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Increased Burden of Comorbidities and Risk of Cardiovascular Death in Atrial Fibrillation Patients in Europe Over Ten Years: A Comparison between EORP-AF Pilot and EHS-AF Registries

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HIGHLIGHTS

- Temporal changes have been found in atrial fibrillation (AF) epidemiology
- AF patients re becoming older and more burdened with comorbidities
- Use of oral anticoagulant (OAC) drugs increased over the last decade in Europe
- OAC use is associated with a reduction in thromboembolic and cardiovascular events
- Despite the increased OAC use, a high risk of cardiovascular death still persists.

ABSTRACT

Background: In 2002, the European Society of Cardiology conducted the Euro Heart Survey (EHS), while in 2014concluded 1-year follow-up of the EURObservational Research Programme AF (EORP-AF) Pilot Registry**.**

Methods: We analysed differences in clinical profiles, therapeutic approaches and outcomes between these two cohorts after propensity score matching (PSM).

Results: After PSM, 5206 patients were analysed. In EORP-AF there were more elderly patients than EHS ($p<0.001$). EORP-AF patients were more burdened with cardiovascular (CV) and non-CV comorbidities, with a higher proportion of patients with high thromboembolic risk. EORP-AF patients used more oral-anticoagulant (OAC) ($p<0.001$). At 1-year follow-up EORP-AF patients had lower risk for thromboembolic and CV events, readmission for AF and other CV reasons (all $p<0.001$), showing conversely a higher risk for CV death ($p=0.015$). Kaplan-Meier curves showed that EORP-AF patients had higher risk for CV death ($p<0.0001$) and all-cause death ($p=0.0019$). Cox regression confirmed that EORP-AF patients were at higher risk for CV death ($p=0.021$).

Conclusions: We found significant changes in AF epidemiology over a decade in Europe, with older patients, more burdened with comorbidities. A greater use of OAC was found. Despite a reduction in risk for thromboembolic events, a high risk of CV-related death was still evident.

KEYWORDS: atrial fibrillation; epidemiology; Europe; thromboembolic risk; mortality.

1. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide[1]. In 2010 an estimated 33 million people were affected by AF, with an estimated prevalence (per 100,000 population) of 596.2 in men and 373.1 in women, progressively increasing from 1990 in both males and females, as well as in both developed and developing countries[2]. Similarly, age-adjusted AF incidence increased in both males and females from 1990 to 2010[2]. In Europe, one out of 4 middle-aged adults will suffer with AF, with up to 17 million subjects projected to be diagnosed by 2030[1].

AF is associated with a significant risk of ischemic stroke, death and other cardiovascular events[1,3] Over the last 20 years, AF-related deaths have been progressively increasing both in male and female patients, as well as in developed and developing countries[2]. Also, recent data have reported changes over time in the clinical profile of AF patients, impacting on clinical outcomes[4].

Oral anticoagulant (OAC) therapy is central to AF management, resulting in a significant reduction in thromboembolic risk[1]. The landscape of stroke prevention in AF has also changed after the introduction of non-vitamin K antagonist oral anticoagulants as an effective and safe alternative to vitamin K antagonists[1]. In a systematic review of AF registries, the overall risk of death was showed to be persistently high, despite an increase in OAC use[5].

In 2003, the European Society of Cardiology conducted the Euro Heart Survey on AF (EHS) a prospective registry about AF management in Europe[6]. After approximately 10 years, the ESC then conducted the EURObservational Research Programme in AF (EORP-AF) Pilot

Registry[7], which described contemporary management of AF patients by European cardiologists and to ascertain European Society of Cardiology guideline implementation for stroke prevention in AF.

We hypothesised temporal differences in clinical and risk profiles, therapeutic approaches and outcomes between AF patients enrolled in EORP-AF and EHS. Our aim was to perform a post-hoc comparison between EHS and EORP-AF to describe differences in baseline characteristics, comorbidities, clinical management and thromboembolic risk, as well as outcomes after 1-year of follow-up.

2. METHODS

2.1 Study Cohort

The EORP-AF Pilot Registry is a prospective, observational, multicentre study, held by European Society of Cardiology in 9 members countries, about AF patients in cardiology practice. The study enrolled, from 67 enrolling centres, consecutive patients presenting with AF as primary or secondary diagnosis to in- and outpatients cardiology services from February 2012 to March 2013. The qualifying AF event was recorded by a 12-lead ECG, 24 h ECG Holter or other electrocardiographic documentation within 12 months before enrolment. A follow-up observation period was planned at 1, 2 and 3 years after enrolment. Details about study protocol and main results have been reported elsewhere[7–9].

Similarly, the EHS on AF was a prospective, observational, multicentre study conducted by the European Society of Cardiology in 35 members countries and 182 sites. The study enrolled consecutive AF patients presenting to cardiology services, with AF diagnosed within

12 months by an established ECG recording technique as primary or secondary diagnosis. The enrolment procedures were performed from September 2003 to July 2004. A 1-year follow-up observation was originally planned. Details about the study protocol and main results have been reported elsewhere[6,10].

Both the studies shared similar exclusion criteria: age below 18 years old, missing electrocardiographic proof of AF, qualifying episode occurred more than 12 months before enrolment, only atrial flutter recorded and taking part in an interventional cardiac trial. All patients, in both the studies, were enrolled after signing the written informed consent. The studies were approved by an institutional review board at every site. Both the studies were conducted according to the Declaration of Helsinki. No major differences between the two study designs were ascertained, being substantially comparable beyond the number of countries included in the surveys.

From the original EORP-AF cohort, 3119 patients were retrieved, while from EHS 5334 patients were included for the analysis. Case report forms were filled by investigators at each enrolling centre, based on patients' demographics, baseline characteristics and clinical history. The two original cohorts have been merged together, constructing an overall study cohort of 8453 patients.

2.2 Datasets Merging and Definitions

Original datasets were similar in main information requested and they overlapped in most of the variables considered. Due to the changes in epidemiological definitions, clinical management and available drugs over the 10 years between the two registries, several adjustments and reclassifications have been made to fully merge the two datasets. as reported

in Supplementary Materials (Table S1). All clinical characteristics reported were collected as part of patients' clinical history and obtained from medical interview and/or from clinical notes/clinical data archives.

Thromboembolic risk was been defined according both $CHADS_2$ (Congestive Heart Failure, Hypertension, Age≥65 years, Diabetes Mellitus, Stroke/Transient Ischemic Attack) and CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Stroke/TIA, Vascular Disease, Age 65-74 years, Sex Category [Female]) scores[11]. Thromboembolic risk was categorised according to $CHADS_2$ as 0, 1 and ≥2. Based on CHA_2DS_2-VASc, patients were categorised as "Low Risk" (CHA_2DS_2-VASc 0 in males and 1 in females), "Moderate Risk" (male patients with CHA_2DS_2-VASc 1) and "High Risk" (CHA_2DS_2-VASc ≥2).

2.3 Follow-Up Procedures

Patients from both studies were contacted 1 year after enrolment and the following major adverse events were recorded: stroke, transient ischemic attack, peripheral embolism, acute coronary syndrome, coronary intervention, any overt coronary artery disease, bleeding (intended as any major or clinically relevant bleeding), hospitalizations and cardiovascular (CV) and all-cause death. All events were collected according to self-reporting from patient and/or relatives and whenever available, from clinical notes/clinical data archives and assigned at investigator level. Follow-up checks were performed both as clinical visit(s) and/or telephonic interview(s).

2.4 Statistical Analysis

Continuous variables are reported as mean±SD or as median and IQR. Between group comparisons were made using a non-parametric test (Kruskal-Wallis test). Categorical variables were reported as counts and percentages. Between group comparisons were made using a chi-square test or Fisher's exact test (if any expected cell count was less than five).

Pooling data together a possible selection bias should be considered. In order to reduce the influence of such selection bias, a PSM procedure was performed to obtain two homogenous groups of patients, in terms of baseline characteristics and risk factors, from the historical cohort and the current cohort. PSM was compiled according to a selection of pre-specified covariates among demographics (age, gender), clinical characteristics (type of AF, systolic blood pressure, diastolic blood pressure, body mass index) and risk factors (hypertension, hypercholesterolemia, diabetes mellitus, current smoking, no regular exercise). Details about the PSM have been reported in Supplementary Methods.

After the PSM procedure, a logistic regression analysis was performed to establish the factors significantly associated with AF as the main reason for admission. A list of major clinical variables (age, gender, hypertension, diabetes mellitus, chronic heart failure, vascular disease, stroke/TIA, previous bleeding event, renal disease, chronic obstructive pulmonary disease) as well as the original study of enrolment exposure (EORP-AF vs. EHS) underwent univariate analysis. All variables associated with the dependent variable with a p-value <0.10 were selected to enter a stepwise regression multivariate analysis.

After PSM, a logistic regression analysis was performed to establish associations between original cohort of study of enrolment exposure and 1-year follow-up major adverse events. Two multivariate models were performed. In the first, the logistic regression analysis was

adjusted for age, gender, type of AF and CHA_2DS_2-VASc score. In the second model, association with the occurrence of major adverse events was adjusted for all the previous covariates plus the use of any OAC.

A survival analysis was performed after the PSM procedure. Plots of the Kaplan-Meier curves for time to CV death and all-cause death according to original study of enrolment exposure (EORP-AF vs. EHS) were performed. The survival distributions were compared using the log-rank test. A Cox regression analysis was also performed for the occurrence of CV death and all-cause death. A pre-specified list of covariates was selected based on biological plausibility (age, gender, type of AF, hypertension, diabetes mellitus, chronic heart failure, vascular disease, stroke/transient ischemic attack, use of any OAC) and in addition to the original study of enrolment exposure (EORP-AF vs. EHS) underwent univariate analysis. The time-to-event analysis was only used for death outcomes, since the exact timing for individual major adverse events was not known. All variables found to be associated with the dependent variable with a p-value <0.10 were entered into the stepwise regression multivariate analysis. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. RESULTS

The merged dataset consisted of 8453 patients (58.5% male) with a median [IQR] age of 69.0 [60.0-76.2], with 29.9% (2530) aged ≥75 years. Most (73.9%, n= 6241) were admitted for AF, with paroxysmal AF in 28.2% (n= 2325) (Tables S1-S2, S4-S6). Median [IQR] $CHADS_2$ score was 2 [1-2], with 52.0% having a $CHADS_2$ score ≥2. Median [IQR] CHA_2DS_2-VASc score was 3 [2-4], with CHA_2DS_2-VASc score ≥2 in 77.3% Overall, 2502 patients (30.1%)

were prescribed aspirin and 5851 (70.5%) with a OAC. An antiarrhythmic drug (AAD) was prescribed in 39.3% (n= 3264). The PSM procedure resulted in a merged population of 5206 patients (Table 1).

3.1 Baseline Characteristics and Management

Baseline characteristics were compared between the two registries both before (Table S2) and after PSM (Table 1, Panel a). Comparing EORP-AF and EHS, the proportion of elderly patients (age ≥75 years or ≥80 years) were higher in EORP-AF than in EHS both before and after PSM. There were no differences in the proportion of females. Patients were more frequently admitted for reason other than AF in EORP-AF than EHS (39.8% vs. 18.0%, p<0.001). Both before and after PSM, patients in EORP-AF were less symptomatic on admission than those enrolled in EHS.

Even after PSM, patients enrolled in EORP-AF were more likely to be diagnosed with several concomitant major cardiac and vascular comorbidities (Table 1, Panel a). Also, prior bleeding was more commonly reported in EORP-AF than in EHS (p<0.001). Among the non-cardiovascular comorbidities, after the PSM, EORP-AF patients were more likely to have renal disease than EHS patients (p<0.001), and less likely to have chronic obstructive pulmonary disease (p=0.014). Catheter ablation was more prevalent in EORP-AF than in EHS (p<0.001).

3.2 Factors Associated with AF as Main Reason for Admission

After univariate analysis (Table S4), age (p<0.001), chronic heart failure (p<0.001), hypertension (p=0.042), vascular disease (p<0.001) and renal disease (p<0.001) were inversely associated with AF as main reason for admission [Figure S1]. Being part of EORP-

AF study was inversely associated with AF as main reason for admission (odds ratio [OR]: 0.34, confidence interval [CI]: 0.29-0.41, p<0.001) [Figure S1].

3.3 Thromboembolic Risk

Higher $CHADS_2$ score, expressed both as mean and median (both p<0.001), was found in EORP-AF than in EHS cohort after PSM (Table 1, Panel c). Similarly, the CHA_2DS_2-VASc score was higher in EORP-AF patients than EHS patients (both p<0.001 in mean and median differences) [Figure S2]. Patients categorized as "high risk" were more prevalent in EORP-AF than EHS. After the PSM, $CHADS_2$ score ≥2 was found in 61.2% in EORP-AF (vs. 50.7% in EHS, p<0.001), while CHA_2DS_2-VASc score ≥2 was reported for 81.8% in EORP-AF (vs. 79.3%, p=0.021).

3.4 Antithrombotic Drugs and Pharmacological Treatments

Use of antithrombotic drugs, as well as the other pharmacological treatments, in EORP-AF and EHS were compared after admission/consultation before (Table S6) and after the PSM matching (Table 1, Panel d).

The use of antithrombotic drugs increased in EORP-AF patients compared to EHS (95.3% vs. 92.9%, p<0.001), after PSM. The use of aspirin, as well as any antiplatelet drug, was similar between the two cohorts. Use of OAC increased both before and after PSM matching. Vitamin K antagonist use was significantly higher in EORP-AF than EHS (72.4% vs. 64.9%, p<0.001) and the use of any OAC was even higher (80.4% vs. 64.9%, p<0.001). Concomitant use of antiplatelet drugs and OAC was also increased (20.3% vs. 8.2%, p<0.001). In high thromboembolic risk patients [Figure 1], the proportion of patients prescribed oral antiplatelet drugs only and no antithrombotic therapy were significantly lower in EORP-AF patients than

in EHS (both p-values <0.001). The proportion of patients treated with combination antiplatelet drug(s) and OAC was significantly higher in EORP-AF compared to EHS [Figure 1].

3.5 Follow-up Analysis

Among the overall cohort, 7757 (91.8%) patients were eligible for the 1-year follow-up analysis (Table S7), while in the PSM cohort, 4768 (91.6%) were available for analysis (Table S8).

In the PSM matched cohort, patients enrolled in EORP-AF had a significant lower rate of stroke/TIA (0.9% vs. 3.3%, p<0.001) as well as stroke/TIA/peripheral embolism (1.0% vs. 3.5%, p<0.001). The rate of coronary artery disease/acute coronary syndrome was significantly lower in EORP-AF than EHS (3.7% vs. 5.9%, p<0.001). No difference in rates of any bleeding events between the two cohorts was evident.

A higher rate of CV death was reported in EORP-AF study compared to EHS (4.3% vs. 2.1%, p<0.001). A non-significant trend for higher rate of all-cause death was also evident in EORP-AF than in EHS (6.5% vs. 5.3%; p=0.090). The readmission rate for AF was significantly lower in EORP-AF than EHS (17.4% vs. 39.0%, p<0.001). Both the rate of readmission for other CV reasons (12.1% vs. 20.1%, p<0.001), as well as the rate of readmission for non-CV reasons (p<0.001) were significantly lower in EORP-AF cohort.

3.6 Multivariate Regression and Survival Analyses

A logistic regression analysis was performed to establish the relationship between the study exposure (EORP-AF vs. EHS) and major adverse events (Table 2, Panel a). Multivariate

model 1, adjusted for age, gender, type of AF and CHA_2DS_2-VASc score found that patients in the EORP-AF study had a lower risk for occurrence of stroke/TIA ($p<0.001$), stroke/TIA/peripheral embolism ($p<0.001$), coronary artery disease/acute coronary syndrome ($p=0.001$), readmission for AF and for other CV reasons (both p-values <0.001). Conversely, the risk of CV death was higher in EORP-AF study than in EHS ($p=0.019$). The fully adjusted model, adding the use of any OAC, confirmed a higher risk for CV death in EORP-AF (OR: 2.54, 95% CI: 1.20-5.40, $p=0.015$), while no difference was reported for all-cause death. Kaplan-Meier analysis [Figure 2] shows that patients in EORP-AF study had a higher risk for CV death ($p<0.0001$) and all-cause death ($p=0.0019$) compared to EHS.

Cox regression analysis (Table 2, Panel b) found that patients in EORP-AF were at higher risk for CV death (hazard ratio [HR]: 2.71, 95% CI: 1.70-4.33, $p<0.001$) and all-cause death (HR: 1.56, 95% CI: 1.15-2.11, $p=0.004$). Multivariate analysis shows that patients enrolled in EORP-AF had a higher risk for CV death (HR: 1.62, 95% CI: 1.08-2.45, $p=0.021$) at 1-year follow-up, independent of other relevant risk factors (Table 4). Multivariate analysis did not show an independent increased risk for all-cause death due to being part of EORP-AF.

4. DISCUSSION

This paper provides a unique insight into temporal changes in atrial fibrillation (AF) epidemiology in Europe over a decade. First, we found that the proportion of elderly and very elderly patients has significantly increased over time, with only 60% of symptomatic patients. Second, patients enrolled in EORP-AF had with a higher prevalence of CV comorbidities (*i.e.* previous myocardial infarction, chronic heart failure, cardiomyopathy, peripheral arterial disease). Third, clinical management of AF patients remained mainly unchanged over ten years, with a significant increase only for catheter ablation use. Fourth, overall thromboembolic risk was increased compared to ten years previously, with a marked increase in the use of OAC therapy. Finally, there was a significant decrease in rates of both thromboembolic and major CV events, but a significant increase in all-cause and CV mortality.

Both AF prevalence and incidence rise according to increasing age, and particularly in elderly and very elderly patients[1]. Importantly, increasing age increases morbidity and mortality in AF patients[12,13]. A similar analysis of trends in AF patients admitted to Medicare beneficiaries in USA, showed that from 1999 to 2013 there was a progressive increase in age and proportion of very elderly patients (age ≥85 years)[4].

Proportionally, various comorbidities were increased among European AF patients. There was a significant increase in the prior history of myocardial infarction and coronary interventions, as well as in chronic heart failure, valvular disease, cardiomyopathy (regardless of type) and peripheral arterial disease, which are relevant for patients' management. One main reason for these strong differences could be related to the increasing age of patients and

higher prevalence of of concomitant comobidities. Furthermore, patients who are more clinically complex could have a higher risk of adverse events, as already reported for clinical characteristics that could be interpreted as health status markers, such as polypharmacy[14,15]. These data also underline how comorbidities have changed over time, as well as the relationship between AF and cardiovascular and vascular diseases[16,17]. Accordingly, thromboembolic risk profile has significantly increased in European AF patients over these ten years.

One of the main findings of our paper is the significant increase in OAC use in the 10 years between EHS and EORP-AF. These data confirm previous reports on how worldwide there has been a progressive increase in the use of OAC[18,19]. The increase in the use of OAC has been driven by increased awareness of AF and stroke, guideline changes and the progressive increase in the uptake of non-vitamin K antagonist oral anticoagulants[18,19]. Nonetheless, a large proportion of high-risk patients are still treated with single antiplatelet therapy (>13%) and more than a quarter of these patients were treated with dual antithrombotic therapy (OAC plus antiplatelet drug), although these data could be related to the presented changes in clinical history of myocardial infarction and coronary interventions.

In the context of an improved management and increased OAC use over the course of ten years European AF patients have less hospital readmissions, both for AF and other CV-related reasons, and fewer thromboembolic and CV events. Nonetheless, despite various cardiovascular prevention drugs were used in the management of AF patients, there was a significant increase of CV death that occurred between EHS and EORP-AF registries. Data coming from the US Medicare programme, reported a similar reduction in 30-day readmission rate, as well as an increase in the 1-year mortality rate, even if after full

adjustment the mortality rate was mostly unchanged[4]. Our data show that even if similar evidence was found for all-cause mortality in PSM, European AF patients still do suffer from a higher risk for CV death, independently of other risk factors.

The increased risk of death and CV death, even despite OAC use, has been highlighted in several previous studies[3,9,13,14]. AF patients may be progressively more clinically complex, due to the progressively increasing age and the higher prevalence of major CV diseases, partly explaining the increase in CV death. Perhaps the time has come for a change on the horizon of clinical management for AF patients. As already highlighted by the 2016 ESC guidelines, a more integrated approach to AF patient management is needed in order to further reduce the risk of major adverse outcomes[1]. Moreover, this approach seems justified by recent data showing how an integrated approach leads to a significant reduction in all-cause death and CV related hospitalizations, although no difference was noted in terms of cerebrovascular events[20]. The use of more integrated approaches to evaluate and treat globally AF patients, with a specific focus in managing and treating concomitant conditions, has been suggested with the ABC pathway[21].

4.1 Limitations

The main limitation of our analysis is due to the observational nature of the study. Also, our analysis is based on differences between two time-points and not supported by a full time-dependent analysis. Further, the small number of variables taken to draw the PSM model may have left residual confounders, as well as the changes to clinical definitions over time could have partially influenced the analysis. As highlighted in Methods section, relevant differences exist between the two original studies, in particular related to number of countries, number of centres and their distribution. Notwithstanding the PSM procedure, these differences could

still persist and bring an inherited bias that could limit the generalizability of the results. Future longitudinal studies could probably verify and better substantiate our hypothesis. Moreover, the 1-year follow-up could be considered as a limited observation time to fully see differences in mortality events. Finally, we were not able to account for differences in social and economic conditions in the time elapsed between the two studies.

5. CONCLUSIONS

Over a decade, significant temporal changes have been found in AF epidemiology, with European AF patients becoming older and more burdened with comorbidities. Relevant changes have been also found in patients' management, with greater OAC usage. Despite the reduction in risk for thromboembolic events, a significant risk of CV-related death still persists. Greater efforts are needed to develop more integrated approaches for AF management that would impact on a significant reduction in CV mortality.

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DISCLOSURES OF INTEREST

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FIGURE LEGENDS

Figure 1: Antithrombotic Drugs Patterns in High-Risk Patients in the Two Cohorts

Legend: OAC= Oral Anticoagulant.

Figure 2: Kaplan-Meier Curves for Cardiovascular and All-Cause Death

Legend: EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation.

Table 1: Baseline Characteristics, Clinical Management, Thromboembolic Risk and Pharmacological Management after Propensity Score Matching

		EORP-AF Pilot 2012-2013 N=2603	EHS 2003-2004 N=2603	p	Std. Diff.
a) Baseline Characteristics					
Demographics					
Age *years*, median [IQR]		69.0 [61.0-77.0]	69.7 [61.4-76.4]	0.297	0.04
Age Classes, n (%)				0.045	0.07
	<65 years	876 (33.7)	891 (34.2)		
	65-74 years	854 (32.8)	918 (35.3)		
	≥75 years	873 (33.5)	794 (30.5)		
Age Classes, n (%)				<0.001	0.12
	<80 years	2143 (82.3)	2257 (86.7)		
	≥80 years	460 (17.7)	346 (13.3)		
Gender, n (%)				0.284	0.03
	Female	1046 (40.2)	1084 (41.6)		
	Male	1557 (59.8)	1519 (58.4)		
Clinical Characteristics					
Admission Main Reason, n (%)				<0.001	0.51
	AF	1566 (60.2)	2144 (82.6)		
	Other than AF	1037 (39.8)	453 (17.4)		
Type of AF, n (%)				0.099	0.07
	First Detected	802 (30.8)	721 (27.7)		
	Paroxysmal	689 (26.5)	713 (27.4)		
	Persistent	665 (25.5)	690 (26.5)		
	Permanent	447 (17.2)	479 (18.4)		
Symptomatic Status, n (%)				<0.001	0.31
	Previously Symptomatic	604 (23.2)	324 (12.8)		
	Currently Symptomatic	1576 (60.5)	1881 (74.3)		
	Never Symptomatic	423 (16.3)	328 (12.9)		
SBP *mmHg*, median [IQR]		130 [120-142]	130 [120-145]	0.065	0.03
DBP *mmHg*, median [IQR]		80 [70-87]	80 [70-90]	0.060	0.03

BMI *kg/m²*, median [IQR]	27.4 [24.7-30.6]	27.1 [24.6-30.1]	0.039	0.00
Risk Factors				
Diabetes Mellitus, n (%)	530 (20.4)	514 (19.7)	0.580	0.02
Hypercholesterolemia, n (%)	1277 (49.1)	1216 (46.7)	0.091	0.05
Current Smoking, n (%)	295 (11.3)	316 (12.1)	0.366	0.03
No Regular Exercise, n (%)	1922 (73.8)	1958 (75.2)	0.252	0.03
Alcohol Excess*, n (%)	190 (7.5)	129 (5.2)	<0.001	0.09
Cardiovascular Comorbidities				
Hypertension, n (%)	1847 (71.0)	1811 (69.6)	0.275	0.03
CAD, n (%)	832 (36.7)	905 (34.8)	0.170	0.04
Previous MI, n (%)	374 (16.5)	100 (3.9)	<0.001	0.43
Previous PCI/CABG, n (%)	390 (17.2)	349 (13.4)	<0.001	0.10
Stable Angina, n (%)	320 (14.1)	586 (22.6)	<0.001	0.22
Chronic Heart Failure, n (%)	1216 (49.0)	804 (31.1)	<0.001	0.37
Valvular Disease, n (%)	1593 (64.9)	639 (25.0)	<0.001	0.88
Cardiomyopathy, n (%)	843 (34.2)	277 (10.8)	<0.001	0.58
Dilated Cardiomyopathy, n (%)	281 (11.4)	153 (5.9)	<0.001	0.20
Hypertrophic Cardiomyopathy, n (%)	101 (4.1)	52 (2.0)	<0.001	0.12
Restrictive Cardiomyopathy, n (%)	13 (0.5)	3 (0.1)	0.010	0.07
Other Cardiomyopathy, n (%)	528 (21.4)	67 (2.6)	<0.001	0.60
Other Cardiac Disease, n (%)	198 (8.2)	240 (9.2)	0.210	0.04
Previous Stroke/TIA, n (%)	290 (11.2)	260 (10.0)	0.150	0.04
Any Thromboembolism, n (%)	346 (13.4)	334 (13.0)	0.680	0.01
PAD, n (%)	291 (11.7)	219 (8.5)	<0.001	0.11
Vascular Disease, n (%)	595 (27.2)	310 (12.1)	<0.001	0.39
Previous Bleeding, n (%)	162 (6.3)	74 (2.9)	<0.001	0.16
Non-Cardiovascular Comorbidities				
COPD, n (%)	297 (11.5)	356 (13.8)	0.014	0.07
Renal Disease, n (%)	357 (13.8)	168 (6.5)	<0.001	0.24
Thyroid Disease, n (%)	268 (10.7)	245 (10.5)	0.831	0.01
Malignancy, n (%)	132 (5.2)	148 (5.8)	0.327	0.03
b) Clinical Management				
Pharmacological Conversion, n (%)	631 (24.4)	662 (25.5)	0.386	0.02
Electrical Conversion, n (%)	509 (19.8)	511 (19.7)	0.940	0.00

Catheter Ablation, n (%)	145 (5.6)	65 (2.5)	<0.001	0.16
Pacemaker Implantation, n (%)	118 (4.5)	119 (4.6)	0.933	0.00
ICD Implantation, n (%)	16 (0.6)	15 (0.6)	0.862	0.00
AF Surgery, n (%)	7 (0.3)	2 (0.1)	0.179	0.05
c) Thromboembolic Risk				
$CHADS_2$, mean (SD)	1.9 (1.3)	1.7 (1.2)	<0.001	0.19
$CHADS_2$, median [IQR]	2 [1-3]	2 [1-2]	<0.001	0.19
$CHADS_2$ Classes, n (%)			<0.001	0.22
0	323 (12.4)	380 (14.6)		
1	687 (26.4)	903 (34.7)		
≥2	1593 (61.2)	1320 (50.7)		
CHA_2DS_2-VASc, mean (SD)	3.3 (1.8)	2.9 (1.6)	<0.001	0.18
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	3 [2-4]	<0.001	0.18
CHA_2DS_2-VASc Classes, n (%)			0.021	0.08
Low Risk	215 (8.3)	219 (8.4)		
Moderate Risk	259 (10.0)	321 (12.3)		
High Risk	2129 (81.8)	2063 (79.3)		
d) Pharmacological Management				
Antithrombotic Therapy				
Aspirin, n (%)	798 (30.7)	805 (31.5)	0.521	0.02
Any Antiplatelet, n (%)	889 (34.2)	882 (34.6)	0.796	0.01
Vitamin K Antagonist, n (%)	1879 (72.4)	1653 (64.9)	<0.001	0.16
Any OAC, n (%)	2087 (80.4)	1653 (64.9)	<0.001	0.35
Any Antithrombotic, n (%)	2478 (95.3)	2371 (92.9)	<0.001	0.10
Any Antiplatelet + OAC, n (%)	527 (20.3)	210 (8.2)	<0.001	0.35
Other Antithrombotic, (%)	29 (1.1)	46 (1.8)	0.040	0.06
Antiarrhythmic Drugs				
Class Ia, n (%)	1 (0.0)	13 (0.5)	0.001	0.09
Class Ic, n (%)	279 (10.7)	233 (9.1)	0.055	0.05
Class III, n (%)	665 (25.6)	900 (35.3)	<0.001	0.21
Amiodarone, n (%)	543 (20.9)	714 (28.0)	<0.001	0.17
Any Antiarrhythmic, n (%)	934 (35.9)	1144 (44.8)	<0.001	0.18
Other Medications				
Beta-Blockers, n (%)	1813 (69.8)	1131 (44.3)	<0.001	0.53

Digoxin, n (%)	507 (19.5)	568 (22.3)	0.015	0.07
Non-DHP CCB, n (%)	165 (6.3)	214 (8.4)	0.005	0.08
ACE Inhibitors, n (%)	1131 (43.5)	1303 (51.1)	<0.001	0.15
ARBs, n (%)	566 (21.8)	339 (13.3)	<0.001	0.22
Statins, n (%)	1280 (49.3)	826 (32.4)	<0.001	0.35
Antidiabetic Drugs, n (%)	465 (17.9)	358 (14.0)	<0.001	0.11

Legend: *≥8 units per week; ACE= Angiotensin Converting Enzyme; AF= Atrial Fibrillation; ARB= Angiotensin Receptor Blockers; BMI= Body Mass Index; CABG= Coronary Artery By-pass Graft; CAD= Coronary Artery Disease; CCB= Calcium-Channel Blockers; COPD= Chronic Obstructive Pulmonary Disease; DBP= Diastolic Blood Pressure; DHP= Dihydropyridine; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; ICD= Implantable Cardioverter Defibrillator; IQR= interquartile feeling; MI= Myocardial Infarction; OAC= Oral Anticoagulant; PAD= Peripheral Arterial Disease; PCI= Percutaneous Coronary Intervention; SBP= Systolic Blood Pressure; SD= Standard Deviation; TIA= Transient Ischemic Attack.

Table 2: Multivariate Regression and Survival Analyses for Outcomes at 1-year Follow-Up after Propensity Score Matching

a) Multivariate Logistic Regression Analyses for EORP-AF Pilot vs. EHS on Outcomes

	MODEL 1*			MODEL 2†		
	OR	***95% CI***	***p***	***OR***	***95% CI***	***p***
Stroke/TIA	0.18	0.07-0.44	<0.001	0.18	0.07-0.44	<0.001
Stroke/TIA/PE	0.21	0.09-0.48	<0.001	0.21	0.09-0.49	<0.001
CAD/MI	0.55	0.38-0.79	0.001	0.56	0.38-0.83	0.004
Any Bleeding	0.72	0.33-1.56	0.400	0.63	0.27-1.50	0.300
CV Death	2.32	1.15-4.68	0.019	2.54	1.20-5.40	0.015
CV Death - Stroke/TIA - Any Bleeding	0.83	0.57-1.21	0.322	0.84	0.57-1.25	0.388
CV Death - CAD/MI	0.87	0.64-1.17	0.352	0.88	0.64-1.21	0.431
All-Cause Death	1.25	0.85-1.85	0.256	1.23	0.82-1.85	0.321
Readmission for AF	0.34	0.26-0.43	<0.001	0.29	0.22-0.38	<0.001
Readmission for Other CV Reasons	0.44	0.32-0.61	<0.001	0.44	0.32-0.61	<0.001

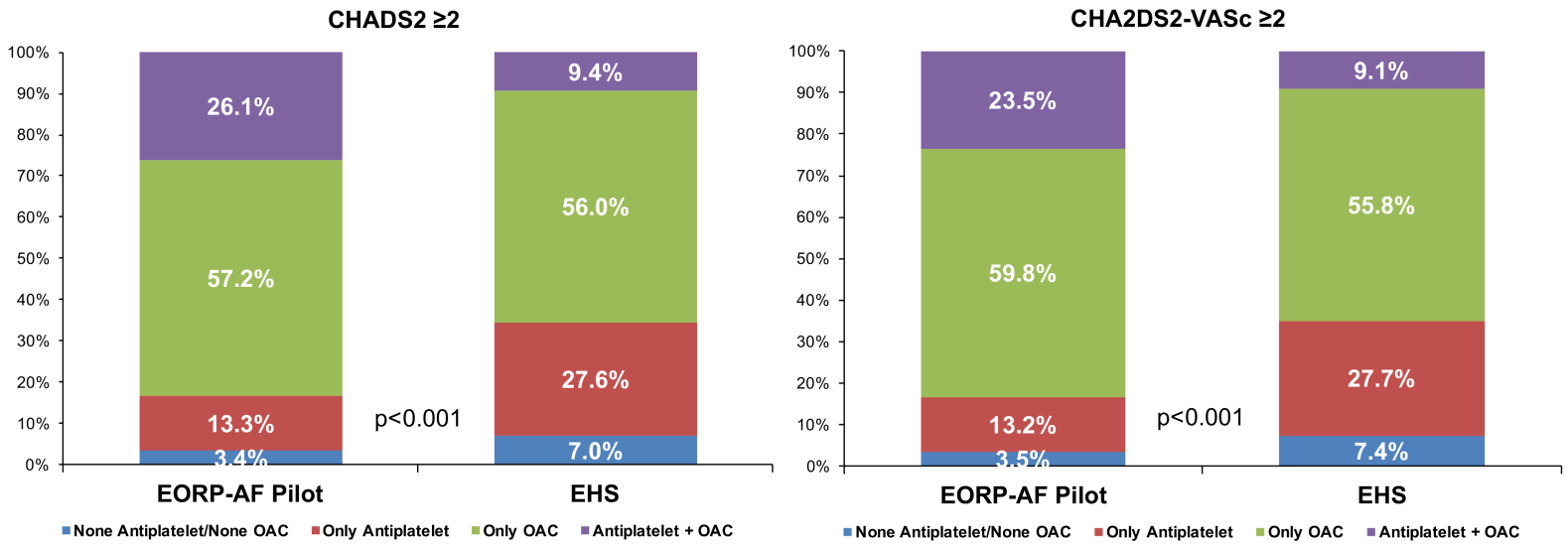
b) Cox Regression Analyses for Cardiovascular Death and All-Cause Death

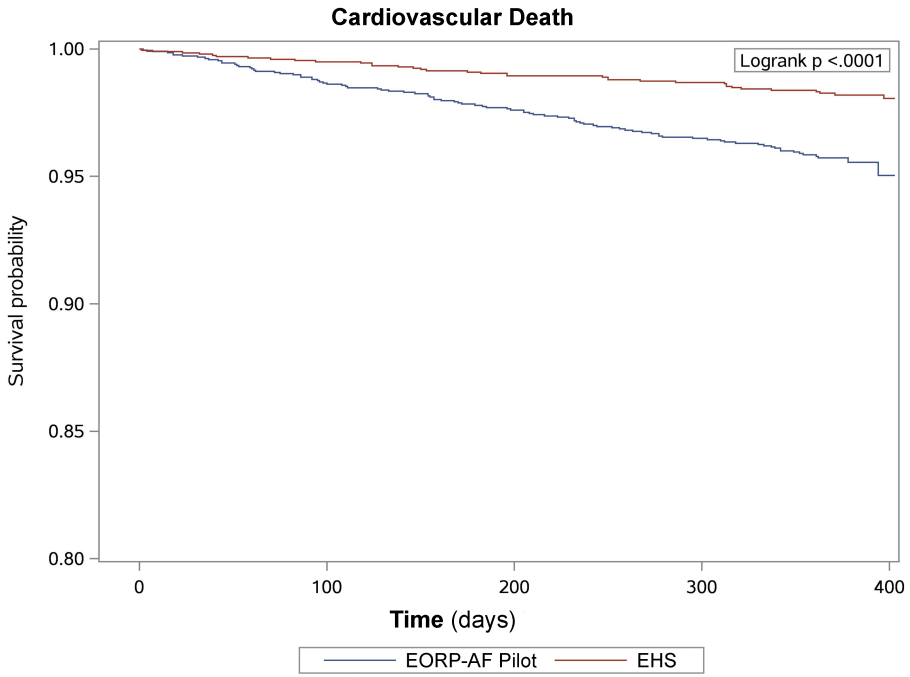
	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
Cardiovascular Death						
Age *(per year)*	1.06	1.02-1.09	<0.001	1.04	1.02-1.06	<0.001
Female Gender	1.56	0.83-2.93	0.163	-	-	-
Type of AF						
First Detected	-	-	-	-	-	-
Paroxysmal	0.21	0.07-0.63	0.006	0.35	0.19-0.64	<0.001
Persistent	0.47	0.21-1.07	0.071	0.53	0.33-0.84	0.007
Permanent	1.04	0.34-3.15	0.950	0.62	0.39-0.97	0.037
Hypertension	0.85	0.45-1.62	0.622	-	-	-
Diabetes Mellitus	2.46	1.29-4.69	0.006	1.84	1.28-2.65	0.001
Vascular Disease	4.43	1.95-10.06	<0.001	2.32	1.60-3.36	<0.001

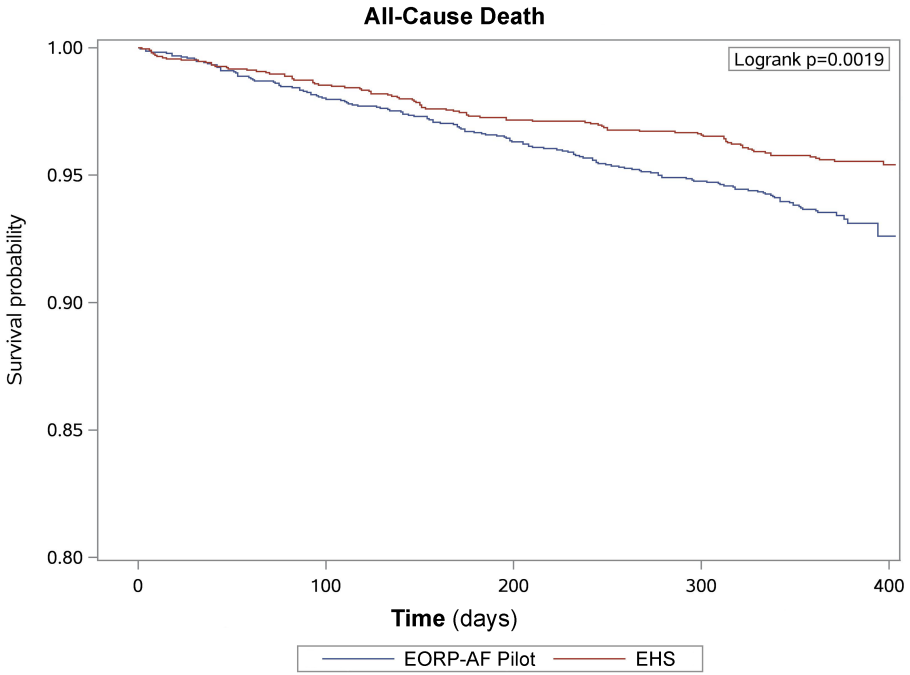
Previous Stroke/TIA	2.14	0.87-5.25	0.096	-	-	-
Chronic Heart Failure	6.29	2.83-13.96	<0.001	4.11	2.64-6.42	<0.001
Any OAC	1.17	0.62-2.19	0.631	-	-	-
EORP-AF Pilot *(vs. EHS)*	2.71	1.70-4.33	<0.001	1.62	1.08-2.45	0.021
All-Cause Death						
Age *(per year)*	1.09	1.06-1.12	<0.001	1.06	1.05-1.08	<0.001
Female Gender	1.19	0.77-1.86	0.432	-	-	-
Type of AF						
First Detected	-	-	-	-	-	-
Paroxysmal	0.44	0.21-0.95	0.037	0.55	0.37-0.81	0.002
Persistent	0.60	0.32-1.13	0.114	0.59	0.41-0.84	0.003
Permanent	2.70	1.12-6.47	0.027	0.81	0.59-1.13	0.221
Hypertension	1.09	0.69-1.72	0.726	-	-	-
Diabetes Mellitus	2.13	1.30-3.50	0.003	1.61	1.22-2.11	<0.001

Vascular disease	2.72	1.59-4.67	<0.001	1.79	1.36-2.34	<0.001
Previous Stroke/TIA	1.56	0.83-2.93	0.163	-	-	-
Chronic Heart Failure	3.48	2.14-5.65	<0.001	2.49	1.88-3.30	<0.001
Any OAC	0.87	0.55-1.39	0.554	-	-	-
EORP-AF Pilot *(vs. EHS)*	1.56	1.15-2.11	0.004	-	-	-

Legend: *Adjusted for age, gender, type of AF, CHA_2DS_2-VASc; †Adjusted for all previous covariates plus use of any OAC; AF= Atrial Fibrillation; CAD= Coronary Artery Disease; CI= Confidence Interval; CV= Cardiovascular; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; HR= Hazard Ratio; MI= Myocardial Infarction; OR= Odds Ratio; OAC= Oral Anticoagulant; PE= Peripheral Embolism; TIA= Transient Ischemic Attack.


CHADS2 ≥2
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
26.1%
57.2%
13.3%
3.4%
p<0.001
9.4%
56.0%
27.6%
7.0%
EORP-AF Pilot
EHS
None Antiplatelet/None OAC
Only Antiplatelet
Only OAC
Antiplatelet + OAC
CHA2DS2-VASc ≥2
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
23.5%
59.8%
13.2%
3.5%
p<0.001
9.1%
55.8%
27.7%
7.4%
EORP-AF Pilot
EHS
None Antiplatelet/None OAC
Only Antiplatelet
Only OAC
Antiplatelet + OAC


Cardiovascular Death
Logrank p <.0001
1.00
0.95
0.90
0.85
0.80
Survival probability
0
100
200
300
400
Time (days)
EORP-AF Pilot
EHS


All-Cause Death
Logrank p=0.0019
1.00
0.95
0.90
0.85
0.80
Survival probability
0
100
200
300
400
Time (days)
EORP-AF Pilot
EHS

Increased Burden of Comorbidities and Risk of Cardiovascular Death in Atrial Fibrillation Patients in Europe Over Ten Years: A Comparison between EORP-AF Pilot and EHS-AF Registries

Supplementary Materials

SUPPLEMENTARY METHODS

Propensity Score Matching

The propensity score matching (PSM) procedure has been performed in order to get two homogenous cohorts to be compared.

The propensity score (PS) has been estimated according to some pre-specified covariates. Four continuous variables (age, body mass index, systolic blood pressure and diastolic blood pressure) and seven categorical variables (gender, type of atrial fibrillation [AF], hypertension, hypercholesterolemia, diabetes mellitus, current smoking, no regular exercise). The score was estimated according to a regression logistic model. Before the model was built some preconditions have been verified:

a. For qualitative variables: Verification of the absence of "Zero cell" in the cross table between the outcome and the covariate. If one "zero cell" is observed, some modalities have to be merged.
b. For categorical variable: Verification of the linear link between study exposure and the covariate (visual verification, using quartiles of the covariate). If none linear link: switch the variable to qualitative variable.
c. Collinearity study: no collinearity between covariate included in the regression logistic.
    - Spearman coefficient between continuous variables (if coefficient > 0.8: collinearity);
    - Chi2 test and phi coefficient if Chi2 test accepted between qualitative variables (if phi coefficient > 0.8: collinearity);
    - ANOVA model (p-value) between 1 continuous variable and 1 qualitative continuous.
    - If 2 covariates were collinear, only one have been selected.

d. Missing value: if more than 20% of observations are missing for one covariate, this covariate was not included in the score.

The matching according to the propensity score has been done as following:

Utilisation of a Greedy Nearest Neighbour matching 1:1 with caliper.

a. Matching on the logit of the PS;
b. 1:1 = matching of 1 patient in the Euro Heart Survey (EHS) and 1 patient in the EURObservation Research Programme in AF (EORP-AF) database. The logit(PS) of EHS must be close to the EORP-AF patient's logit(PS);
c. With caliper = caliper is a limit of the closeness/distance between the two logit(PS) in a matching pair. This caliper is often compute with the distribution of the PS: 0.2*standard deviation of logit(PS).

For this matching, has been use the "%PSMatch_Multi" SAS Macro (implemented according to http://lexjansen.com/nesug/nesug10/ad/ad05.pdf).

The PS matching goal is balance the 11 covariates used in the PS estimation between the two groups.

Table S1: Differing Variables and Reclassifications Made to Fully Merge the Datasets

EORP-AF PILOT	EHS
Baseline Characteristics	
Type of AF - First Detected - Paroxysmal - Persistent *(Obtained merging Persistent with Long-Standing Persistent from original CRF)* - Permanent	Type of AF - First Detected - Paroxysmal - Persistent - Permanent
Cardiomyopathy - Hypertrophic - Dilated - Restrictive - Other *(Obtained merging Hypertensive and Other from original CRF)*	Cardiomyopathy - Hypertrophic - Dilated - Restrictive - Other *(Obtained merging Tachycardiomyopathy, Constrictive, Congestive and Other from original CRF)*
Any Antiplatelet - Aspirin - Clopidogrel - Prasugrel - Ticagrelor - Ticlopidine - Indobufen	Any Antiplatelet - Aspirin - Clopidogrel - Dipyridamole
Any OAC - Vitamin K Antagonist - Dabigatran - Rivaroxaban - Apixaban - Edoxaban	Any OAC - Vitamin K Antagonist
Class III Antiarrhythmic Drugs	Class III Antiarrhythmic Drugs

EORP-AF PILOT	EHS
Baseline Characteristics	
- Amiodarone - Dronedarone - Sotalol	- Amiodarone - Sotalol
1-y Follow-Up Outcomes	
CAD/ACS - ACS - Coronary Intervention - Overt CAD	CAD/ACS - New CAD - CAD Worsening

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CAD= Coronary Artery Disease; CRF= Case Report Form; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; OAC= Oral Anticoagulant.

Table S2: Baseline Characteristics According Original Cohort before Propensity Score Matching

	Not Propensity Score Matching Adjusted			
	Whole Cohort N=8453	**EORP-AF Pilot N=3119**	**EHS N=5334**	**p**
Demographics				
Age *years*, median [IQR]	69.0 [60.0-76.2]	69.0 [62.0-77.0]	68.3 [59.0-75.8]	<0.001
Missing	5	0	5	
Age Classes, n (%)				<0.001
<65 years	3160 (37.4)	1030 (33.0)	2130 (40.0)	
65-74 years	2758 (32.6)	1038 (33.3)	1720 (32.3)	
≥75 years	2530 (29.9)	1051 (33.7)	1479 (27.8)	
Missing	5	0	5	
Age Classes, n (%)				<0.001
<80 years	7230 (85.6)	2565 (82.2)	4665 (87.5)	
≥80 years	1218 (14.4)	554 (17.8)	664 (12.5)	
Missing	5	0	5	
Gender, n (%)				0.108
Female	3510 (41.5)	1260 (40.4)	2250 (42.2)	
Male	4943 (58.5)	1859 (59.6)	3084 (57.8)	
Clinical Characteristics				
Admission Main Reason, n (%)				<0.001
AF	6241 (73.9)	1877 (60.2)	4364 (82.0)	
Other than AF	2202 (26.1)	1242 (39.8)	960 (18.0)	
Missing	10	0	10	
Type of AF, n (%)				<0.001
First Detected	1901 (23.0)	923 (30.3)	978 (18.8)	
Paroxysmal	2325 (28.2)	808 (26.5)	1517 (29.2)	
Persistent	1960 (23.7)	792 (26.0)	1168 (22.4)	
Permanent	2067 (25.0)	526 (17.3)	1541 (29.6)	
Missing	200	70	130	
Symptomatic Status, n (%)				<0.001
Previously Symptomatic	1510 (18.3)	717 (23.0)	793 (15.5)	
Currently Symptomatic	5556 (67.3)	1882 (60.3)	3674 (71.6)	
Never Symptomatic	1184 (14.4)	520 (16.7)	664 (12.9)	
Missing	203	0	203	
SBP *mmHg*, median [IQR]	130 [120-150]	130 [120-142]	133 [120-150]	<0.001
Missing	74	0	74	

DBP *mmHg*, median [IQR]	80 [70-90]	80 [70-87]	80 [70-90]	<0.001
Missing	76	2	74	
BMI kg/m^2, median [IQR]	27.1 [24.6-30.2]	27.4 [24.7-30.7]	27.0 [24.5-30.1]	<0.001
Missing	535	122	413	
Risk Factors				
Diabetes Mellitus, n (%)	1601 (19.0)	638 (20.6)	963 (18.1)	0.005
Missing	22	18	4	
Hypercholesterolemia, n (%)	3335 (40.2)	1474 (48.4)	1861 (35.4)	<0.001
Missing	156	73	83	
Current Smoking, n (%)	989 (11.9)	337 (11.1)	652 (12.4)	0.084
Missing	176	93	83	
No Regular Exercise, n (%)	6230 (78.5)	2134 (74.0)	4096 (81.1)	<0.001
Missing	519	237	282	
Alcohol Excess*, n (%)	498 (6.4)	226 (7.8)	272 (5.6)	<0.001
Missing	713	214	499	
Cardiovascular Comorbidities				
Hypertension, n (%)	5558 (65.9)	2194 (70.7)	3364 (63.1)	<0.001
Missing	22	16	6	
CAD, n (%)	2607 (32.5)	977 (36.3)	1630 (30.6)	<0.001
Missing	434	431	3	
Previous MI, n (%)	603 (7.5)	439 (16.3)	164 (3.1)	<0.001
Missing	448	431	17	
Previous PCI/CABG, n (%)	1071 (13.4)	459 (17.1)	612 (11.5)	<0.001
Missing	454	431	23	
Stable Angina, n (%)	1393 (17.4)	365 (13.6)	1028 (19.4)	<0.001
Missing	469	431	38	
Chronic Heart Failure, n (%)	3060 (37.0)	1411 (47.5)	1649 (31.1)	<0.001
Missing	187	147	40	
Valvular Disease, n (%)	3211 (39.3)	1860 (63.4)	1351 (25.7)	<0.001
Missing	273	186	87	
Cardiomyopathy, n (%)	1586 (19.3)	999 (33.8)	587 (11.1)	<0.001
Missing	227	167	60	
Dilated Cardiomyopathy, n (%)	661 (8.0)	340 (11.5)	321 (6.1)	<0.001
Missing	224	164	60	
Hypertrophic Cardiomyopathy, n (%)	221 (2.7)	115 (3.9)	106 (2.0)	<0.001
Missing	221	161	60	
Restrictive Cardiomyopathy, n (%)	22 (0.3)	15 (0.5)	7 (0.1)	0.002

Missing	217	157	60	
Other Cardiomyopathy, n (%)	775 (9.4)	626 (21.2)	149 (2.8)	<0.001
Missing	231	171	60	
Other Cardiac Disease, n (%)	695 (8.5)	239 (8.3)	456 (8.5)	0.684
Missing	235	235	0	
Previous Stroke/TIA, n (%)	872 (10.3)	339 (11.0)	533 (10.0)	0.164
Missing	25	24	1	
Any Thromboembolism, n (%)	1060 (12.7)	405 (13.1)	655 (12.4)	0.376
Missing	84	24	60	
PAD, n (%)	738 (9.0)	328 (11.0)	410 (7.8)	<0.001
Missing	242	144	98	
Vascular Disease, n (%)	1248 (15.9)	692 (26.6)	556 (10.6)	<0.001
Missing	623	516	107	
Previous Bleeding, n (%)	358 (4.3)	181 (5.8)	177 (3.3)	<0.001
Missing	51	24	27	
Non-Cardiovascular Comorbidities				
COPD, n (%)	1052 (12.6)	339 (11.0)	713 (13.5)	<0.001
Missing	77	33	44	
Renal Disease, n (%)	717 (8.5)	408 (13.1)	309 (5.8)	<0.001
Missing	35	12	23	
Thyroid Disease, n (%)	815 (10.4)	305 (10.2)	510 (10.6)	0.543
Missing	649	122	527	
Malignancy, n (%)	448 (5.4)	163 (5.4)	285 (5.4)	0.868
Missing	168	74	94	

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; CABG= Coronary Artery By-pass Graft; CAD= Coronary Artery Disease; COPD= Chronic Obstructive Pulmonary Disease; DBP= Diastolic Blood Pressure; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; IQR= interquartile feeling; MI= Myocardial Infarction; PAD= Peripheral Arterial Disease; PCI= Percutaneous Coronary Intervention; SBP= Systolic Blood Pressure; TIA= Transient Ischemic Attack; *≥8 units per week.

Table S3: Differences in Atrial Fibrillation Clinical Management before Propensity Score Matching

	Not Propensity Score Matching Adjusted			
	Whole Cohort N=8453	**EORP-AF Pilot N=3119**	**EHS N=5334**	**p**
Pharmacological Conversion, n (%)				0.002
Missing	1889 (22.5)	750 (24.3)	1139 (21.4)	
	46	34	12	
Electrical Conversion, n (%)	1532 (18.2)	612 (19.9)	920 (17.3)	0.003
Missing	52	39	13	
Catheter Ablation, n (%)	320 (3.8)	186 (6.0)	134 (2.5)	<0.001
Missing	23	10	13	
Pacemaker Implantation, n (%)	338 (4.0)	134 (4.3)	204 (3.8)	0.295
Missing	23	4	19	
ICD Implantation, n (%)	48 (0.6)	21 (0.7)	27 (0.5)	0.325
Missing	24	7	17	
AF Surgery, n (%)	17 (0.2)	9 (0.3)	8 (0.2)	0.171
Missing	23	6	17	

Legend: AF= Atrial Fibrillation; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; ICD= Implantable Cardioverter Defibrillator.

Table S4: Univariate Logistic Analysis for Atrial Fibrillation as Reason for Admission

	OR	95% CI	p
Age (*per year*)	0.96	0.95-0.97	<0.001
Chronic Heart Failure	0.25	0.20-0.31	<0.001
Hypertension	0.74	0.61-0.89	0.002
Diabetes Mellitus	0.62	0.50-0.76	<0.001
Stroke/TIA	0.63	0.48-0.83	0.001
Vascular Disease	0.21	0.16-0.27	<0.001
Female Gender	0.92	0.77-1.09	0.315
Previous Bleeding Event	0.35	0.23-0.53	<0.001
Renal Disease	0.20	0.15-0.28	<0.001
COPD	0.63	0.50-0.80	<0.001
EORP-AF Pilot (*vs. EHS*)	0.31	0.27-0.36	<0.001

Legend: CI= Confidence Interval; COPD= Chronic Obstructive Pulmonary Disease; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; OR= Odds Ratio; TIA= Transient Ischemic Attack.

Table S5: Thromboembolic Risk Patterns before Propensity Score Matching

	Not Propensity Score Matching Adjusted			
	Whole Cohort N=8453	**EORP-AF Pilot N=3119**	**EHS N=5334**	**p**
$CHADS_2$, mean (SD)	1.7 (1.3)	1.9 (1.3)	1.6 (1.2)	<0.001
$CHADS_2$, median [IQR]	2 [1-2]	2 [1-3]	1 [1-2]	<0.001
$CHADS_2$ Classes, n (%)				<0.001
0	1390 (16.4)	392 (12.6)	998 (18.7)	
1	2671 (31.6)	846 (27.1)	1825 (34.2)	
≥2	4392 (52.0)	1881 (60.3)	2511 (47.1)	
CHA_2DS_2-VASc, mean (SD)	2.9 (1.7)	3.2 (1.8)	2.8 (1.7)	<0.001
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	3 [2-4]	3 [1-4]	<0.001
CHA_2DS_2-VASc Classes, n (%)				<0.001
Low Risk	912 (10.8)	251 (8.0)	661 (12.4)	
Moderate Risk	1005 (11.9)	320 (10.3)	685 (12.8)	
High Risk	6536 (77.3)	2548 (81.7)	3988 (74.8)	

Legend: EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; IQR= Interquartile Range; SD= Standard Deviation.

Table S6: Pharmacological Treatments after Admission/Consultation before Propensity Score Matching

	Not Propensity Score Matching Adjusted			
	Whole Cohort N=8453	**EORP-AF Pilot N=3119**	**EHS N=5334**	**p**
Antithrombotic Therapy				
Aspirin, n (%)	2502 (30.1)	957 (30.8)	1545 (29.7)	0.312
Missing	139	7	132	
Any Antiplatelet, n (%)	2747 (33.0)	1065 (34.2)	1682 (32.3)	0.076
Missing	139	7	132	
Vitamin K Antagonist, n (%)	5592 (67.3)	2228 (71.6)	3364 (64.8)	<0.001
Missing	150	9	141	
Any OAC, n (%)	5851 (70.5)	2487 (80.0)	3364 (64.8)	<0.001
Missing	151	10	141	
Any Antithrombotic, n (%)	7726 (92.9)	2964 (95.2)	4762 (91.5)	<0.001
Missing	138	6	132	
Any Antiplatelet + OAC, n (%)	1005 (12.1)	625 (20.1)	380 (7.3)	<0.001
Missing	151	10	141	
Other Antithrombotic, (%)	132 (1.6)	36 (1.2)	96 (1.8)	0.015
Missing	139	7	132	
Antiarrhythmic Drugs				
Class Ia, n (%)	21 (0.3)	1 (0.0)	20 (0.4)	0.002
Missing	138	6	132	
Class Ic, n (%)	813 (9.8)	317 (10.2)	496 (9.5)	0.335
Missing	138	6	132	
Class III, n (%)	2424 (29.2)	804 (25.8)	1620 (31.1)	<0.001
Missing	139	7	132	
Amiodarone, n (%)	1946 (23.4)	663 (21.3)	1283 (24.7)	<0.001
Missing	138	6	132	
Any Antiarrhythmic, n (%)	3264 (39.3)	1111 (35.7)	2153 (41.4)	<0.001
Missing	139	7	132	
Other Medications				
Beta-Blockers, n (%)	4425 (53.2)	2159 (69.4)	2266 (43.6)	<0.001
Missing	142	10	132	
Digoxin, n (%)	2032 (24.4)	613 (19.7)	1419 (27.3)	<0.001
Missing	139	7	132	
Non-DHP CCB, n (%)	668 (8.0)	190 (6.1)	478 (9.2)	<0.001
Missing	140	8	132	

ACE Inhibitors, n (%)	3909 (47.0)	1344 (43.2)	2565 (49.3)	<0.001
Missing	141	9	132	
ARBs, n (%)	1349 (16.2)	677 (21.8)	672 (12.9)	<0.001
Missing	140	8	132	
Statins, n (%)	2847 (34.3)	1532 (49.3)	1315 (25.3)	<0.001
Missing	144	12	132	
Antidiabetic Drugs, n (%)	1266 (15.2)	557 (17.9)	709 (13.6)	<0.001
Missing	138	6	132	

Legend: ACE= Angiotensin Converting Enzyme; ARB= Angiotensin Receptor Blockers; CCB= Calcium-Channel Blockers; DHP= Dihydropyridine; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; OAC= Oral Anticoagulant.

Table S7: Outcomes at 1-year Follow-Up before Propensity Score Matching

	Not Propensity Score Matching Adjusted			
	Whole Cohort N=7757	**EORP-AF Pilot N=2785**	**EHS N=4972**	**p**
Major Adverse Events				
Stroke/TIA, n (%)	154 (2.4)	22 (1.0)	132 (3.2)	<0.001
Stroke/TIA/PE, n (%)	170 (2.7)	25 (1.1)	145 (3.6)	<0.001
CAD/ACS, n (%)	308 (4.7)	85 (3.7)	223 (5.3)	0.003
Any Bleeding, n (%)	94 (1.4)	25 (1.1)	69 (1.6)	0.071
CV Death, n (%)	201 (3.0)	107 (4.1)	94 (2.3)	<0.001
CV Death - Stroke/TIA - Any Bleeding, n (%)	423 (6.6)	153 (6.5)	270 (6.6)	0.802
CV Death - CAD/ACS, n (%)	494 (7.6)	192 (8.0)	302 (7.4)	0.434
All-Cause Death, n (%)	407 (5.9)	167 (6.3)	240 (5.7)	0.289
Readmissions				
Readmission for AF, n (%)	1375 (28.2)	411 (18.0)	964 (37.1)	<0.001
Readmission for Other CV Reasons, n (%)	776 (15.7)	271 (11.7)	505 (19.2)	<0.001
Readmission for Non-CV Reasons, n (%)	756 (14.8)	288 (12.5)	468 (16.7)	<0.001

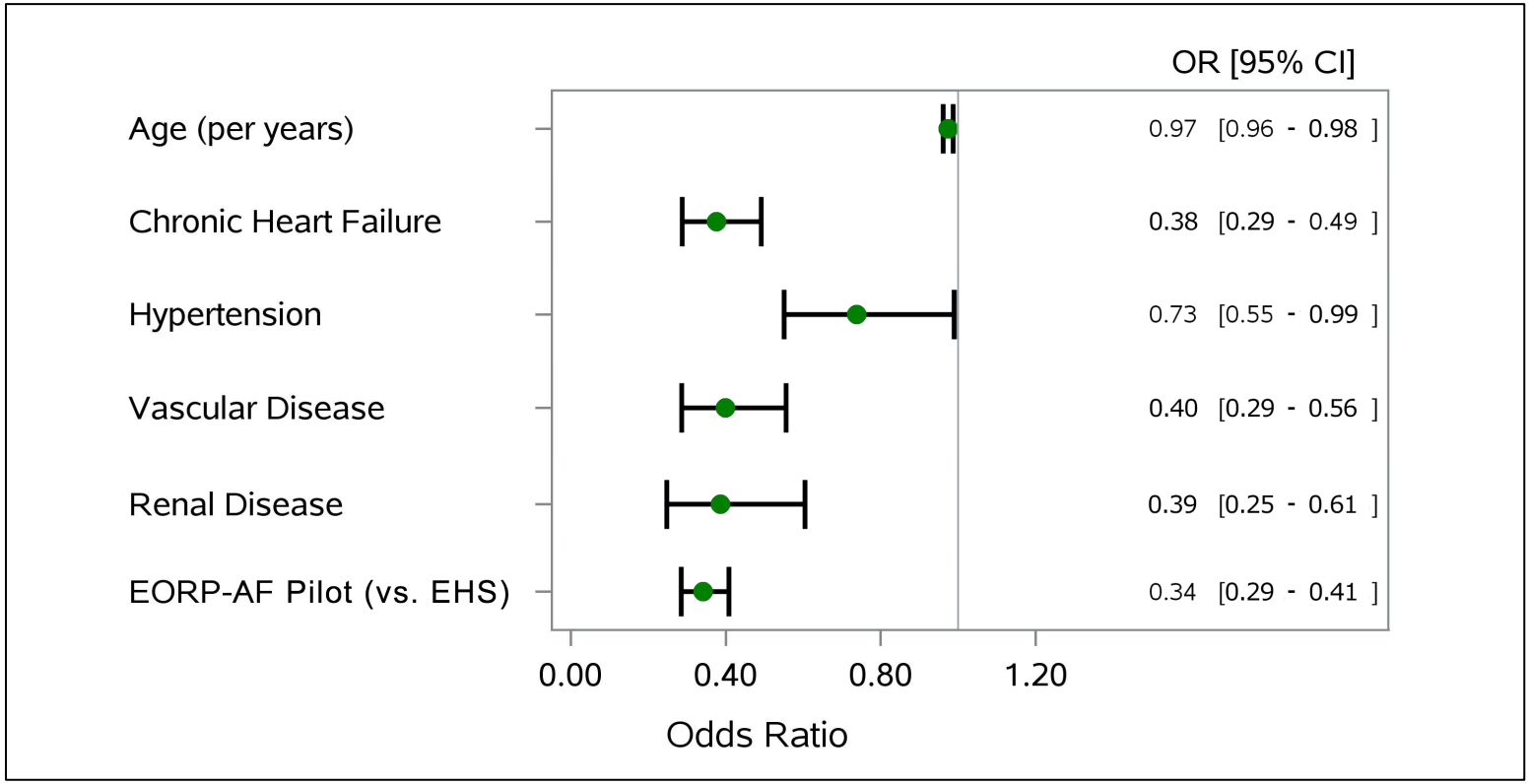
Legend: AF= Atrial Fibrillation; ACS= Acute Coronary Syndrome; CAD= Coronary Artery Disease; CV= Cardiovascular; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; PE= Peripheral Embolism; TIA= Transient Ischemic Attack.

Table S8: Outcomes at 1-year Follow-Up after Propensity Score Matching

	EORP-AF Pilot N=2335	**EHS N=2433**	**p**	**Std. Diff.**
Major Adverse Events				
Stroke/TIA, n (%)	17 (0.9)	67 (3.3)	<0.001	0.17
Stroke/TIA/PE, n (%)	19 (1.0)	70 (3.5)	<0.001	0.17
CAD/ACS, n (%)	72 (3.7)	123 (5.9)	<0.001	0.11
Any Bleeding, n (%)	23 (1.2)	36 (1.7)	0.134	0.05
CV Death, n (%)	93 (4.3)	41 (2.1)	<0.001	0.13
CV Death - Stroke/TIA - Any Bleeding, n (%)	132 (6.5)	131 (6.5)	0.982	0.00
CV Death - CAD/ACS, n (%)	165 (8.1)	155 (7.7)	0.707	0.01
All-Cause Death, n (%)	146 (6.5)	110 (5.3)	0.090	0.05
Readmissions				
Readmission for AF, n (%)	337 (17.4)	479 (39.0)	<0.001	0.50
Readmission for Other CV Reasons, n (%)	237 (12.1)	245 (20.1)	<0.001	0.22
Readmission for Non-CV Reasons, n (%)	240 (12.2)	240 (18.3)	<0.001	0.17

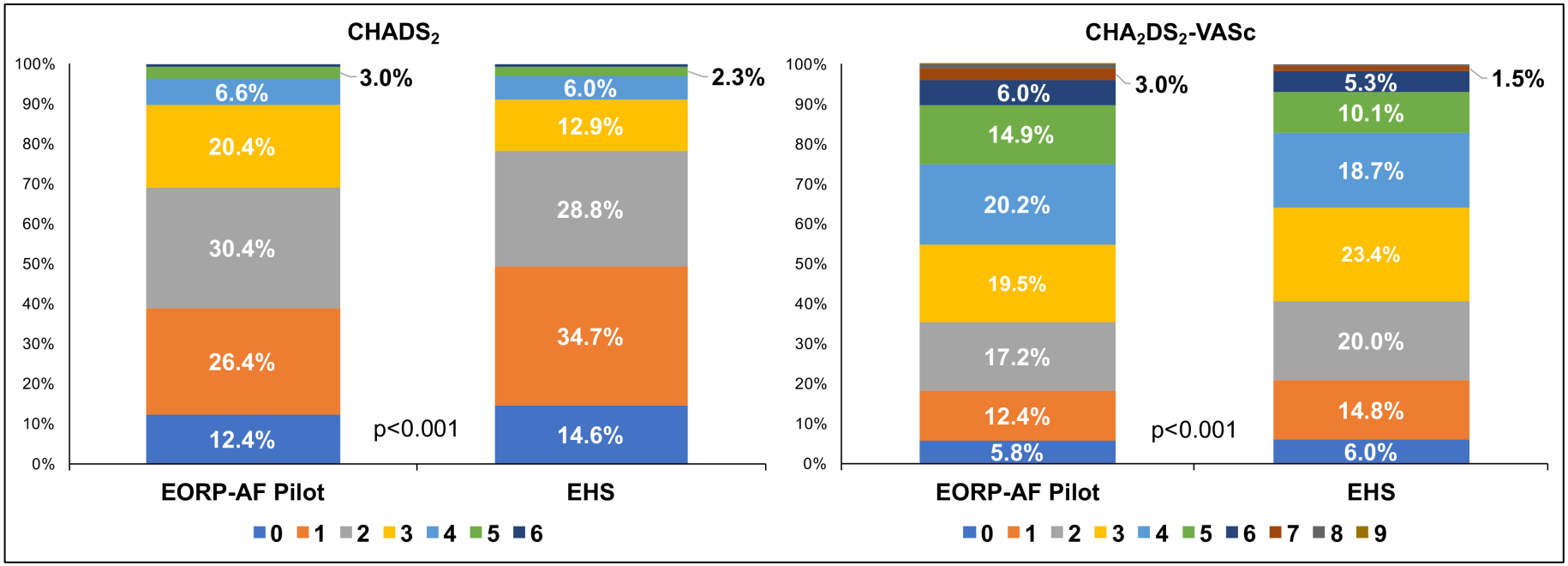
Legend: AF= Atrial Fibrillation; ACS= Acute Coronary Syndrome; CAD= Coronary Artery Disease; CV= Cardiovascular; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; PE= Peripheral Embolism; TIA= Transient Ischemic Attack

Figure S1: Multivariate Logistic Analysis for AF as Main Reason for Admission



Legend: CI= Confidence Interval; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; OR= Odds Ratio.

Figure S2: Distribution of $CHADS_2$ and CHA_2DS_2-VASc Risk Scores between the Two Cohorts



Legend: CI= Confidence Interval; EHS= European Heart Survey; EORP-AF= EURObservational Research Program Atrial Fibrillation; OR= Odds Ratio.

Appendix

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