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'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme–Atrial Fibrillation (EORP-AF) General Pilot Registry

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Aims Atrial fibrillation (AF) has different presentations (first detected, paroxysmal, persistent, permanent), with uncertain impact on outcome. The aim of this study was to investigate clinical presentation, management, and outcome of paroxysmal and non-paroxysmal AFs within the EURObservational Research Programme–Atrial Fibrillation General Pilot Registry.

Methods and results Overall 2589 patients with available 1-year follow-up data were evaluated according to AF type. Patients with paroxysmal AF (26.8%) were younger, had lower prevalence of heart disease (particularly valvular), and major co-morbidities, as well as lower $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. Patients with first-detected AF (29.9%) had characteristics similar to persistent AF patients (25.9%), but lower use of oral anticoagulants. Patients with permanent AF represented 17.4% of the cohort. At 1 year, the rate of stroke/transient ischaemic attack and thromboembolism was low (0.6–1.0%) and did not differ between paroxysmal and non-paroxysmal AFs. All-cause mortality was higher in non-paroxysmal vs. paroxysmal AF (log rank test, $P = 0.0018$). Using a multivariable Cox model, non-paroxysmal AF was not an independent predictor of death during follow-up. Independent predictors of death were age, chronic heart failure, chronic kidney disease, diabetes, restrictive cardiomyopathy, and physical activity.

Conclusion In this 'real-world' contemporary observational registry, patients with non-paroxysmal AF had a worse outcome, in terms of all-cause mortality, which was related to a more severe clinical profile. The risk of stroke at 1 year was relatively low, perhaps reflecting the high rates of anticoagulation use in this cohort.

Keywords Atrial fibrillation • Mortality • Prognosis • Registry • Stroke

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What's new?

- The relationship between the type of atrial fibrillation (AF) and outcomes, in terms of death or stroke, has been object of several studies, performed in different patient settings and with variable degrees of patient selection.
- Our analysis was performed in a 'real-world' cohort of AF patients prospectively enrolled in the EURObservational Research Programme–Atrial Fibrillation General Pilot Registry, with no exclusion of co-morbidities (i.e. chronic renal disease) and also including some patients with valvular AF.
- In this 'real-world' contemporary observational registry, patients with non-paroxysmal AF had a worse outcome, in terms of all-cause mortality, which was related to a more severe clinical profile.
- In this cohort, the risk of stroke at 1 year was relatively low, perhaps reflecting the current high rates of anticoagulants use.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its incidence and prevalence are increasing worldwide.[1] Atrial fibrillation may be related to various clinical conditions or being isolated and may have different clinical presentations that have been classified as first-diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF.[1]

Atrial fibrillation is associated with an increased risk of stroke and thromboembolic events.[1] There is growing interest on assessing if the risk of stroke and embolic events, as well as the risk of death, is related to the type of AF, in terms of clinical presentation and arrhythmia duration. An analysis from the Stroke Prevention in Atrial Fibrillation (SPAF) trial, published 20 years ago, showed that in patients treated with aspirin the risk of stroke did not differ in patients with intermittent vs. permanent AF, and this has been the basis for the recommendations of consensus guidelines on thromboembolic prophylaxis.[2] These data are consistent with a subsidy of the ACTIVE W trial performed on patients treated with warfarin or combined antiplatelet therapy.[3] However, an analysis from the SPORTIF trials found lower stroke rates in paroxysmal AF compared with non-paroxysmal AF.[4] Also, more recent data from randomised trials on patients with non-valvular AF show a lower risk of stroke in paroxysmal AF when compared with persistent or permanent AF.[5–7]

Randomized clinical trials that evaluated non-vitamin K antagonist oral anticoagulants (NOACs) vs. warfarin in the setting of so-called 'non-valvular AF'[1,8,9] had specific exclusion criteria such as renal dysfunction (i.e. estimated creatinine clearance of <30 mL/min), anaemia, thrombocytopenia, conditions at increased risk of bleeding, and expected life expectancy shorter than the duration of the trial, thus leading to exclusion of more complex and frail patients.[9] This emphasizes the need for 'real-world' registries evaluating treatments for stroke prevention in relatively unselected patients with AF.

The objective of this article is to investigate the relationships between the type of AF, related to clinical presentation and arrhythmia duration and 1-year outcomes, in terms of stroke and mortality in 'real-world' European AF patients prospectively enrolled in the EURObservational Research Programme–Atrial Fibrillation (EORP-AF) General Pilot Registry[10–15] enrolling consecutive in- and out-patients presenting with documented AF to cardiologists, in participating centres from nine European countries.

Methods

The methods and baseline data from the EORP-AF Pilot General Registry have previously been published.[10] As previously reported,[10] an electrocardiogram (ECG) diagnosis confirming AF was necessary for enrolment in EORP-AF, and the qualifying episode of AF should have occurred within the last year (patients did not need to be in AF at the time of enrolment). The registry was commenced in early 2012. One-year follow-up phase ('pilot phase' or Phase 1) data were focused on patients from nine countries [for a broad representation of European Society of Cardiology (ESC) member countries] recruited into this dataset.[10]

In brief, the registry population comprised consecutive in- and out-patients presenting with AF to cardiologists, enrolled in 67 centres in 9 countries.[10] Consecutive patients were screened at the time of their presentation to a cardiologist (hospital or medical centre), and potential participants were approached to obtain written informed consent according to local rules. Enrolment required ECG-confirmed diagnosis of AF, with a qualifying episode of AF documented in the 12 months prior to enrolment.

In this registry, the type of AF was classified according to European Guidelines[1] and was investigator-defined. In the present analysis, patients with persistent AF and long-standing persistent AF were considered together. Patients presenting with persistent AF, but with history of paroxysmal AF, were classified as patients with persistent AF.

We recorded outcomes for all-cause mortality, cardiovascular death, thromboembolism (TE), and bleeding. Thromboembolism refers to stroke, transient ischaemic attack (TIA), acute coronary syndrome (ACS), coronary intervention, cardiac arrest, peripheral embolism, and pulmonary embolism—each of these as recorded by the investigator, in this 'real-world' observational registry.

Statistical analyses

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean $\pm$ SD and/or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a χ^2 test or a Fisher's exact test if any expected cell count was less than five. For qualitative variables with more than two possibilities, the Monte Carlo estimates of the exact *P*-values are used.

Plots of the Kaplan–Meier curves for time to all-cause death in relation to AF-type subgroup were performed. The survival distributions have been compared using the log rank test. A stepwise Cox model was used to determine the predictors of death including into the model all the candidate variables (variables with $P < 0.10$ in univariate, except those with a high number of missing data). A significance level of 0.05 is required to allow a variable into the model (SLENTRY $= 0.05$), and a significance level of 0.05 is 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, and in the final model, proportional hazard assumption was tested by the Kolmogorov-type supremum test.

Odds ratios [95% confidence intervals (CIs)] comparing the categories of baseline AF were derived from a logistic regression model. Odds ratios are reported unadjusted first and then after adjustment for age,

Table 1 Patient characteristics at enrolment according to the type of AF

	First-detected AF (n = 774)	Paroxysmal AF (n = 693)	Persistent AF (n = 671)	Permanent AF (n = 451)	P-value
Demographics					
Age in years, median (IQR)	70 (61–77)	67 (60–75)	69 (62–76)	74 (66–81)	<0.0001
Age ≥ 75 years (%)	34.4	25.8	29.4	48.6	<0.0001
Age > 65 years (%)	63.7	55.8	62.3	76.7	<0.0001
Age ≤ 50 years (%)	8.9	8.1	5.4	2.4	<0.0001
Female gender (%)	35.8	41.6	39.5	42.4	0.0651
Concomitant disease (%)					
Lone AF	4.5	6.8	3.1	0.2	<0.0001
Coronary artery disease	35.6	33.9	35.6	40.9	0.1426
Myocardial infarction	48.8	43.6	35.3	48.5	0.0189
PTCA/CABG	56.3	47.5	30.9	53.3	<0.0001
Stable angina	30.4	36.8	42.0	38.2	0.0797
Chronic heart failure	45.2	29.1	52.1	62.9	<0.0001
of whom NYHA III/IV	42.9	27.4	42.6	49.5	<0.0001
Valvular heart disease	65.0	46.4	67.1	77.4	<0.0001
Dilated cardiomyopathy	10.4	4.3	15.2	17.7	<0.0001
Hypertrophic cardiomyopathy	2.7	3.1	6.1	3.4	0.0064
Restrictive cardiomyopathy	0.7	0	0.8	1.1	0.0443[a]
Hypertensive heart disease	15.5	18.5	27.1	17.5	<0.0001
Other cardiac disease	7.8	7.1	9.6	9.7	0.2701
Chronic obstructive pulmonary disease	13.3	7.5	11.9	14.1	0.0009
Hyperthyroidism	1.9	3.3	3.6	4.1	0.1085
Hypothyroidism	8.3	6.3	7.1	6.7	0.4712
Chronic kidney disease	15.5	8.0	11.7	19.1	<0.0001
Peripheral vascular disease	12.7	8.4	14.3	11.2	0.0089
Cardiovascular risk factors (%)					
Diabetes	21.1	16.8	20.1	25.7	0.0036
Hypertension	70.8	69.6	73.0	69.2	0.4605
Current smoker	12.0	12.6	11.3	8.3	0.1504
Hypercholesterolaemia	48.4	46.5	49.8	47.4	0.6517
Alcohol ≥ 2–3/day	10.6	4.9	9.3	9.0	0.0012
Physical activity (%)					
None	42.0	32.0	34.3	51.3	<0.0001
Occasional	31.8	38.0	37.7	29.3	
Regular	22.8	23.1	23.5	15.2	
Intense	3.4	7.0	4.5	4.2	
Co-morbidities (%)					
Ischaemic thromboembolic complications	13.3	10.6	13.0	14.9	0.1734
Previous stroke	6.7	4.6	5.8	8.0	0.1125
Previous TIA	3.5	3.4	4.4	5.3	0.3011
Haemorrhagic events	6.7	5.1	5.3	9.6	0.0119
Haemorrhagic stroke	3.8	2.9	5.7	2.3	0.9426[a]
Major bleeding	23.1	28.6	22.9	32.6	0.6984
Malignancy	5.8	4.8	5.5	4.3	0.6249
Symptoms (%)					
EHRA I	43.3	36.9	26.2	65.9	<0.0001
EHRA II–IV	56.7	63.1	73.8	34.1	
$CHADS_2$ score					
Mean score ± SD	1.9 ± 1.3	1.6 ± 1.2	1.9 ± 1.2	2.3 ± 1.3	<0.0001
Two or more (%)	59.4	47.3	61.7	74.1	<0.0001
CHA_2DS_2-VASc score					
Mean score ± SD	3.2 ± 1.9	2.8 ± 1.8	3.2 ± 1.8	3.8 ± 1.7	<0.0001

Table 1 *Continued*

	First-detected AF (n = 774)	Paroxysmal AF (n = 693)	Persistent AF (n = 671)	Permanent AF (n = 451)	*P*-value
Two or more (%)	80.6	73.0	82.6	92.5	<0.0001
HAS-BLED score					
Mean score ± SD	1.4 ± 1.1	1.2 ± 1.0	1.4 ± 1.1	1.6 ± 1.1	<0.0001
Two or more (%)	44.1	31.9	39.9	46.3	<0.0001

The Kruskal–Wallis test is used for quantitative data.
[a]χ^2 or Fisher's exact test is used for binary variables.
For qualitative variables with more than two possibilities, the Monte Carlo estimates of the exact *P*-values are used.
IQR, interquartile range; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty; CABG,coronary artery bypass graft.

lone AF, chronic heart failure, valvular heart disease, dilated cardiomyopathy, restrictive cardiomyopathy, chronic obstructive pulmonary disease, chronic kidney disease, peripheral vascular disease, diabetes, alcohol ≥2–3/day, physical activities, ischaemic thromboembolic complications, previous stroke, antiarrhythmic drugs at enrolment, digoxin, diuretics, and aldosterone blockers, i.e. variables that are statistically significant between the AF type.

A two-sided *P*-value of <0.05 was considered as statistically significant. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 2589 patients were enrolled in the registry, and those with known AF type and with available 1-year follow-up data or at least information on vital status at 1 year were analysed for outcomes according to AF type. Supplementary material online, *Figure S1*, shows the study flow from the population of AF patients initially enrolled in EORP-AF pilot study.[10]

Clinical characteristics associated with different atrial fibrillation types

The clinical characteristics of enrolled patients according to the type of AF are shown in *Table 1*. According to a series of variables, patients with paroxysmal AF tended to be younger, with a lower prevalence of structural heart disease (particularly valvular heart disease), concomitant co-morbidities (heart failure, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease), as well as lower estimated thromboembolic and bleeding risk ($CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, respectively). First-detected AF, which was present in 29.9%, had characteristics quite similar to persistent AF. For this reason, patients with persistent, permanent, and first-detected AF were grouped as 'non-paroxysmal AF'.

A comparison between patients with paroxysmal and non-paroxysmal AFs (the latter group including persistent, permanent, and first-detected AF), as shown in *Table 2*, confirms that patients with paroxysmal AF were younger and had a lower prevalence of structural heart disease (especially valvular heart disease), concomitant diseases, and major co-morbidities (i.e. heart failure, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease), as well as lower estimated thromboembolic and bleeding risks.

Prescribed interventions and medications

As expected, use of pharmacological and electrical cardioversion, antiarrhythmic drugs, and left atrial ablation was significantly different according to AF type (Supplementary material online, *Table S1*). First-detected AF differed from paroxysmal AF since rhythm control strategies were less commonly used. In the group of patients with first-detected AF the prescription of oral anticoagulants, if indicated (i.e. CHA2DS2-VASc ≥ 2 or cardioversion planned), was the lowest among all the types of AF. A comparison between patients with paroxysmal and non-paroxysmal AFs (*Table 3*), based on strategy and treatments at discharge from EORP visit, highlights a more limited use of rate control as unique strategy and a much more common use of antiarrhythmic drugs and catheter ablation, among patients with paroxysmal AF.

Paroxysmal vs. non-paroxysmal atrial fibrillation

Results were analysed by comparing paroxysmal with non-paroxysmal AF (the latter group including, first-detected, persistent, and permanent AF). During follow-up, the occurrence of any TE and of stroke/TIA did not differ and the absolute rates of stroke/TIA were particularly low. All-cause mortality was significantly higher in non-paroxysmal AF patients (*Table 4*). The Kaplan–Meier curves (*Figure 1*) show that the difference in outcome between paroxysmal and non-paroxysmal AFs was related to all-cause mortality and not due to non-cardiovascular mortality (log rank test, $P = 0.0018$ for all-cause mortality, $P = 0.0826$ for cardiovascular mortality). Descriptive statistics of patients who died and patients who survived during 1-year follow-up is shown in Supplementary material online, *Table S2*.

Adjustment was based on the results of descriptive statistics comparing patients who died and patients who survived (Supplementary material online, *Table S2*). The non-adjusted Cox model for the type

Table 2 Patient characteristics at enrolment in paroxysmal and non-paroxysmal AFs

	Paroxysmal AF (n = 693)	Non-paroxysmal AF (n = 1896)	P-value
Demographics			
Age in years, median (IQR)	67 (60–75)	70 (63–78)	<0.0001
Age ≥ 75 years (%)	25.8	36.0	<0.0001
Age > 65 years (%)	55.8	66.3	<0.0001
Age ≤ 50 years (%)	8.1	6.1	0.0758
Female gender (%)	41.6	38.7	0.1816
Concomitant disease (%)			
Lone AF	6.8	3.0	<0.0001
Coronary artery disease	33.9	36.9	0.1943
Myocardial infarction	43.6	44.1	0.9028
PTCA/CABG	47.5	46.9	0.8713
Stable angina	36.8	36.4	0.9331
Chronic heart failure	29.1	52.0	<0.0001
of whom NYHA III/IV	27.4	44.7	<0.0001
Valvular heart disease	46.4	68.8	<0.0001
Dilated cardiomyopathy	4.3	13.9	<0.0001
Hypertrophic cardiomyopathy	3.1	4.1	0.2954
Restrictive cardiomyopathy	0	0.8	0.0163[a]
Hypertensive cardiomyopathy	18.5	20.1	0.3904
Other cardiac disease	7.1	8.9	0.1556
Chronic obstructive pulmonary disease	7.5	13.0	0.0001
Hyperthyroidism	3.3	3.0	0.7161
Hypothyroidism	6.3	7.5	0.2833
Chronic kidney disease	8.0	15.0	<0.0001
Peripheral vascular disease	8.4	12.9	0.0026
Cardiovascular risk factors (%)			
Diabetes	16.8	21.8	0.0051
Hypertension	69.6	71.2	0.4211
Current smoker	12.6	10.9	0.2228
Hypercholesterolaemia	46.5	48.7	0.3270
Alcohol ≥ 2–3/day	4.9	9.8	0.0001
Physical activity (%)			
None	32.0	41.6	<0.0001
Occasional	38.0	33.2	
Regular	23.1	21.2	
Intense	7.0	4.0	
Co-morbidities (%)			
Ischaemic thromboembolic complications	10.6	13.6	0.0446
Previous stroke	4.6	6.7	0.0552
Previous TIA	3.4	4.3	0.2994
Haemorrhagic events	5.1	6.9	0.0903
Haemorrhagic stroke	2.9	3.8	>0.999[a]
Major bleeding	28.6	26.2	0.7740
Malignancy	4.8	5.3	0.6125
Symptoms (%)			
EHRA I	36.9	42.6	<0.0001
EHRA II–IV	63.1	57.4	
$CHADS_2$ score			
Mean score ± SD	1.6 ± 1.2	2.0 ± 1.3	<0.0001
Two or more (%)	47.3	63.7	<0.0001
CHA_2DS_2-VASc score			
Mean score ± SD	2.8 ± 1.8	3.4 ± 1.8	<0.0001
Two or more (%)	73.0	84.1	<0.0001

Table 2 *Continued*

	Paroxysmal AF (n = 693)	Non-paroxysmal AF (n = 1896)	P-value
HAS-BLED score			
Mean score ± SD	1.2 ± 1.0	1.4 ± 1.1	<0.0001
Two or more (%)	31.9	43.1	<0.0001

[a]χ^2 or Fisher's exact test used for binary variables.

Table 3 Prescribed interventions and medications at discharge in paroxysmal and non-paroxysmal AFs

	Paroxysmal AF (n = 693)	Non-paroxysmal AF (n = 1896)	P-value
Management strategy			<0.0001
Rate control	16.3	47.2	
Rate and rhythm control	59.3	37.5	
Rhythm control only	21.2	10.8	
Observation	3.2	4.5	
Interventions (%)			
N (on inpatients only)	463	1194	
Pharmacological cardioversion	36.7	26.1	<0.0001
Electrical cardioversion	22.7	24.6	0.4420
Catheter ablation	21.9	5.0	<0.0001
Pacemaker implantation	5.0	3.9	0.3508
ICD implantation	1.3	0.9	0.5868[a]
Surgical therapy	0.2	0.3	>0.999[a]
Antithrombotic treatments (%)			
None	5.3	3.6	0.0546
Antiplatelets	33.8	33.3	0.8182
Oral anticoagulant if indicated[a]	81.3	83.8	0.1418
Vitamin K antagonists	69.8	74.9	0.0086
NOAC	7.6	7.7	0.9564
Antiarrhythmic drugs (%)			
At least one	48.5	30.6	<0.0001
Amiodarone	23.4	20.2	0.0814
Beta-blockers	68.4	70.0	0.4113
Digoxin	5.6	24.3	<0.0001
ACE inhibitors	40.4	44.4	0.0696
ARBs	22.6	21.2	0.4562
Diuretics	36.3	56.9	<0.0001
Aldosterone blockers	12.6	28.9	<0.0001

NOAC, novel oral anticoagulant; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; ICD, implantable cardioverter-defibrillator.
[a]χ^2 or Fisher's exact test used for binary variables.

of AF alone as a predictor of death found a hazard ratio (HR) of 2.140 (95% CI 1.387–3.301, $P = 0.0006$) for non-paroxysmal vs. paroxysmal AF. Based on the final, adjusted multivariable Cox model (*Table 5*), only age, chronic heart failure, chronic kidney disease, diabetes, restrictive cardiomyopathy, and occasional or regular physical activity were associated predictors of death during 1-year follow-up; however, paroxysmal vs. non-paroxysmal AF was no longer a predictor of death in this adjusted analysis. The goodness of fit was $P = 0.25$. For each parameter, the null hypothesis of proportional hazard could not be rejected.

A multivariable analysis of the effect of non-paroxysmal AF subtype vs. paroxysmal AF on outcomes during follow-up (occurrence

Table 4 Outcome in terms of adverse events during a 1-year follow-up for paroxysmal vs. non-paroxysmal AF

	Paroxysmal AF (n = 693)	Non-paroxysmal AF (n = 1896)	P-value
No. of patients	693	1896	
Events, n (%)			
All-cause death	28 (4.0%)	138 (7.3%)	0.0029
Cardiovascular death	13 (1.9%)	59 (3.2%)	0.0826
Any TE	23 (3.6%)	63 (3.9%)	0.7982
Stroke/TIA	4 (0.6%)	17 (1.0%)	0.3607
Bleeding	2 (0.3%)	22 (1.4%)	0.0304
All-cause death + any TE	51 (7.7%)	201 (11.4%)	0.0087
Cardiovascular death + any TE	36 (5.6%)	122 (7.2%)	0.1566
All-cause death + any TE or bleeding	53 (8.1%)	221 (12.8%)	0.0014
Cardiovascular death + any TE or bleeding	38 (5.9%)	142 (8.6%)	0.0337

Non-paroxysmal AF includes first-detected, persistent, and permanent AF.
TE, thrombosis-related event; any thrombosis-related event—stroke, TIA, ACS, coronary intervention, cardiac arrest, peripheral embolism, or pulmonary embolism; ACS, acute coronary syndrome; TIA, transient ischaemic attack.

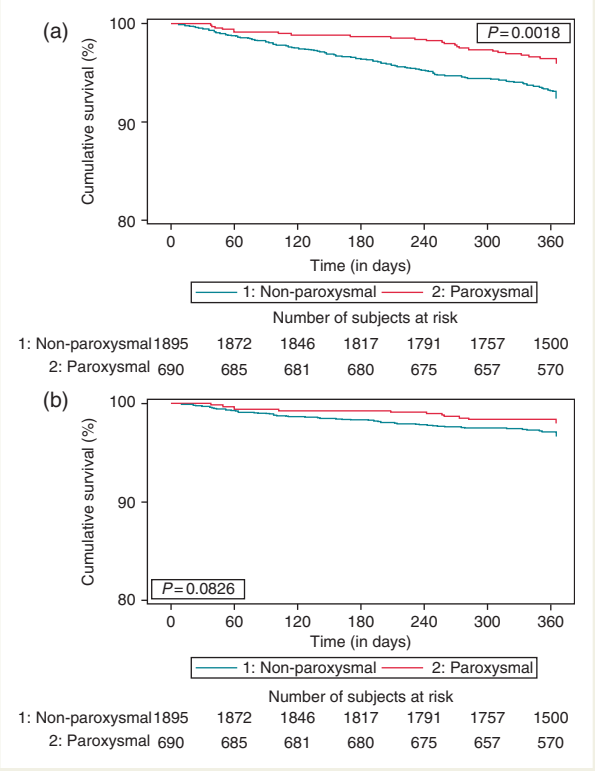

Figure 1 The Kaplan–Meier curves of freedom from all-cause death (top) and cardiovascular death (bottom) comparing patients with paroxysmal and non-paroxysmal AFs.

of stroke/TIA, any TE, bleeding, and cardiovascular death + TE), adjusted for a series of variables, is shown in *Table 6*. Adjustment was based on the results of descriptive statistics for patients with paroxysmal and non-paroxysmal AFs (*Tables 2* and *3*). As shown in this adjusted analysis, non-paroxysmal AF was not significantly associated to any of the outcomes in the 1-year follow-up.

Table 5 Results of the final Cox model with predictors for death, after adjustment

Analysis of maximum likelihood estimates				
Parameter	**Pr > χ^2**	**HR**	**95% HR confidence limits**	
Paroxysmal vs. non-paroxysmal AF	0.2372	1.324	0.831	2.109
Age (in years)	<0.0001	1.049	1.030	1.069
Chronic heart failure	<0.0001	2.662	1.801	3.934
Restrictive cardiomyopathy	0.0305	3.055	1.111	8.400
Chronic kidney disease	<0.0001	2.508	1.788	3.518
Diabetes mellitus	0.0004	1.820	1.304	2.539
Intense physical activity (>7 h/week for at least 2 years)	0.3129	0.550	0.172	1.756
Occasional physical activity (<3 h/week for at least 2 years)	<0.0001	0.469	0.321	0.685
Regular physical activity (3 h/week for at least 2 years)	<0.0001	0.176	0.077	0.406

Discussion

Our study shows that in terms of all-cause mortality, the overall 1-year outcome of patients with non-paroxysmal AF is worse when compared with paroxysmal AF. However, this difference is related not to the arrhythmia itself but to the worse clinical risk profile in terms of age, underlying cardiac disease, co-morbidities, and risk factors.

The relationship between AF type and outcome, in terms of death or stroke, has been the object of several studies, performed in different patient settings and with variable degrees of patient selection.[2–7,16] Recently, most of the evaluations were performed on patients with non-valvular AF, in the cohorts enrolled in trials on

Table 6 Multivariable effect of non-paroxysmal AF subtype vs. paroxysmal AF on outcomes during follow-up, after adjustment for a series of variables[a]

	1-Year outcome	Odds ratio	95% CI	*P*-value
Non-paroxysmal AF	All-cause death	0.907	[0.520–1.583]	0.7318
	Cardiovascular death	0.550	[0.252–1.200]	0.1331
	Any TE	0.704	[0.394–1.257]	0.2353
	Stroke/TIA	1.615	[0.337–7.727]	0.5486
	Bleeding	3.486	[0.772–15.734]	0.1044
	All cause of death + any TE	0.776	[0.512–1.176]	0.2318
	Cardiovascular death + any TE	0.629	[0.391–1.012]	0.0558
	All cause of death + any TE or bleeding	0.900	[0.603–1.344]	0.6068
	Cardiovascular death + any TE or bleeding	0.783	[0.499–1.228]	0.2866

The reference is paroxysmal AF.
[a]Adjustment was done for age, lone AF, chronic heart failure, valvular heart disease, dilated cardiomyopathy, restrictive cardiomyopathy, chronic obstructive pulmonary disease, chronic kidney disease, peripheral vascular disease, diabetes, alcohol ≥ 2–3/day, physical activity, ischaemic thromboembolic complications, previous stroke, vitamin K antagonists, antiarrhythmic drugs, digoxin, diuretics, and aldosterone blockers at discharge.
TE, thrombosis-related event; any thrombosis-related event—stroke, TIA, ACS, coronary intervention, cardiac arrest, peripheral embolism, or pulmonary embolism.

NOACs.[4–7] All these trials are based on highly selected anticoagulated trial cohorts.

Our analysis was performed in a 'real-world' cohort of AF patients prospectively enrolled in the EORP-AF General Pilot Registry, with no exclusion of co-morbidities (i.e. chronic renal disease) and also including some patients with valvular AF, thus giving a picture of European patients not included in controlled trials currently treated, either as in-patients or out-patients, in general cardiology clinical practice. According to the results of our study, adequate adjustment for co-morbidities and risk factors, which could act as confounders, appears absolutely necessary in comparing different types of AF with regard to the risk of death.[5]

According to our study, clinical risk factors and clinical variables are the most important determinants of outcome, and their variable association in patients with paroxysmal vs. non-paroxysmal AF explains the worse overall outcome in terms of mortality found in non-paroxysmal AF. Therefore, patients presenting in real-world practice with non-paroxysmal AF require a holistic approach with collaborative, personalized, patient-centred care, with integration of different health-care specialists for appropriate management of all co-morbidities.[1] Of note, our cohort had a rate of all-cause death that was higher than the rates around 3.9–4.8% reported in analysis derived from the recent randomized trials.[5–7]

In evaluating patients with paroxysmal AF, we should take into account that the definition of paroxysmal AF is based on clinical elements and does not include a precise quantification of the time spent in AF, that is, AF burden.[17,18] In studies performed on patients with a dual-chamber electrical device, with continuous monitoring of AF presence and duration, AF burden was an independent predictor of the risk of stroke, and thus, more precise assessments can be considered in specific populations with a device *in situ*.[18]

Our study also shows that in the current European practice of patients referred to cardiologists for definition of treatment strategy and the high prescription of oral anticoagulants, the outcome at 1 year is characterized by relatively few events related to stroke, systemic embolism, and TIA, with no significant differences among AF subtypes within our cohort. Previous analysis on the outcome of patients with paroxysmal vs. non-paroxysmal AF resulted in conflicting results.[2–7,19] Some studies reported higher stroke rates in patients with permanent compared with paroxysmal AF,[4,5] while others did not confirm this increased risk.[2,3,7,16,19] The prior studies were characterized by heterogeneity with regard to patient selection and type of antithrombotic treatment applied, and management was generally left to physician's judgement or defined by a protocol. Within this complex scenario, our 'real-world' study contributes to the general debate by showing that contemporary (high) prescription of oral anticoagulants in Europe has much improved compared with the past and results in relatively low overall rates of stroke/cardiac embolism at 1 year (up to 1%). Of note, oral anticoagulants not only reduces stroke (by 64%), but significantly reduce all-cause mortality (by 26%) when compared with control/placebo.[20]

As known, AF may have different clinical presentations and has been classified by consensus guidelines into different types, including paroxysmal, persistent, permanent, and first-diagnosed AF.[1] Our study shows that first-diagnosed or first-detected AF, a clinical entity usually not of specific focus in trials, relevant for daily practice, has a clinical risk profile quite similar to persistent and permanent AF, but different from paroxysmal AF. In the group of patients with first-detected AF the prescription of oral anticoagulants, if indicated according to guidelines, was the lowest among all the types of AF. Finally, the outcome of patients with first-detected AF, in terms of all-cause death and cardiovascular death, was worse than for paroxysmal AF and comparable with that of patients with permanent AF (Supplementary material online, *Table S4*). In summary, a series of findings related to clinical profile, management, and treatments, as well as outcome, indicate that patients with first-detected AF are, in real-world practice, quite different from those presenting with paroxysmal AF. These findings are original, since the previous analysis of AF patterns from the Euro Heart Survey excluded cases of first-detected AF.[19]

What are the clinical implications? Current guidelines on AF management[1] recommend that the pattern of AF should not influence the prescription of oral anticoagulants, and the present study

confirms that these indications are currently translated into 'real-world' practice, although with need to better manage patients presenting with first-detected AF.

Limitations

Despite the methodological desirability of consecutive enrolment, this cannot be fully proved in the sample of ambulatory patients with AF. In any case, local audits were performed to check quality of data and consecutiveness of enrolment. Since the classification of AF type according to European Guidelines[1] was investigator-defined, we cannot exclude some variability in interpreting clinical history and AF presentation.

While representativeness is a frequent limitation of observational studies, the centres in the registry sample were selected in proportion to the size of the population of the participating countries as well as taking into account the different technological levels of the cardiology centres. The patients were enrolled through cardiology clinics, and therefore, the study population may not be representative of the entire AF population, so its findings cannot be generalized to patients treated by internists or general practitioners. Some of the variables that we considered have a low prevalence, but appeared to have an influence on outcomes on the multivariable model, albeit with large 95% CIs; thus, their interpretation should be with some caution.

Finally, as shown in Supplementary material online, *Figure S1*, related to the study flow, the present analysis considered 2589 of the 3109 patients initially enrolled in the EORP-AF pilot study,[10] corresponding to 83.3% of the initial patients cohort. These patients represent—as previously reported[12]—those patients who were alive for start of the follow-up phase of EORP. We recognize the limitations of follow-up data, available for 83% of patients, inherent with a registry-type design.[12] When we evaluated the baseline profile of patients with and without availability of post-discharge follow-up (Supplementary material online, *Tables S5–S7*), no profound differences emerged notwithstanding that the prevalence of heart failure was slightly higher in patients without 1-year follow-up data (54.9 vs. 46.0%, but the prevalence of New York Functional Class III/IV heart failure did not differ significantly).

Conclusions

In conclusion, in a real-world observational registry, patients with non-paroxysmal AF had a worse outcome, in terms of all-cause mortality, which was related to a more severe clinical profile. The risk of stroke at 1 year was relatively low, perhaps reflecting the current high rates of anticoagulants use.

Supplementary material

Supplementary material is available at *Europace* online.

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An unusual cause of superior vena cava syndrome after pacemaker implantation

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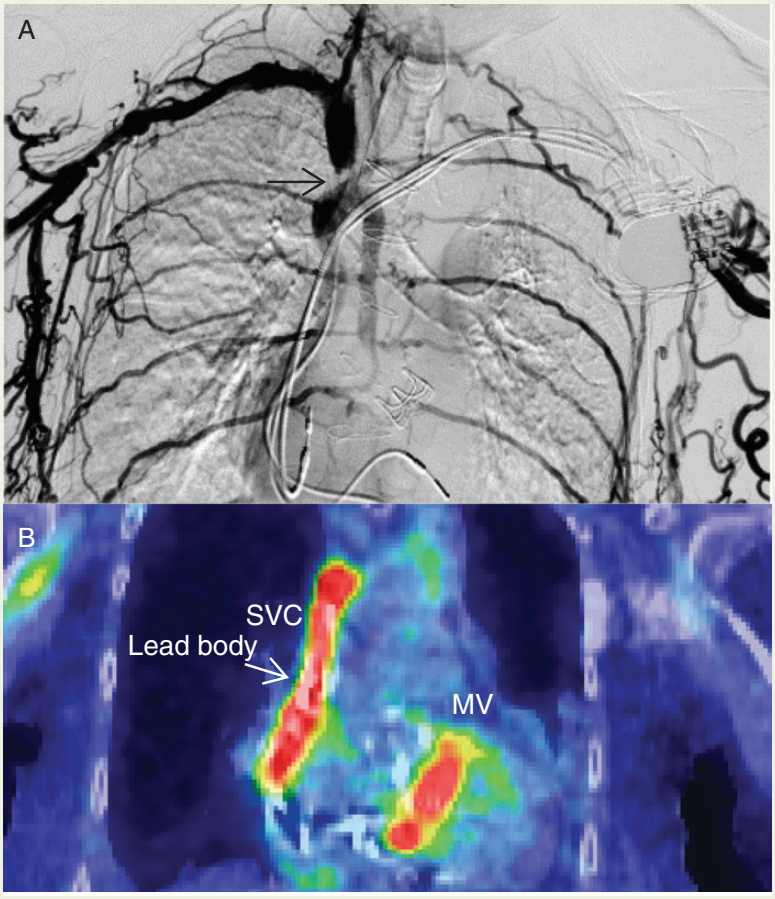
An 81-year-old woman with a history of aortic valve replacement and DDD pacemaker implantation 5 years earlier was admitted to our hospital. She had had the ventricular lead with a VDD pacemaker re-inserted 3 years prior because the pacing threshold had increased in both the atrial and ventricular leads. She presented with oedema of the face and arms. A chest radiograph showed a pleural effusion. On electrocardiography, we found a new atrial undersensing. Bilateral upper-extremity venography revealed superior vena cava (SVC) obstruction above the azygos arch and the development of chest wall venous collaterals (*Panel A*). Echocardiography and contrast-enhanced computed tomography (CT) revealed an anterior mitral leaflet (AML) tumour extending continuously from the interventricular to the interatrial septum, involving the soft tissue surrounding the pacing lead in the SVC. Notably, ^{18}F-FDG positron emission tomography (PET)/CT revealed enhanced isotope uptake in the left ventricular septal wall, annulus of the mitral valve, and from the atrioventricular septum to the SVC, involving both the body and tip of the lead, implying tumour participation in the development of the SVC syndrome (*Panel B*). Her haemodynamics deteriorated progressively, and she died. The histopathology of the tumour remains unknown. The differential diagnosis should include a primary cardiac sarcoma and an inflammatory myofibroblastic tumour. The development of unusual pacemaker-associated difficulties may suggest the presence of a comorbid myocardial tumour.



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