chronic kidney disease (OR 3.099, 95% CI 2.123-4.522), chronic heart failure (OR 2.154, 95% CI 1.419-3.270), referral for reasons other than atrial fibrillation only (OR 2.121, 95% CI 1.374-3.273), minor bleeding (OR 2.138, 95% CI 1.210-3.776), previous transient ischemic attack (OR 2.327, 95% CI 1.266-4.278), chronic obstructive pulmonary disease (OR 1.669, 95% CI 1.078-2.583), malignancy (OR 1.896, 95% CI 1.049-3.428) were significantly associated with 1 year all-cause mortality, whilst a treatment with statins (OR 0.659, 95% CI 0.462-0.941) was associated with a lower mortality. There was no significant association with EHRA I score (OR 1.424, 95% CI 0.973-2.085).

Moreover, on multivariate analysis, older age (OR 1.062, 95% CI 1.043-1.081), chronic kidney disease (OR 2.688, 95% CI 1.885-3.832), chronic heart failure (OR 2.086, 95% CI 1.435-3.032), referral for reasons other than atrial fibrillation only (OR 2.322, 95% CI 1.567-3.441), minor bleeding (OR 1.938, 95% CI 1.129-3.330), previous transient ischemic attack (OR 2.348, 95% CI 1.322-4.172) and malignancy (OR 1.788, 95% CI 1.019-3.139) were significantly associated with the composite end-point of 'stroke, transient

ischemic attack, peripheral embolism or death' at 1 year. There was no significant association with EHRA I score (OR 1.136, 95% CI 0.800-1.615).

Discussion

In this study our principal findings are first, 40% of atrial fibrillation patients are asymptomatic and that among those with symptoms more than one half have mild symptoms (EHRA score II in 51.2%). Second, the prognostic implications of asymptomatic atrial fibrillation are evident by our data showing that asymptomatic atrial fibrillation is not benign but is associated with an even higher mortality at 1 year as compared to symptomatic atrial fibrillation.

Asymptomatic atrial fibrillation is common (1, 6, 11) and there is growing interest on its characterization in daily "real world" clinical practice. The EHRA symptoms classification, as originally proposed in ESC guidelines (16), is a valid mean of quantifying atrial fibrillation symptoms severity and correlates well with one disease-specific quality of life instrument (Atrial Fibrillation Effect on QualiTy-of-life, AFEQT Questionnaire) and with another general measure for the health-related quality of life (EQ-5D, incorporating the Visual Analog Scale, VAS) and can be used to assess atrial fibrillation -related symptoms in clinical practice without prior training (22).

In our cohort asymptomatic atrial fibrillation was predicted by male gender, age, previous myocardial infarction and no physical activity and these may have practical implications in the perspective of screening strategies based on appropriate targeting of the population (11).

The pattern of atrial fibrillation was not the same between symptomatic and asymptomatic patients, since permanent atrial fibrillation was around threefold more common in asymptomatic atrial fibrillation and persistent atrial fibrillation was around two-fold more common in symptomatic patients. In asymptomatic patients a lower use of resources, in terms of rate/rhythm control strategies and interventions, was applied and this was in accordance with current guidelines (16). Heart rate during atrial fibrillation was on average around 20 beats/min lower in asymptomatic as compared with symptomatic atrial fibrillation and this finding, apart the therapeutic implications, may be important in interpreting the complex relationship between presence of atrial fibrillation and development of symptoms (4, 23).

symptomatic atrial fibrillation patients, the scores for thromboembolic risk (CHA₂DS and CHA₂DS₂-

VASc), as well as the HAS-BLED score were higher in patients with asymptomatic atrial fibrillation.

However, detection of asymptomatic atrial fibrillation resulted in around the same rate of overall

prescription of oral anticoagulants as compared to symptomatic patients, when indicated (ie, CHA₂DS₂-

VASc ≥ 2 or pharmacological cardioversion planned). The proportion of use of vitamin K antagonists and

non-vitamin K antagonist oral anticoagulants differed, since non-vitamin K antagonist oral anticoagulants

were more commonly prescribed in symptomatic patients, a finding that in part is explained by the

association between asymptomatic atrial fibrillation and prior myocardial infarction, suggesting preferential

use of warfarin rather than non-vitamin K antagonist oral anticoagulants (24).

Our study also focused on fully asymptomatic atrial fibrillation, who were compared with asymptomatic

atrial fibrillation with previous symptoms. Fully asymptomatic atrial fibrillation is associated with the

highest median age, as well as chronic heart failure (25). Our data show that asymptomatic atrial fibrillation

constitutes a setting where oral anticoagulants are still underused, despite the high mean CHADS₂ and

CHA₂DS₂-VASc scores among all atrial fibrillation symptom subgroups. The lower propensity to prescribe

oral anticoagulants in fully asymptomatic atrial fibrillation patients could be related to the higher HAS-

BLED score (highest among all atrial fibrillation symptom subgroups) but this is a questionable decision

making, since the reduced use of oral anticoagulants appears to be compensated by an increased use of

antiplatelet agents, not justified by current guidelines and current evidence of benefit in terms of protection

from the risk of stroke (1, 14, 16, 17, 26).

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (27), 12% of

patients did not report atrial fibrillation -related symptoms in the 6 months before study entry. In contrast to

our cohort, coronary artery disease was more frequent in symptomatic vs. asymptomatic patients and at 5

years a trend toward better survival in asymptomatic patients was observed, although mortality became

similar after correction for baseline characteristics. In the more selected patients with persistent atrial

fibrillation enrolled in the RAte Control versus Electrical cardioversion for persistent atrial fibrillation

(RACE) trial, patients with asymptomatic atrial fibrillation were more often men and had less cardiac

disease (28). During follow-up, the asymptomatic patients experienced fewer heart failure hospitalizations, but without significant differences in cardiovascular mortality.

Our study shows that in asymptomatic patients, mortality at 1 year was more than 2-fold that of symptomatic patients. On multivariate analysis, age and co-morbidity rather than symptoms per se were independently associated with mortality at 1 year. Thus, in asymptomatic patients mortality is worse because the asymptomatic status is associated with older age and more co-morbidities, putting these patients at higher risk (29, 30). The clinical implications of our findings in daily cardiology practice means recognition of asymptomatic atrial fibrillation should not decrease - but conversely, intensify patient care.

Limitations

Our study was based on an ongoing observational registry (18) but recruited consecutive patients seen by cardiologists, and the clinical picture of these patients cannot be generalized to those seen by internists, or general practitioner. The registry was focused on European centers, belonging to countries with a different health care systems (31). Also, follow-up was incomplete in 15% of patients.

In conclusion, asymptomatic atrial fibrillation is common in daily cardiology practice, but its management is challenging, being associated with elderly age and more co-morbidities, as well as high thromboembolic and hemorrhagic risks. A higher 1-year mortality was evident in asymptomatic atrial fibrillation compared to symptomatic atrial fibrillation.

Authorship:

All authors had access to the data and played a role in writing this manuscript.

Conflict of interest:

G.B.—received small speaker's fee from Boehringer, Medtronic Inc and Boston Scientific. L.H.R.—speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. L.T. — consultant and Speakers bureau member for Servier; Committee Member for Servier, Medtronic, St Jude Medical, CVIE Therapeutics, Boston Scientific, Vifor Pharma, Cardiorientis. G.Y.H.L.—consultant for Bayer, Medtronic, Sanofi, BMS/Pfizer, Daiichi-Sankyo, and Boehringer Ingelheim, and has been a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Medtronic. Other authors—none declared in relation to this manuscript.

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Figures Legends

Figure 1. Top panel: Type of AF at enrollment in symptomatic and asymptomatic AF patients ($p<0.0001$).

Bottom panel: Type of AF at enrollment in fully asymptomatic AF patients and in asymptomatic patients with previous symptoms ($p<0.0001$). Legend: AF= atrial fibrillation.

Figure 2. Panel A (on the left) Therapeutic strategies used in asymptomatic vs. symptomatic patients.

From top to bottom panel: management strategy ($p<0.0001$), antithrombotic treatment and type of oral anticoagulant when oral anticoagulants were indicated (ie, $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ or pharmacological cardioversion planned). **Panel B (on the right)** Therapeutic strategies used in fully asymptomatic vs. previously symptomatic AF patients. From top to bottom panel: management strategy ($p<0.0001$), antithrombotic treatment and type of oral anticoagulant when oral anticoagulants were indicated (ie, $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ or pharmacological cardioversion planned). Legend: AF= atrial fibrillation, NOACs= non-vitamin K antagonist oral anticoagulants.

Figure 3. Survival at 1 year for asymptomatic (EHRA I) and symptomatic (EHRA II-IV) atrial fibrillation patients.

Table 1. Patient characteristics at enrollment.

	All	EHRA I	EHRA II - IV	P-value
N° of patients	3119	1237	1882	
Demographics				
Age in years Median (IQR)	69 (62-77)	72 (64-78)	68 (61-76)	<0.0001
Age ≥ 75 yrs (%)	33.7	40.4	29.3	<0.0001
Age > 65 yrs (%)	63.9	71.1	59.2	<0.0001
Age < =50 yrs (%)	6.5	5.3	7.3	0.0214
Female gender (%)	40.4	35.0	43.9	<0.0001
Concomitant disease (%)				
Lone AF	3.9	2.8	4.6	0.0115
Coronary artery disease	36.3	40.1	33.8	0.0008
Myocardial infarction	44.9	54.2	37.3	<0.0001
PTCA/CABG	47.0	59.8	36.3	<0.0001
Stable angina	37.4	30.5	43.1	<0.0001
Chronic heart failure	47.5	44.3	49.6	0.0044
of whom NYHA III/IV	41.5	45.9	38.9	0.0098
Valvular heart disease	63.4	64.5	62.7	0.2976
Dilated cardiomyopathy	11.5	9.4	12.9	0.0037
Hypertrophic cardiomyopathy	3.9	2.4	4.9	0.0004
Restrictive cardiomyopathy	0.5	0.9	0.2	0.0085
Hypertensive heart disease	19.5	14.5	22.8	<0.0001
Other cardiac disease	8.3	10.1	7.0	0.0034
Chronic obstructive pulmonary disease	11.0	12.1	10.2	0.0997
Hyperthyroidism	3.0	2.1	3.6	0.0158
Hypothyroidism	7.2	7.3	7.2	0.8664
Chronic kidney disease	13.1	15.6	11.5	0.0011
Peripheral vascular disease	11.0	13.0	9.7	0.0041
Cardiovascular risk factors (%)				
Diabetes	20.6	22.3	19.4	0.0548
Hypertension	70.7	70.1	71.1	0.5202
Current smoker	11.1	10.0	11.9	0.1075
Hypercholesterolaemia	48.4	46.9	49.4	0.1714
Alcohol ≥ 2-3/day	7.8	9.6	6.6	0.0028
Physical activity (%)				
None	39.2	48.0	33.4	<0.0001
Occasional	34.9	31.5	37.0	
Regular	21.3	17.0	24.2	
Intense	4.6	3.5	5.3	
Co-morbidities (%)				
Ischaemic thrombo-embolic complications	13.1	14.8	11.9	0.0184
Previous stroke	6.3	7.7	5.4	0.0082
Previous Transient Ischaemic Attack	4.1	4.9	3.6	0.0707
Haemorrhagic events	5.8	8.3	4.2	<0.0001
Haemorrhagic stroke	5.0	4.9	5.1	>0.999[a]
Major bleeding	27.6	29.4	25.3	0.5411
Malignancy	5.4	5.5	5.2	0.7472
CHADS ₂ score				
Mean score ± SD	1.92 ±1.27	2.00 ±1.31	1.87 ±1.25	0.0145
Two or more	60.3	62.2	59.0	
CHA ₂ DS ₂ - VASc score				
Mean score ± SD	3.24 ±1.79	3.41 ±1.78	3.14 ±1.79	<0.0001
Two or more	81.7	84.7	79.7	
HAS-BLED score				
Mean score ± SD	1.37 ±1.06	1.46 ±1.04	1.31 ±1.07	<0.0001
Two or more	40.7	44.1	38.4	

Legend: AF= atrial fibrillation, CABG= coronary artery bypass graft, CHADS₂= Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke [Doubled], CHA₂DS₂-VASc = Congestive heart failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]- Vascular disease, Age 65-74, and Sex category [female], HAS-BLED= Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/ alcohol concomitantly ; NYHA= New York Heart Association, PTCA= percutaneous transluminal coronary angioplasty.

Table 2. Patient characteristics at enrollment in fully asymptomatic patients and in asymptomatic patients with previous symptoms .

	Fully asymptomatic	Asymptomatic with previous symptoms	P-value
N° of patients	520	717	
Demographics			
Age in years Median (IQR)	74 (67-80)	70 (62-77)	<0.0001
Age ≥ 75 yrs (%)	48.8	34.3	<0.0001
Age > 65 yrs (%)	78.1	66.0	<0.0001
Age ≤ 50 yrs (%)	4.4	5.9	0.2643
Female gender (%)	29.8	38.8	0.0011
Concomitant disease (%)			
Lone AF	1.3	3.9	0.0074
Coronary artery disease	42.9	38.0	0.0977
Myocardial infarction	65.8	44.4	<0.0001
PTCA/CABG	67.3	53.5	0.0032
Stable angina	24.3	35.7	0.0093
Chronic heart failure	49.7	40.3	0.0012
CHF of whom NYHA III/IV	49.8	42.4	0.0882
Valvular heart disease	66.1	63.4	0.3295
Dilated cardiomyopathy	10.8	8.4	0.1483
Hypertrophic cardiomyopathy	1.4	3.1	0.0558
Restrictive cardiomyopathy	0.6	1.2	0.3708[a]
Hypertensive cardiomyopathy	14.9	14.3	0.7926
Other cardiac disease	10.3	10.0	0.8562
Chronic obstructive pulmonary disease	16.0	9.3	0.0005
Hyperthyroidism	2.2	2.0	0.8508
Hypothyroidism	7.0	7.6	0.7269
Chronic kidney disease	17.4	14.2	0.1307
Peripheral vascular disease	15.8	11.0	0.0154
Cardiovascular risk factors (%)			
Diabetes	24.7	20.6	0.0906
Hypertension	71.5	69.0	0.3435
Current smoker	11.1	9.2	0.2713
Hypercholesterolaemia	46.0	47.5	0.5892
Alcohol ≥ 2-3/day	12.5	7.6	0.0054
Physical activity (%)			
None	52.9	44.3	0.0226
Occasional	27.6	34.5	
Regular	15.8	17.8	
Intense	3.7	3.4	
Co-morbidities (%)			
Ischaemic thrombo-embolic complications	17.3	13.0	0.0375
Previous stroke	8.5	7.2	0.3972
Previous Transient Ischaemic Attack	6.4	3.8	0.0382
Haemorrhagic events	9.1	7.7	0.3793
Haemorrhagic stroke	4.3	5.5	>0.999[a]
Major bleeding	31.9	27.3	0.6080
Malignancy	4.5	6.2	0.1967
CHADS ₂ score			
Mean score ± SD	2.18 ± 1.32	1.87 ± 1.28	<0.0001
Two or more	68.3	57.9	
CHA ₂ DS ₂ - VASc score			
Mean score ± SD	3.71 ± 1.78	3.19 ± 1.76	<0.0001
Two or more	89.6	81.2	
HAS-BLED score			
Mean score ± SD	1.61 ± 1.05	1.36 ± 1.03	<0.0001
Two or more	50.8	39.3	

a]: Fisher exact test.

Legend: AF= atrial fibrillation, CABG= coronary artery bypass graft,, CHADS₂= Congestive heart failure, Hypertension, Age \geq 75, Diabetes, Stroke [Doubled], CHA₂DS₂-VASc = Congestive heart failure, Hypertension, Age \geq 75 [Doubled], Diabetes, Stroke [Doubled]- Vascular disease, Age 65-74, and Sex category [female], CHF= chronic heart failure, HAS-BLED= Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/ alcohol concomitantly, NYHA= New York Heart Association, PTCA= percutaneous transluminal coronary angioplasty.

ACCEPTED MANUSCRIPT

Table 3. Age and AF-related symptoms as expressed by EHRA score.

	Fully asymptomatic	EHRA I but previous symptoms	EHRA II	EHRA III	EHRA IV	P-value
N° of patients	520	717	963	746	173	
Demographics						
Age in years	74 (67-80)	70 (62-77)	67 (60-74)	69 (61-77)	71 (61-78)	<0.0001
Median (IQR)						

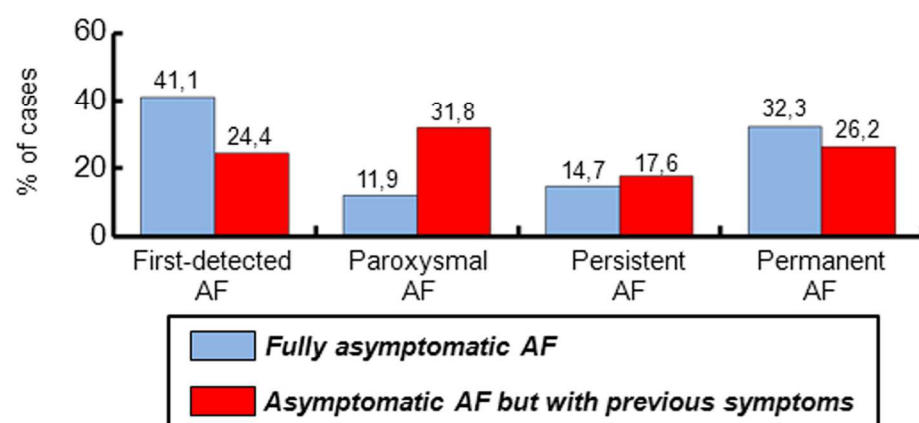
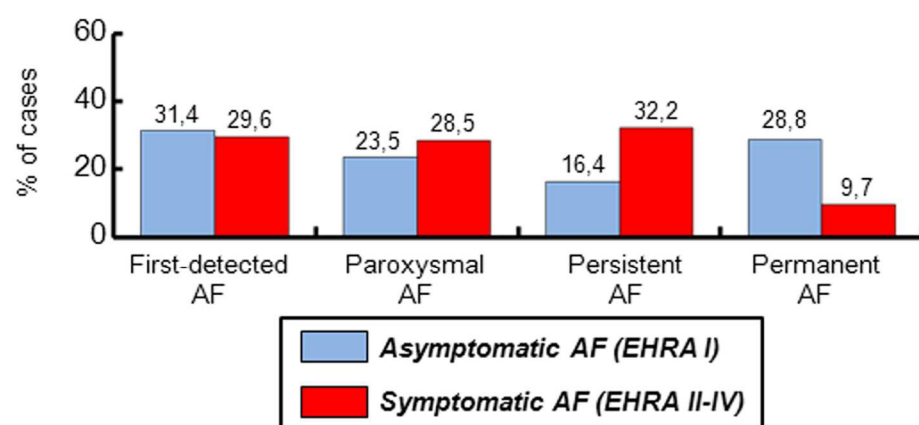
Kruskal-Wallis test is used for quantitative data. IQR, interquartile range

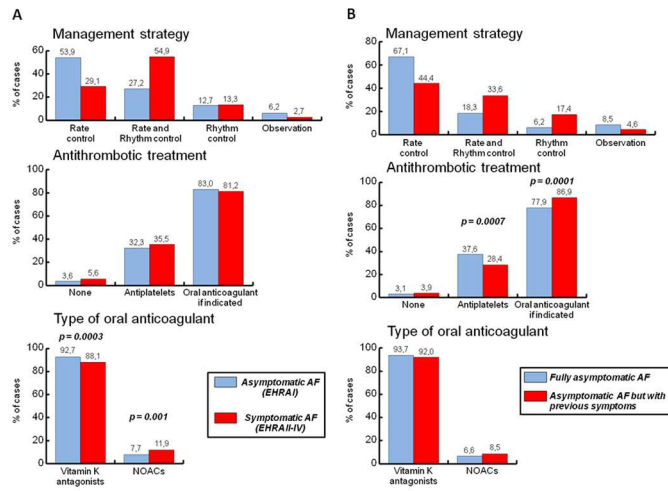
Table 4. One-year outcomes in asymptomatic (EHRA I) vs. symptomatic (EHRA II-IV) AF patients.

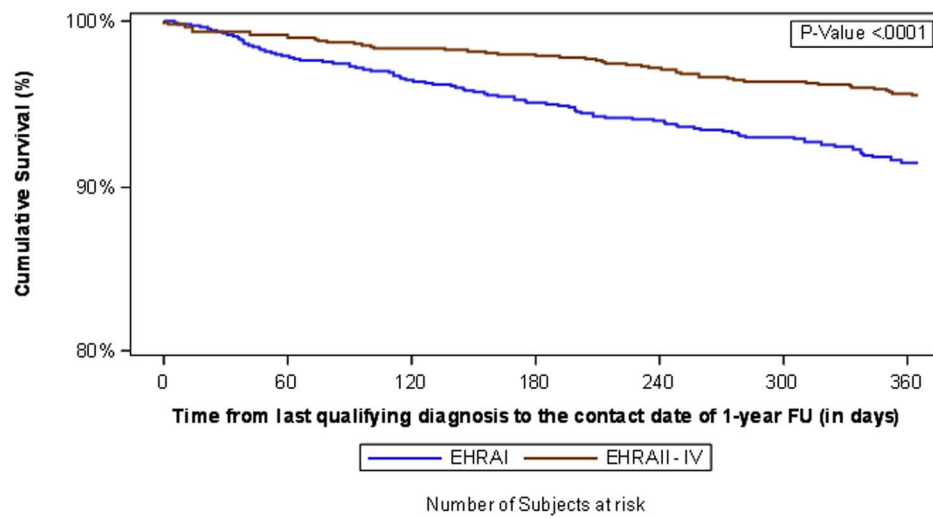
	EHRA I	EHRA II-IV	P-Values
Mortality	102/1086 (9.4%)	65/1556 (4.2%)	<0.0001
Cardiovascular hospitalisations	226/949 (23.8%)	396/1334 (29.7%)	0.0019
Stroke/TIA/Peripheral embolism	10/962 (1.0%)	15/1344 (1.1%)	0.8610
Stroke/TIA/Peripheral embolism or Death	112/1064 (10.5%)	80/1409 (5.7%)	<0.0001

Legend: TIA= transient ischemic attack.

AF type at enrollment







EHRA I	1234	1065	1045	1027	1011	984	853
EHRA II - IV	1881	1562	1547	1532	1513	1483	1260

Asymptomatic atrial fibrillation: clinical correlates, management and outcomes.

A report from the EurObservational Research Programme – Atrial Fibrillation

(EORP-AF) General Pilot Registry

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SUPPLEMENTARY MATERIAL

Tables S1, S2, S3, S4 online-only

Supplementary material

Table S1. Patient history and result of clinical evaluation at enrollment

	All	Asymptomatic AF EHRA I	Symptomatic AF EHRA II - IV	P-value
N° of patients	3119	1237	1882	
Previous interventions				
Pharmacological cardioversion	36.3	23.3	44.6	<0.0001
Electrical cardioversion	28.7	27.8	29.2	0.4094
Catheter ablation	7.7	6.5	8.5	0.0460
Pacemaker implantation	6.9	8.6	5.8	0.0034
ICD implantation	1.5	2.6	0.7	<0.0001
AF surgery	0.9	0.9	0.9	0.9675
Body Mass Index (kg/m ²)	27 (25-31)	27 (25-30)	28 (25-31)	0.0234
Systolic Blood Pressure(mmHg)	130 (120-142)	130 (120-140)	130 (120-150)	<0.0001
Diastolic Blood Pressure(mmHg)	80 (70-87)	80 (70-80)	80 (70-90)	<0.0001
Electrocardiogram				
QRS duration (ms) (Median (IQR))	98 (82-110)	100 (87-118)	96 (80-109)	<0.0001
Left BBB (%)	53.8	54.6	53.0	0.7531
Right BBB (%)	46.2	45.4	47.0	
Heart rate (bpm)(Median (IQR))				
during AF	92 (76-119)	82 (71-98)	100 (80-125)	<0.0001
in sinus rhythm	67 (58-77)	66 (57-77)	68 (59-78)	0.2178
Echocardiogram				
LA size (mm)(Median (IQR))	44 (40-50)	47 (41-53)	43 (39-48)	<0.0001
LVEF (%) (Median (IQR))	55 (45-60)	55 (44-60)	55 (45-60)	0.6672
LVH (%)	31.3	26.5	34.4	<0.0001

IQR=Interquartile range, ICD=Implantable cardioverter-defibrillator,

BBB: bundle branch block; LA: left atrial; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

[a]: Fisher exact test.

Table S2 . Prescribed interventions and medications

	Asymptomatic AF		Symptomatic AF	P-value
	All	EHRA I	EHRA II - IV	
N° of patients	3119	1237	1882	
Interventions (%)				
N (on inpatients only)	1994	669	1325	
Pharmacological cardioversion	30.0	13.9	38.1	<0.0001
Electrical cardioversion	22.9	15.4	26.8	<0.0001
Catheter ablation	9.1	6.0	10.7	0.0006
Pacemaker implantation	4.3	4.2	4.3	0.8979
ICD Implantation	1.2	2.0	0.8	0.0185
Surgical therapy	0.3	0.1	0.3	0.6692[a]
Drug prescriptions				
Antiarrhythmic drugs (%)				
At least one	35.7	26.4	41.8	<0.0001
Amiodarone	21.3	13.0	26.7	<0.0001
Beta-blockers	69.4	69.6	69.3	0.8885
Digoxin	19.7	18.6	20.4	0.1948
ACE inhibitors	43.2	46.0	41.4	0.0102
ARBs	21.8	19.7	23.1	0.0233
Diuretics	50.6	55.1	47.6	<0.0001
Aldosterone blockers	24.5	28.1	22.1	0.0001

IQR=Interquartile range, ICD=Implantable cardioverter-defibrillator, ACE: angiotensin converting enzyme; ARV: angiotensin receptor blockers.
[a]: Fisher exact test

Table S3. Patient history and result of clinical evaluation at enrollment			
	Fully asymptomatic	Asymptomatic with previous symptoms	P-value
N° of patients	520	717	
Previous interventions			
Pharmacological cardioversion	13.4	30.8	<0.0001
Electrical cardioversion	17.6	35.4	<0.0001
Catheter ablation	1.8	9.9	<0.0001
Pacemaker implantation	6.9	9.8	0.0782
ICD implantation	2.1	2.9	0.3736
AF surgery	1.0	0.8	>0.999[a]
Body Mass Index (kg/m ²)	27 (24-30)	27 (25-30)	0.0949
Systolic Blood Pressure(mmHg)	130 (120-140)	130 (120-140)	0.8294
Diastolic Blood Pressure(mmHg)	80 (70-80)	80 (70-81)	0.3411
Electrocardiogram			
QRS duration (ms) (Median (IQR))	100 (86-117)	100 (88-118)	0.4387
Left BBB (%)	44.9	61.9	0.0221
Right BBB (%)	55.1	38.1	
Heart rate (bpm)(Median (IQR))			
during AF	82 (70-96)	83 (72-100)	0.0731
in sinus rhythm	70 (63-82)	64 (57-75)	0.0047
Echocardiogram			
LA size (mm)(Median (IQR))	47 (43-53)	46 (40-54)	0.3450
LVEF (%) (Median (IQR))	54 (40-60)	57 (45-61)	0.0006
LVH (%)	28.5	25.0	0.1994

IQR=Interquartile range, ICD=Implantable cardioverter-defibrillator,

BBB: bundle branch block; LA: left atrial; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

[a]: Fisher exact test.

Table S4. Prescribed interventions and medications.

	Fully asymptomatic	Asymptomatic with previous symptoms	P-value
N° of patients	520	717	
Interventions (%)			
N (on inpatients only)	285	384	
Pharmacological cardioversion	11.6	15.6	0.1409
Electrical cardioversion	9.5	19.8	0.0002
Catheter ablation	1.4	9.4	<0.0001
Pacemaker implantation	3.2	4.9	0.2529
ICD Implantation	2.5	1.6	0.4160
Surgical therapy	0.4	0	0.4266[a]
Antiarrhythmic drugs (%)			
At least one	17.7	32.7	<0.0001
Amiodarone	13.5	12.7	0.6886
Beta-blockers	70.0	69.3	0.7788
Digoxin	18.3	18.7	0.8671
ACE inhibitors	48.8	44.0	0.0918
ARBs	18.9	20.3	0.5613
Diuretics	59.8	51.7	0.0044
Aldosterone blockers	34.4	23.6	<0.0001

IQR=Interquartile range, ICD=Implantable cardioverter-defibrillator,

BBB: bundle branch block; LA: left atrial; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

[a]: Fisher exact test.

Clinical significance

- In the EORP AF General Pilot Registry, focused on cardiology practice, asymptomatic AF was common - accounting for around 40% of AF cases consecutively collected. . Permanent AF was threefold more common in asymptomatic than in symptomatic patients.
- Male gender, older age, previous MI, and limited physical activity were significantly associated with asymptomatic AF.
- Asymptomatic AF is associated with a higher mortality compared to symptomatic AF.