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Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general registry

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ABSTRACT

Background: Contemporary European data regarding patients with atrial fibrillation (AF) allow us to assess the use of oral anticoagulants (OACs) and long-term outcomes.
Methods: Patients with AF presenting to cardiologists in 9 European Society of Cardiology participating countries were enrolled and followed-up for 3-years.
Results: Among the 2119 patients (40.4% female; mean age 69 ± 11 years) the prevalent types of AF at baseline were first-detected (30.5%) and paroxysmal AF (27.0%).
The composite of stroke/TIA/peripheral embolism/all-cause death at 3-years occurred in 18.2%, with first detected AF and permanent AF reporting the highest event rates (22.5% and 27.3%, respectively; $p < 0.0001$). Age, diabetes mellitus, heart failure, restrictive cardiomyopathy, chronic kidney disease and no physical activity were significant predictors of all-cause death. Paroxysmal and persistent AF patients were more likely to be hospitalised than other types of AF (34.1% and 37.9%, $p < 0.0001$).
At follow-up, OAC drugs were used in 80.1% of patients, with non-vitamin K antagonists (NOACs) accounting for 24.3% of patients. OAC treatment at follow-up visits changed throughout time, with a shift from VKA to NOACs reported in 5.4% of the cases, while the reverse shift (from NOACs to VKA) occurred in 8.6%. Discontinuation of OAC was recorded in while in 9.5% of visits.
Conclusions: Patients outcomes at 3-years follow-up differ according to type of AF at baseline, with worse outcomes in patients presenting with first-detected or permanent AF. Changes in the type of OAC use with shifts from NOACs to VKA and vice-versa are not uncommon, as were interruptions of OAC.
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1. Introduction

Atrial fibrillation (AF) is common in clinical practice, and is particularly frequent in the elderly [1,2]. AF is associated with adverse outcomes, with a significantly increased risk of stroke, death and heart failure [3]. Oral anticoagulant (OAC) therapy significantly reduces the risk of AF-related thromboembolic events and mortality, and therefore

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should be recommended in every patient at risk, as suggested by the guidelines [1].

In recent years the availability of non-vitamin K antagonist oral anticoagulants (NOACs) as an effective and safer alternative to vitamin K antagonist (VKA) offered new opportunities for stroke prevention in AF patients, but there is the need to assess the actual implementation of these evidence-based therapies in "real-world" clinical practice and the maintenance of OAC over time.

The European Society of Cardiology (ESC) supported the EURObservational Research Programme in AF (EORP-AF) Pilot Registry in order to evaluate management and outcomes of AF patients prospectively enrolled in a sample of European countries [4–6].

The main aim of this paper is to report about antithrombotic treatment changes, clinical management and mortality outcomes at 3-years follow-up, in relation to clinical presentation of patients enrolled in the EORP-AF Pilot General Registry.

2. Methods

Details about study design, baseline and 1-year and 2-years follow-up from the EORP-AF Pilot General Registry have been previously published. The registry started enrolment in February 2012 and was completed in March 2013 [4–6]. The study population comprised of consecutive AF inpatients and outpatients, enrolled in 67 centres in 9 countries, treated by a cardiologist. All 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 regulations. Enrolment was based on electrocardiogram recording of AF, with the qualifying arrhythmia episode should have occurred no later than 12 months before enrolment. The Ethics Committee of all participating centres approved the study protocol and the study was conducted in agreement with the principles of the Declaration of Helsinki. All patients provided written informed consent.

In order to optimize the rate of valid and available follow-up and to obtain reliable data about long-term observation, only those enrolling centres that were able to keep active throughout the study and to provide follow-up data for at least 75% of patients originally enrolled in the study were included in the 3-years follow-up analysis. Stroke risk was categorized according to the CHA_2DS_2-VASc score [7], while bleeding risk was categorized using the HAS-BLED score [8]. Types of AF have been defined as first detected AF, paroxysmal AF, persistent AF, long-standing AF and permanent AF according to the 2010 ESC Clinical Guidelines for management of AF patients [9]. Type of AF was established according to the qualifying arrhythmia episode, as registered by a 12 lead ECG, 24 h ECG Holter or other electrocardiographic documentation, as well as clinical history and documented changes to 12 lead ECG.

Outcomes considered during follow-up observation were: stroke, transient ischemic attack (TIA), peripheral embolism, acute coronary syndrome, coronary intervention, cardiac arrest, peripheral embolism, pulmonary embolism, any bleeding, cardiovascular (CV) death and all-cause death. A composite outcome of stroke/TIA/peripheral embolism/all-cause death was also considered.

2.1. Statistical analysis

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean ± standard deviation (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 counts and percentages (without missing values if applicable). Among–group comparisons were made using a chi-square test or a Fisher's exact test if any expected cell count was <5. For qualitative variables with more than two possibilities, the Monte Carlo estimates of exact *p*-values were used.

Plots of Kaplan-Meier curves for time to all-cause death in relation to type of AF were drafted, with survival distribution compared using the log-rank test.

A logistic regression analysis was performed to assess the clinical factors associated with the switch of OAC treatment or the switch from OAC treatment to another antithrombotic treatment. After univariate analysis, a multivariate regression model was constructed. A significance level of 0.05 was required to allow a variable into the model (SLENTRY = 0.05) and a significance level of 0.05 was required for a variable to stay in the model (SLSTAY = 0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal.

A stepwise multiple Cox regression was used to determine the predictors of all-cause death including into the model all the candidate variables (variables with $p < 0.10$ in univariate). A significance level of 0.05 was required to allow a variable into the model (SLENTRY = 0.05) and a significance level of 0.05 was required for a variable to stay in the model (SLSTAY = 0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal. A two-sided *p*-value of <0.05 was considered as statistically significant. All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

A total of 2119 patients (40.4% female; mean age 69 ± 11 years) from the active centres were retrieved for this analysis. Mean follow-up time was 942 ± 344 days, with a median (IQR) of 1089 (973–1112) days, with valid follow-up data available for 91.4 ± 1.6% of patients (median [IQR]: 96.5% [84–100%]).

A comparison between the 2119 patients enrolled in centres that participated to 3-years follow-up of EORP-AF Pilot General Registry and the 930 patients enrolled in centres who did not participate is shown in Table S1. Patients from centres involved in the 3-years follow-up were slightly older, had more frequently an asymptomatic AF and reported some differences in baseline comorbidities (Table S1); despite that, overall the patients reported a similar baseline clinical profile both for stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED) risk.

The cohort considered for this analysis was differentially burdened by the different types of AF. The most prevalent type at baseline was first-detected AF (30.5%), followed by paroxysmal (27.0%) and persistent (21.0%) AF, while long-standing persistent AF and permanent AF accounted for 5.6% and 15.8%, respectively. Patients with paroxysmal AF were younger and with a lower burden of associated diseases and risk factors (Table S2).

3.1. Outcomes at 3-years follow-up observation

Follow-up data on 2119 patients considered in the 3-years follow-up phase according to type of AF at baseline are shown in Table 1, Panel A.

Hospital readmissions related to AF (or atrial tachyarrhythmias) occurred in more than a quarter of patients, with paroxysmal and persistent AF patients were more likely to be admitted than other types of AF (34.1% and 37.9%, respectively; $p < 0.0001$). Hospital admissions for non-cardiovascular causes were not negligible, accounting for 22–27% of the cases of hospitalization without any differences according to type of AF at baseline.

After 3-years follow-up observation all-cause death occurred in 15.0% of patients, with first detected AF (19.8%) and permanent AF (22.1%) patients reporting the higher proportion of all-cause death compare to other types of AF ($p < 0.0001$). One out of three all-cause death events (36.6%) were due to cardiac or vascular reasons, with almost half of patients with permanent AF dying from cardiovascular causes, with another quarter of patients reporting a non-cardiovascular related death. The composite of stroke/TIA/peripheral embolism/all-cause death at 3-years occurred in 18.2%, with first detected AF and permanent AF reporting the highest event rates (22.5% and 27.3%, respectively; $p < 0.0001$).

Kaplan-Meier curves for occurrence of all-cause death [Fig. 1] showed that survival differed significantly according to the type of AF, with the lowest survival for first detected and permanent AF ($p < 0.0001$) patients.

After univariate analysis (Table S3), a multivariate Cox regression analysis was performed to identify clinical factors significantly associated with occurrence of all-cause death at 3-years follow-up (Table 1, Panel B). Increasing age, diabetes mellitus, chronic heart failure, restrictive cardiomyopathy and chronic kidney disease, as well as the absence of any physical activity were all associated with an increased risk of death. Compared to first detected AF, those with permanent and paroxysmal AF had a lower risk for all-cause death (odds ratio [OR]: 0.702, 95% confidence interval [CI]: 0.520–0.946 and OR: 0.485, 95% CI: 0.334–0.705, respectively).

3.2. Antithrombotic treatment at 3-years follow-up

After 3-years follow-up, OAC were prescribed in 80.1%, while antiplatelets alone were prescribed to 19.8% of patients (Table S4). Among those patients treated with OAC, a vitamin K antagonist (VKA)

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