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# Asymptomatic atrial fibrillation

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# Accepted Manuscript


Asymptomatic atrial fibrillation: clinical correlates, management and outcomes in the EORP-AF Pilot General Registry

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Clinical Research Study

# Asymptomatic atrial fibrillation: clinical correlates, management and outcomes in the EORP-AF Pilot General Registry

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**Abstract**

*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.

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## Introduction

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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] ($CHADS_2$) score and the Congestive heart failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]- Vascular disease, Age 65-74, and Sex category [female] ($CHA_2DS_2$-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 < 2years 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±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.

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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

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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 ($CHA_2DS_2$ and $CHA_2DS_2$-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, $CHA_2DS_2$-VASc $\geq 2$ 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 (27.7 vs. 35.1%).

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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, *t*he 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 dsease, 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 $CHA_2DS_2$-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, acccording to guidelines (ie, $CHA_2DS_2$-VASc $\geq$ 2 or cardioversion planned) oral anticoagulants were prescribed in a significantly lower proportion of fully asymtomatic 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].

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On multivariate analysis (adjusting for male gender, age, previous myocardial infarction, $CHA_2DS_2$-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 1266-4.278), 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).

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**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).

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While prescribed interventions and medications for rate/rhythm control differed between asymptomatic and symptomatic atrial fibrillation patients, the scores for thromboembolic risk ($CHA_2DS$ and $CHA_2DS_2$-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, $CHA_2DS_2$-VASc $\geq 2$ 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 $CHADS_2$ and $CHA_2DS_2$-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.

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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.

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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, $CHA_2DS_2$-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, CHA2DS2-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 symptomatiic (EHRA II-IV) atrial fibrillation patients.

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**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 | |
| $CHA_2DS_2$- 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, $CHADS_2$= Congestive heart failure, Hypertension, Age 75, Diabetes, Stroke [Doubled], $CHA_2DS_2$-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.

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**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 | |
| $CHA_2DS_2$- 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,, $CHADS_2$= Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke [Doubled], $CHA_2DS_2$-VASc = Congestive heart failure, Hypertension, Age ≥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.

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**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 Median (IQR) | 74 (67-80) | 70 (62-77) | 67 (60-74) | 69 (61-77) | 71 (61-78) | <0.0001 |

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

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**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**.**

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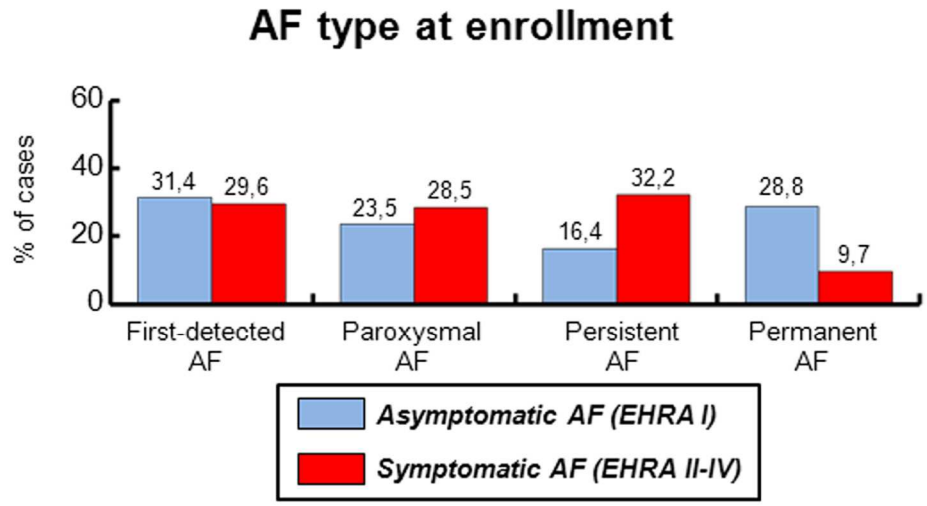


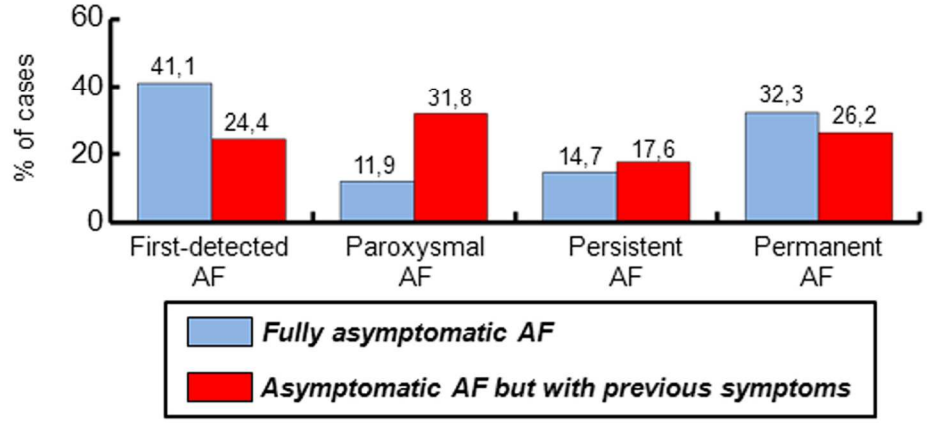


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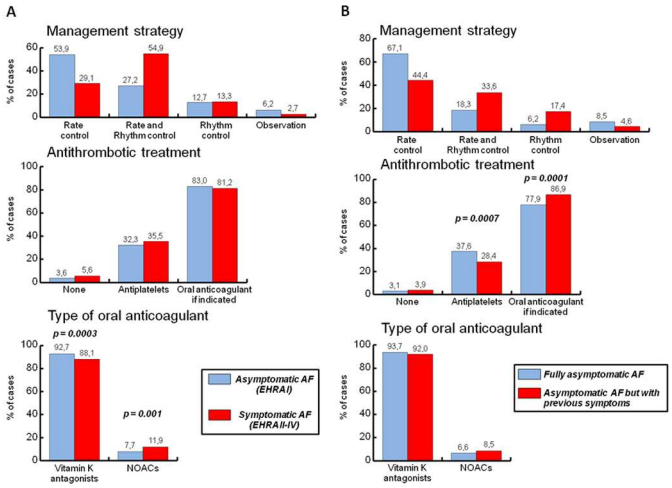


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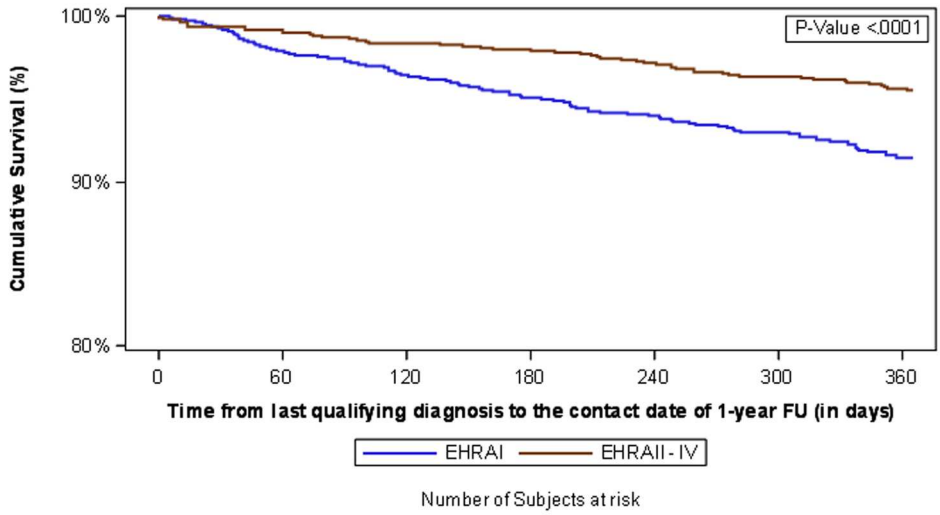


Number of Subjects at risk

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

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# 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

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## 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/m²) | 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.

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**Table S2 . Prescribed interventions and medications**

| | All | Asymptomatic AF EHRA I | Symptomatic AF EHRA II - IV | P-value |
|---|---|---|---|---|
| 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

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| 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/m²) | 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.

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**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.

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**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.

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