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'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase

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Aims Atrial fibrillation (AF) is commonly associated with a high risk of stroke, thromboembolism, and mortality. The 1-year follow-up of the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) Pilot Registry demonstrated a high mortality but good outcomes with European Society of Cardiology guideline-adherent therapy. Whether these 'real-world' observations on patients managed by European cardiologists extend to 2 years remains uncertain.

Methods and results In this report from the EORP-AF General Registry Pilot Phase, we provide data on the 2-year follow-up outcomes. Consistent with the 1-year follow-up report, only a small proportion of patients were symptomatic (24.9%), with minor differences between the different AF subtypes. Persistence of oral anticoagulant (OAC) therapy remains high at 2-years, with ~80% of patients treated with OAC. The prescribing rates of non-vitamin K antagonist oral anticoagulants are progressively increasing (13.7% at 2 years). Rate and rhythm control approaches remained consistent across the entire follow-up observation. Overall mortality rates remained high, with 5.0% of patients dead during the 2-year follow-up, mostly due to cardiovascular causes (61.8%). Atrial fibrillation readmissions were frequent, particularly related to arrhythmias and heart failure. On multivariate analyses, any cardiovascular reason for admission rather than AF was significantly associated with increased mortality during the 2-year follow-up.

Conclusion In this 2-year follow-up report from EORP-AF, mortality rates with AF remain high from cardiovascular causes, despite the high prevalent use of OAC. Improved management strategies to reduce major adverse outcomes in AF patients are needed.

Keywords Atrial fibrillation • Stroke • Mortality • Prognosis • Registry

Introduction

Atrial fibrillation (AF) represents one of the most common arrhythmias reported in adult patients.[1] With the progressive ageing population, both AF prevalence and incidence have been progressively increasing, according to older age and male sex.[1] In Europe, the current AF prevalence in subjects older than 55 years has been estimated to be 8.8 million in 2010 and projected to rise to 17.9 million in 2050.[1]

Atrial fibrillation confers a high-risk for both cardiovascular and non-cardiovascular complications, particularly with a five-fold higher risk of stroke and thromboembolism compared with non-AF

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What's new?

- In the 2-year follow-up of EURObservational Research Programme on Atrial Fibrillation General Registry Pilot Phase, there was a high rate of adverse events, particularly all-cause mortality, despite a high prevalence of oral anticoagulant use.
- The high mortality risk was associated with major cardiovascular co-morbidities other than atrial fibrillation (AF).
- Greater efforts are needed to ensure optimal medical management of associated co-morbidities in AF patients to improve mortality rates.

population.[1,2] Considering the huge clinical impact and healthcare burden associated with AF, the collection of prospective data from 'real-world' AF cohorts could help establish best practice and explore options in reducing both morbidity and mortality. Importantly, the introduction of the non-vitamin K oral anticoagulants (NOACs)[3] have led to a major change in the landscape of stroke prevention in AF. Indeed, recent data from the GLORIA-AF Phase II study show how the percentage of patients treated with NOACs is increasing worldwide.[4] Nonetheless, the proportion of high-risk patients being untreated or treated with antiplatelet (AP) drugs is higher than expected, as reported in the 1-year follow-up from the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Registry Pilot Phase.[5] The 1-year follow-up of the EORP-AF Pilot Registry also demonstrated good outcomes with European Society of Cardiology (ESC) guideline-adherent therapy.[6]

Whether these 'real-world' observations on patients managed by European cardiologists extend to 2 years remains uncertain. In this report from the EORP-AF General Registry Pilot Phase, we provide data on the 2-year follow-up outcomes.

Methods

The EORP-AF General Registry is a prospective, observational, multicentre European-wide registry about AF patients in current cardiology practice held by ESC. Details about study protocol, design, and main results have been published elsewhere.[5–7]

Briefly, EORP-AF Pilot Phase enrolled consecutive AF patients managed by cardiologists in nine ESC members European countries (Belgium, Denmark, Netherlands, Norway, Poland, Romania, Greece, Italy, and Portugal). The study enrolled both in- and outpatients accessing to cardiology services (either hospital or office-based centres) with AF as a primary or secondary diagnosis. The qualifying AF event was recorded by a 12-lead ECG, 24 h ECG Holter, or other electrocardiographic documentation and should have been occurred within the 12 months before the enrolment.

Follow-up was performed by the local cardiologist investigator every 1 year after enrolment, for a total of 3-year planned follow-up time. Endpoints of interest were mortality, stroke/thromboembolism, cardiovascular co-morbidities, and hospital readmissions. Data about first-year follow-up analysis was recently published.[5] For the purposes of the present paper, we focus on the outcomes recorded during the second-year follow-up.

Based on the ESC guidelines,[2] thromboembolic risk was defined according to the CHA_2DS_2-VASc score.[1] 'Low-risk' patients were defined as males with a CHA_2DS_2-VASc 0 or females with a CHA_2DS_2-VASc equal to 1; 'moderate risk' was defined as male patients with a CHA_2DS_2-VASc score 1; and 'high risk' was defined as CHA_2DS_2-VASc score ≥ 2.[1] Moreover, bleeding risk was assessed based on the HAS-BLED bleeding score.[1]

Statistical analysis

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean $\pm$ SD and/or as median and inter-quartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical

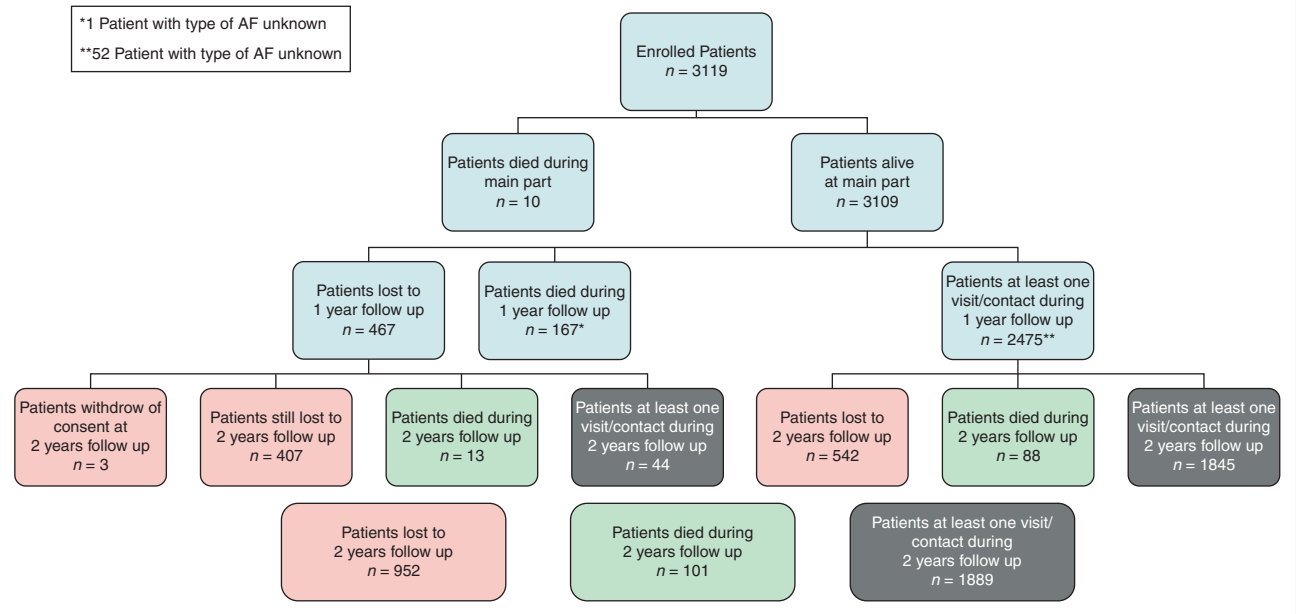


Figure 1 Patient flow as part of the EORP-AF Pilot General Registry.

Table 1 **Demographic and baseline characteristics according to atrial fibrillation subtype**

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
Age (years) (mean ± SD)	68.6 ± 11.2 (*n* = 1953)	68.5 ± 12.2 (*n* = 552)	66.6 ± 10.9 (*n* = 525)	67.4 ± 10.6 (*n* = 430)	69.9 ± 10.2 (*n* = 100)	72.9 ± 9.9 (*n* = 346)	<0.0001*
Age (years) (median [IQR])	69.0 [62.0–77.0] (*n* = 1953)	70.0 [62.0–77.0] (*n* = 552)	67.0 [60.0–74.0] (*n* = 525)	68.0 [61.0–75.0] (*n* = 430)	69.0 [63.0–78.5] (*n* = 100)	74.0 [66.0–80.0] (*n* = 346)	
Age (years, %)							<0.0001**
≤65	36.3 (708/1953)	34.4 (190/552)	43.0 (226/525)	41.9 (180/430)	32.0 (32/100)	23.1 (80/346)	
>65	63.7 (1245/1953)	65.6 (363/552)	57.0 (299/525)	58.1 (250/430)	68.0 (68/100)	76.9 (80/346)	
Gender (%)							0.2098**
Male	60.6 (1183/1953)	63.9 (353/552)	57.9 (304/525)	61.9 (266/430)	61.0 (61/100)	57.5 (199/346)	
Female	39.4 (770/1953)	36.1 (199/552)	42.1 (221/525)	38.1 (164/430)	39.0 (39/100)	42.5 (147/346)	
CHA_2DS_2-VASc (%)							<0.0001**
Low risk	8.1 (159/1953)	7.8 (43/552)	13.0 (68/525)	7.2 (31/430)	4.0 (4/100)	3.8 (13/346)	
Moderate risk	11.2 (218/1953)	11.2 (218/1953)	11.2 (218/1953)	11.2 (218/1953)	11.2 (218/1953)	11.2 (218/1953)	
High risk	80.7 (1576/1953)	80.1 (442/552)	73.1 (384/525)	79.8 (343/430)	88.0 (88/100)	92.2 (319/346)	
HAS-BLED score class (%)							0.0007**
0–2	86.5 (1690/1953)	86.2 (476/552)	90.7 (476/525)	87.4 (376/430)	80.0 (80/100)	81.5 (282/346)	
≥3	13.5 (263/1953)	13.8 (76/552)	9.3 (49/525)	12.6 (54/430)	20.0 (20/100)	18.5 (64/346)	
Follow-up duration (days) (mean ± SD)	742.3 ± 74.0 (*n* = 1855)	737.5 ± 68.9 (*n* = 511)	742.9 ± 77.8 (*n* = 514)	742.6 ± 72.8 (*n* = 411)	750.7 ± 91.8 (*n* = 99)	745.9 ± 71.2 (*n* = 320)	0.0046*
Follow-up duration (days) (median [IQR])	735 [721–760] (*n* = 1855)	738 [719–760] (*n* = 511)	733 [720–757] (*n* = 514)	737 [726–760] (*n* = 411)	730 [721–735] (*n* = 99)	742 [723–761] (*n* = 320)	
Current symptoms at 2-year follow-up (%)	24.9 (462/1855)	18.4 (94/511)	23.9 (123/514)	28.5 (117/411)	27.3 (27/99)	31.6 (101/320)	0.0002**
Palpitations (%)	65.6 (303/462)	63.8 (60/94)	82.1 (101/123)	65.0 (76/117)	63.0 (17/27)	48.5 (49/101)	<0.0001**
Dizziness (%)	10.8 (50/462)	10.6 (10/94)	10.6 (13/123)	11.1 (13/117)	11.1 (3/27)	10.9 (11/101)	0.9999**
General non-wellbeing (%)	28.8 (133/462)	26.6 (25/94)	29.3 (36/123)	27.4 (32/117)	51.9 (14/27)	25.7 (26/101)	0.0986**
Fatigue (%)	44.6 (206/462)	40.4 (38/94)	32.5 (40/123)	46.2 (54/117)	63.0 (17/27)	56.4 (57/101)	0.0016**
Shortness of breath (%)	41.3 (191/462)	42.6 (40/94)	39.0 (48/123)	31.6 (37/117)	55.6 (15/27)	50.5 (51/101)	0.0311**
Chest pain (%)	11.3 (52/462)	14.9 (14/94)	13.8 (17/123)	9.4 (11/117)	7.4 (2/27)	7.9 (8/101)	0.4083**
Fear/anxiety (%)	8.2 (38/462)	7.4 (7/94)	8.1 (10/123)	6.8 (8/117)	18.5 (5/27)	7.9 (8/101)	0.3825**
Other (%)	1.5 (7/462)	0.0 (0/94)	0.8 (1/123)	5.1 (6/117)	0.0 (0/27)	0.0 (0/101)	0.0142**

*P-values for among-group comparisons are from Fisher's exact test.
**P-values for among-group comparisons are from Kruskall–Wallis test.

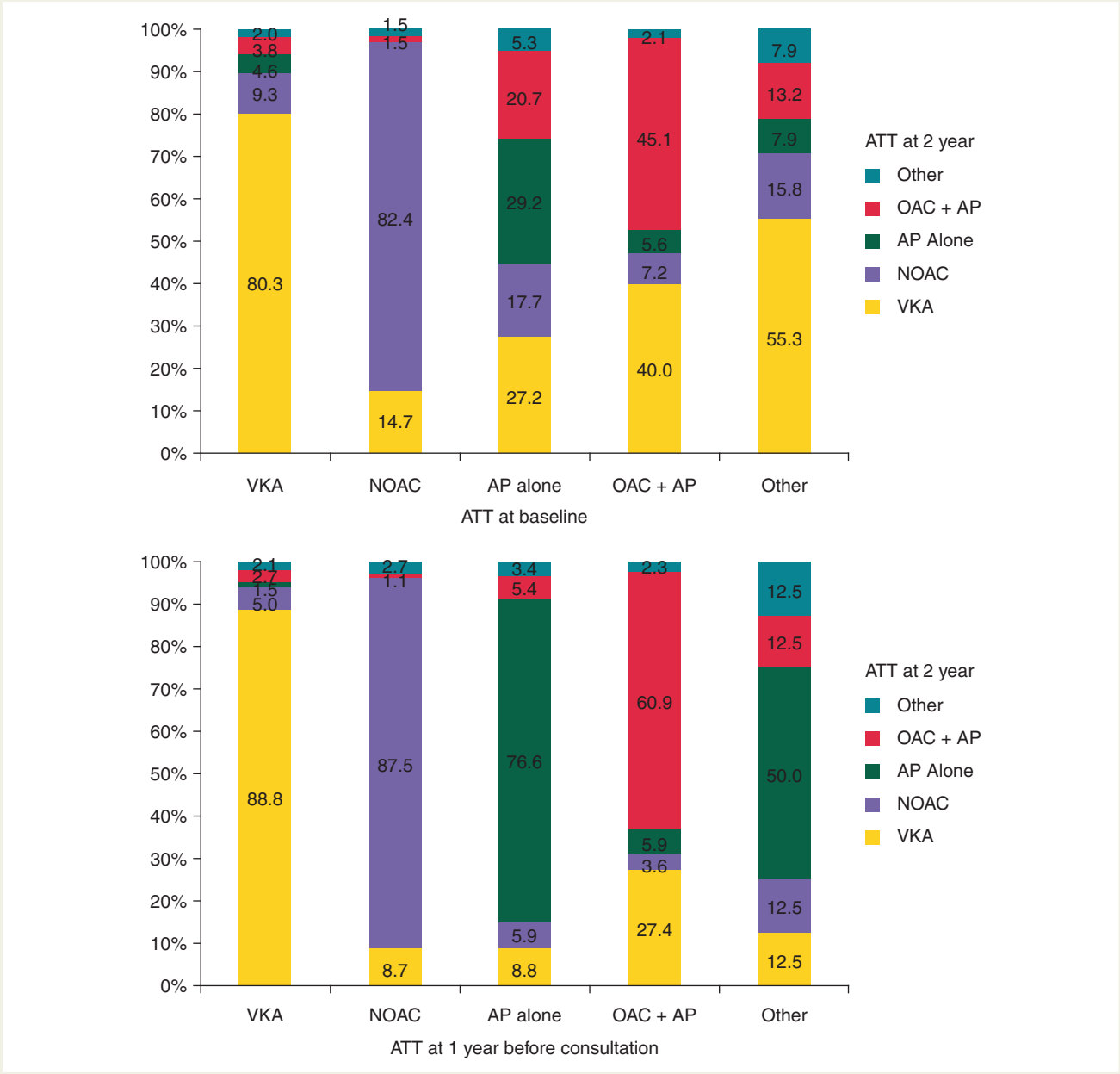


Figure 2 Antithrombotic therapy at 2-year follow-up according to baseline and 1-year. AP, antiplatelet; ATT, antithrombotic therapy; OAC, oral anticoagulant; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

variables were reported as percentages. Among-group comparisons were made using a χ^2 test or Fisher's exact test if any expected cell count was <5. Plots of the Kaplan–Meier curves for time to all-cause death in relation to AF subtype were performed. The survival distributions between the types of AF have been compared using the log-rank test. All the variables at entry that were statistically significant at univariate analysis and variables considered of relevant clinical interest were included in the multivariable model (logistic regression) to identify the independent predictors of the composite outcome of stroke/transient ischaemic attack (TIA)/peripheral embolism and/or death during the second-year follow-up period. Cox regression analysis was performed to establish clinical factors independently associated with death occurrence. A two-sided *P*-value of <0.05 was considered as statistically significant. All analyses were performed using the SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

The original study cohort comprised 3109 AF patients enrolled from 2012 to 2013. During the first-year follow-up, 167 (5.4%) patients died, while 467 (15.0%) patients were lost to follow-up. Clinical status during the second-year follow-up was available for 1990 (64.0%) patients (*Figure 1*). Of these, 101 (5.1%) died and 1889 had at least one visit/contact during the second-year follow-up.

Table 2 Pharmacological treatments prescribed at follow-up

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(A) Antithrombotic drugs by AF subgroup							
Oral anticoagulant (at least one) (%)							
Before consultation	79.5 (1475/1855)	69.5 (355/511)	79.0 (406/514)	85.9 (353/411)	79.8 (79/99)	88.1 (282/320)	<0.0001
After consultation	79.2 (1469/1855)	71.0 (363/511)	77.6 (399/514)	84.2 (346/411)	79.8 (79/99	88.1 (282/320)	<0.0001
VKA (at least one) (%)							
Before consultation	65.0 (1205/1855)	55.2 (282/511)	62.3 (320/514)	69.3 (285/411)	71.7 (71/99)	77.2 (247/320)	<0.0001
After consultation	64.2 (1190/1855)	56.8 (290/511)	60.1 (309/514)	67.4 (277/411)	71.7 (71/99)	75.9 (243/320)	<0.0001
NOAC (at least one) (%)							
Before consultation	13.3 (246/1855)	12.9 (66/511)	15.2 (78/514)	14.4 (59/411)	8.1 (8/99)	10.9 (35/320)	0.2045
After consultation	13.7 (255/1855)	13.1 (67/511)	15.8 (81/514)	14.6 (60/411)	8.1 (8/99)	12.2 (39/320)	0.2382
Antiplatelet drug (at least one) (%)							
Before consultation	25.1 (466/1855)	25.6 (131/511)	23.0 (118/514)	25.8 (106/411)	39.4 (39/99)	22.5 (72/320)	0.0097
After consultation	23.8 (441/1855)	23.9 (122/511)	23.2 (119/514)	22.9 (94/411)	36.4 (36/99)	21.9 (70/320)	0.0479

	Total	Low risk	Moderate risk	High risk	*P*-value
(B) Antithrombotic drugs by thromboembolic risk					
Oral anticoagulant (at least one) (%)					
Before consultation	79.7 (1505/1889)	44.7 (71/159)	74.3 (165/222)	84.2 (1269/1508)	<0.0001
After consultation	79.3 (1498/1889)	43.4 (69/159)	73.9 (164/222)	83.9 (1265/1508)	<0.0001
VKA (at least one) (%)					
Before consultation	65.1 (1230/1889)	32.7 (52/159)	52.7 (117/222)	70.4 (1061/1508)	<0.0001
After consultation	64.2 (1213/1889)	31.4 (50/159)	52.3 (116/222)	69.4 (1047/1508)	<0.0001
NOAC (at least one) (%)					
Before consultation	13.2 (250/1889)	10.7 (17/159)	19.4 (43/222)	12.6 (190/1508)	0.0129
After consultation	13.8 (260/1889)	11.3 (18/159)	19.4 (43/222)	13.2 (199/1508)	0.0289
Antiplatelet drug (at least one) (%)					
Before consultation	25.0 (473/1889)	17.6 (28/159)	17.1 (38/222)	27.0 (407/1508)	0.0005
After consultation	23.7 (447/1889)	16.4 (26/159)	18.0 (40/222)	25.3 (381/1508)	0.0046

Continued

Table 2 *Continued*

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(C) Rhythm/rate control drugs							
Class Ic (flecainide/propafenone) (%)							
Before consultation	8.5 (158/1855)	6.3 (32/511)	15.0 (77/514)	11.4 (47/411)	1.0 (1/99)	0.3 (1/320)	<0.0001
After consultation	8.5 (158/1855)	6.7 (34/511)	14.8 (76/514)	11.2 (46/411)	1.0 (1/99)	0.3 (1/320)	<0.0001
Class II (β-blockers) (%)							
Before consultation	67.0 (1243/1855)	67.5 (345/511)	67.9 (349/514)	63.7 (262/411)	68.7 (68/99)	68.4 (219/320)	0.6192
After consultation	66.8 (1239/1855)	67.5 (345/511)	66.1 (340/514)	64.7 (266/411)	66.7 (66/99)	69.4 (222/320)	0.7403
Class III (amiodarone/sotalol) (%)							
Before consultation	20.9 (387/1855)	18.8 (96/511)	24.7 (127/514)	30.7 (126/411)	21.2 (21/99)	5.3 (17/320)	<0.0001
After consultation	16.1 (298/1855)	15.3 (78/511)	20.6 (106/514)	21.7 (89/411)	11.1 (11/99)	4.4 (14/320)	<0.0001
Digitalis (digoxin) (%)							
Before consultation	47.9 (889/1855)	43.1 (220/511)	37.4 (192/514)	48.4 (199/411)	62.6 (62/99)	67.5 (216/320)	<0.0001
After consultation	48.5 (899/1855)	43.8 (224/511)	37.9 (195/514)	48.7 (200/411)	62.6 (62/99)	68.1 (218/320)	<0.0001

P-values for among-group comparisons are from Pearson's χ^2 test.
AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

Demographic and baseline characteristics according to AF subtype were reported in *Table 1*, with 37 (1.9%) patients being excluded because no data about AF subtype were available. Mean follow-up duration for the entire cohort was 742.3 days ± SD 74.0 (median 735 [IQR: 721–760] days).

Similar to the 1-year follow-up analysis,[5] permanent AF patients were older than those in other AF clinical subtypes ($P < 0.0001$). No difference was found in gender distribution across AF subtypes ($P = 0.2098$). High-stroke-risk patients were more prevalent in patients with long-standing persistent and permanent AF ($P < 0.0001$), as was high bleeding risk, according to HAS-BLED score ($P = 0.0007$).

Symptomatic status at 2-year follow-up

At 2-year follow-up, one-quarter of patients were symptomatic ($n = 462$, 24.9% of patients). The presence of symptoms progressively increased across the AF subtypes, being more prevalent in patients with permanent AF ($P = 0.0002$). Of the various symptoms, palpitations were more frequently reported in paroxysmal AF ($P < 0.0001$), while fatigue and shortness of breath were more prevalent with long-standing persistent and permanent AF ($P = 0.0016$ and 0.0311, respectively).

Antithrombotic therapy at 2-year follow-up

Antithrombotic therapy use at the 2-year follow-up according to baseline and 1-year follow-up are reported in *Figure 2*. Similar to previously reported data, most of the patients who were treated with vitamin K antagonist (VKA) and NOACs at the baseline and at 1-year follow-up were still treated with the same oral anticoagulants (OACs) (i.e. 80.3 and 82.4%, respectively). A relatively large proportion of patients treated with AP at baseline were changed to VKA (27.2%) or to a NOAC (17.7%), or prescribed with AP + OAC (20.7%).

As reported in *Table 2*, the overall proportion of patients treated with OAC remained consistently high, both before and after consultation (79.5 and 79.2%, respectively). Patients with permanent AF were more frequently treated with OAC than patients in other AF subtypes ($P < 0.0001$), with same proportion before and after the consultation (88.1%). The proportion of patients treated with VKA progressively increased from patients with first detected AF to permanent AF, both before and after consultation ($P < 0.0001$). Patients with long-standing persistent AF were more frequently treated with AP before consultation ($P = 0.0097$), with the proportion reduced after consultation ($P = 0.0479$).

When considered thromboembolic risk (*Table 2*), patients at high thromboembolic risk were more frequently treated with OAC (79%), compared with AP drugs ($P < 0.0001$). Prescription of VKA progressively increased from low to high thromboembolic risk, both before and after consultation ($P < 0.0001$), while NOACs were significantly more prescribed in AF patients at moderate risk ($P = 0.0129$ and 0.0289, respectively, before and after consultation). Antiplatelet was more frequently used in patients at high thromboembolic risk.

Clinical management at 2-year follow-up

The use of rhythm and rate control drugs is summarized in *Table 2*. β-Blockers were still the most commonly used drugs, but no

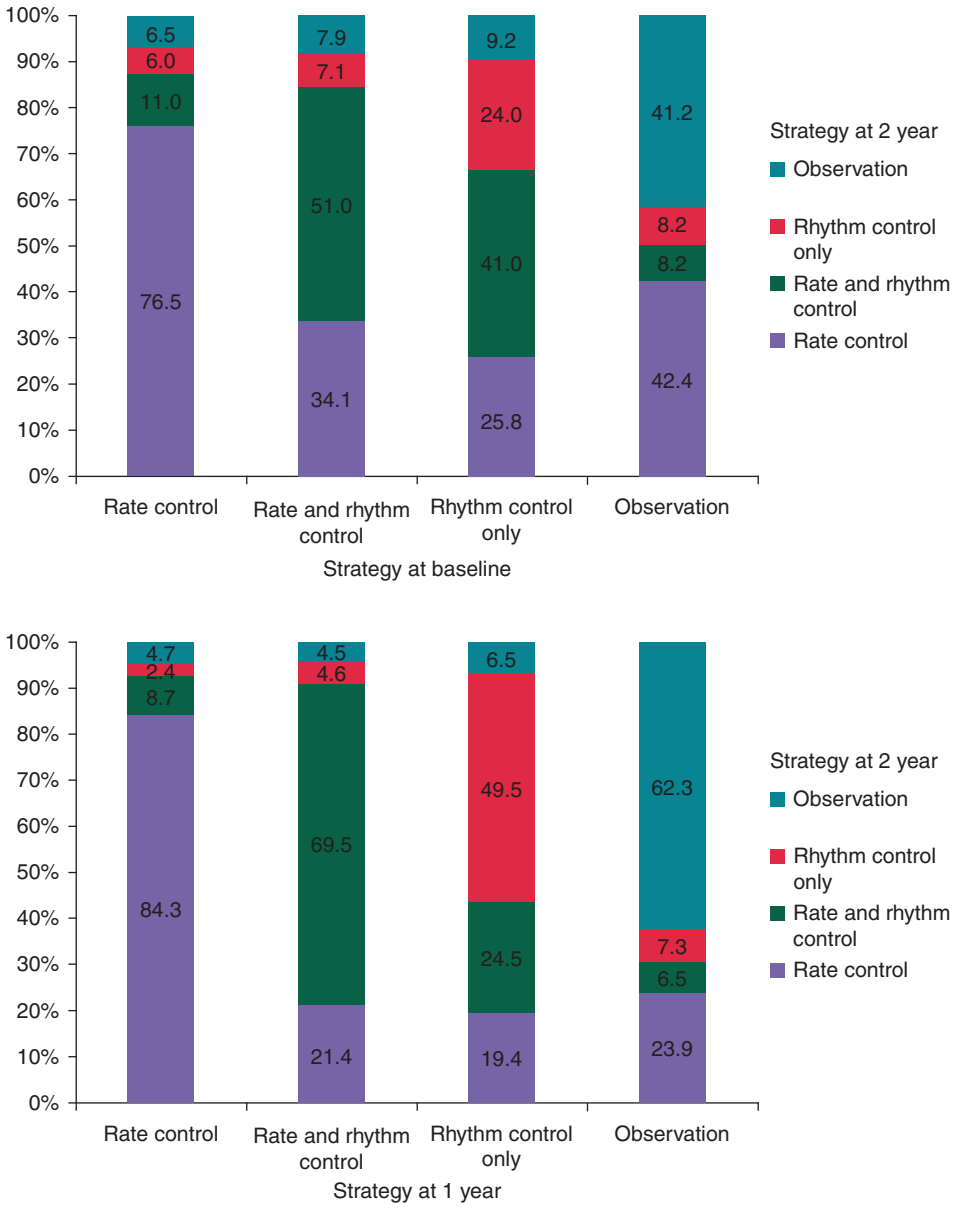


Figure 3 Clinical management at 2-year follow-up according to baseline and 1-year.

differences were found between the different AF subtypes ($P = 0.7403$). Digoxin was still used in almost the half of the patients, being more frequently prescribed in patients with long-standing persistent AF and permanent AF ($P < 0.0001$). As expected, both Class Ic and Class III antiarrhythmics were more frequently prescribed to patients with paroxysmal and persistent AF (both $P < 0.0001$).

A high proportion of patients assigned to rate control at baseline were continued on that approach, consistently throughout the observation period (*Figure 3*). Interventional procedures were used in a minority of patients ($n = 260$, 14.2%), with electrical cardioversion being the most performed ($n = 107$, 5.8%). Both pharmacological and electrical cardioversion, as well as catheter ablation, were more likely used in patients with paroxysmal AF (10.1, 8.9, and 5.1% respectively; all $P < 0.0001$).

Mortality and morbidity

A total of 98 patients from the 1953 (5.0%) whose follow-up status was known died during the 2-year follow-up (*Table 3*). Similar to what was reported for the 1-year follow-up, the highest death rates were reported for patients with both first detected (7.4% of patients) and permanent AF (7.5%) subtypes ($P < 0.0001$).

The highest proportion of patients died owing to cardiac cause (52.6%), particularly from heart failure (77.5%). Kaplan–Meier curves (*Figure 4*) for death according to AF subtypes found a significant difference in death risk between the AF subtypes, with the highest risk among patients with first detected AF or permanent AF, and lowest risk among patients with paroxysmal AF ($P < 0.0001$).

Table 3 Mortality and morbidity by 2-year follow-up

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(A) Mortality							
Death (%)	5.0 (98/1953)	7.4 (41/552)	2.1 (11/525)	4.4 (19/430)	1.0 (1/100)	7.5 (26/346)	<0.0001
Causes of death (details) (%)							0.1336
Cardiac	52.6 (40/76)	36.4 (12/33)	50.0 (4/8)	64.7 (11/17)	–	72.2 (13/18)	
Vascular	9.2 (7/76)	18.2 (6/33)	0.0 (0/8)	5.9 (1/17)	–	0.0 (0/18)	
Non-cardiovascular	38.2 (29/76)	45.5 (15/33)	50.0 (4/8)	29.4 (5/17)	–	27.8 (5/18)	
Cardiac (%)							0.1109
Acute myocardial infarction	5.0 (2/40)	8.3 (1/12)	0.0 (0/4)	0.0 (0/11)	–	7.7 (1/13)	
Heart failure	77.5 (31/40)	83.3 (10/12)	75.0 (3/4)	54.5 (6/11)	–	92.3 (12/13)	
Arrhythmia	7.5 (3/40)	0.0 (0/12)	25.0 (1/4)	18.2 (2/11)	–	0.0 (0/13)	
Other	10.0 (4/40)	8.3 (1/12)	0.0 (0/4)	27.3 (3/11)	–	0.0 (0/13)	
Vascular (%)							0.9999
Ischaemic stroke	42.9 (3/7)	33.3 (2/6)	–	100.0 (1/1)	–	–	
Haemorrhagic stroke	14.3 (1/7)	16.7 (1/6)	–	0.0 (0/1)	–	–	
Systemic haemorrhage	42.9 (3/7)	50.0 (3/6)	–	0.0 (0/1)	–	–	
(B) Readmissions							
AF/atrial flutter/atrial tachycardia (%)	12.0 (209/1743)	9.7 (48/494)	20.8 (103/495)	11.6 (42/363)	9.8 (8/82)	2.6 (8/309)	<0.0001
Other cardiovascular events (%)	8.2 (145/1778)	9.7 (48/496)	5.0 (25/500)	5.0 (19/383)	5.7 (5/87)	15.4 (48/312)	<0.0001
ACS	4.2 (6/143)	6.4 (3/47)	8.3 (2/24)	5.3 (1/19)	0.0 (0/5)	0.0 (0/48)	0.2486
Heart failure	42.4 (61/144)	46.8 (22/47)	24.0 (6/25)	31.6 (6/19)	20.0 (1/5)	54.2 (26/48)	0.0749
MI/angina	13.3 (19/143)	12.8 (6/47)	16.7 (4/24)	10.5 (2/19)	40.0 (2/5)	10.4 (5/48)	0.4116
Arrhythmia, other than AF/atrial flutter	9.8 (14/143)	8.5 (4/47)	20.8 (5/24)	5.3 (1/19)	0.0 (0/5)	8.3 (4/48)	0.4703
Cardiac arrest	0.7 (1/143)	2.1 (1/47)	0.0 (0/24)	0.0 (0/19)	0.0 (0/5)	0.0 (0/48)	0.6723
Stroke	6.3 (9/143)	6.4 (3/47)	4.2 (1/24)	0.0 (0/19)	0.0 (0/5)	10.4 (5/48)	0.6872
TIA	2.8 (4/143)	2.1 (1/47)	8.3 (2/24)	0.0 (0/19)	0.0 (0/5)	2.1 (1/48)	0.5024
Peripheral embolism	2.1 (3/143)	2.1 (1/47)	0.0 (0/24)	5.3 (1/19)	20.0 (1/5)	0.0 (0/48)	0.0378
Pulmonary embolism	0.7 (1/143)	0.0 (0/47)	0.0 (0/24)	5.3 (1/19)	0.0 (0/5)	0.0 (0/48)	0.1685
Other cardiovascular events	16.8 (24/143)	8.5 (4/47)	20.8 (5/24)	31.6 (6/19)	0.0 (0/5)	18.8 (9/48)	0.1600
Non-cardiovascular events (%)	9.7 (156/1604)	12.3 (55/447)	9.1 (42/464)	8.9 (31/348)	8.2 (6/73)	8.1 (22/272)	0.2967
Bleeding	11.0 (16/145)	11.8 (6/51)	11.9 (5/42)	3.7 (1/27)	0.0 (0/5)	20.0 (4/20)	0.4924
Other non-cardiovascular events	90.2 (138/153)	94.4 (51/54)	85.4 (35/41)	96.8 (30/31)	83.3 (5/6)	81.0 (17/21)	0.1274

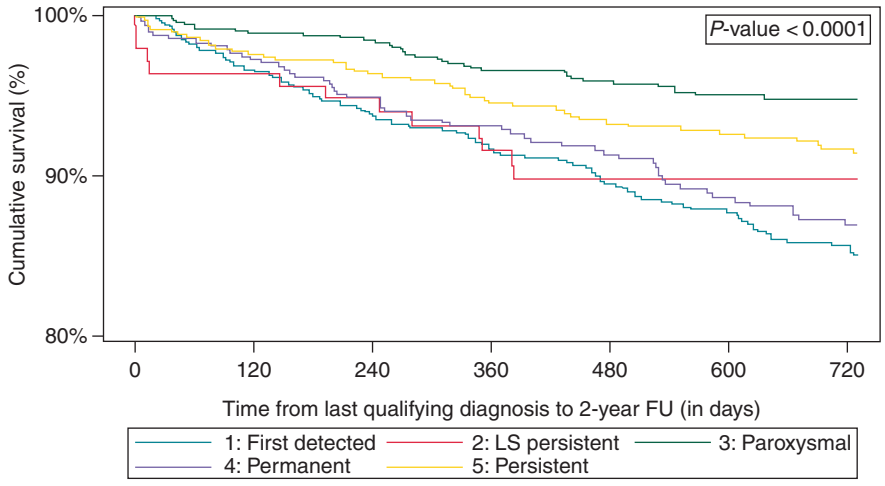
P-values for among-group comparisons are from Pearson's χ^2 test.
AF, atrial fibrillation; MI, myocardial infarction; TIA, transient ischaemic attack.

Patients with paroxysmal AF were more frequently readmitted to hospital ($P < 0.0001$) due to AF, atrial flutter, or atrial tachycardia (*Table 3*). Patients with permanent AF were more frequently re-admitted to the hospital for other cardiovascular events ($P < 0.0001$). Readmissions related to chronic heart failure (CHF) occurrence were the most common (42.4%) but with no difference across AF subtypes.

Multivariate analyses

A logistic regression analysis to establish clinical factors associated with the composite outcome of stroke/TIA/peripheral embolism and/or death occurrence was compiled (*Table 4*). Of the clinical characteristics, age ($P < 0.0001$), other main reason for admission ($P < 0.0001$), first detected AF ($P = 0.0083$), no physical activity ($P = 0.0001$), CHF ($P < 0.0001$), chronic kidney disease ($P < 0.0001$), diabetes ($P = 0.0018$), malignancy ($P = 0.0208$), calcium-channel blockers ($P = 0.0013$), and angiotensin-converting enzyme (ACE) inhibitors ($P = 0.0031$) were independently associated with the occurrence of the composite outcome (*Figure 5A*).

Cox regression analysis (*Table 5*) shows that age ($P < 0.0001$), other main reason for admission ($P < 0.0001$), first detected AF ($P = 0.0005$), no physical activity ($P = 0.0001$), CHF ($P < 0.0001$), chronic kidney disease ($P < 0.0001$), diabetes ($P = 0.0003$), malignancy ($P = 0.0430$), and heparin use ($P = 0.0327$) were independently associated with death (*Figure 5B*); conversely, statins ($P = 0.0053$), calcium-channel blockers ($P = 0.0050$), and ACE inhibitors ($P = 0.0032$) were protective against death during the 2-year follow-up (*Figure 5B*).



Number of subjects at risk

1: First detected	923	770	743	706	552	521	424
2: LS persistent	145	121	119	114	100	99	86
3: Paroxysmal	807	697	690	654	555	524	442
4: Permanent	524	452	438	413	347	330	273
5: Persistent	645	553	545	516	435	414	360

Figure 4 Kaplan–Meier curves for death according to atrial fibrillation subtypes. FU, follow-up; LS, long-standing.

Table 4 Logistic regression analysis for predictors of stroke/TIA/peripheral embolism and/or mortality by 2-year follow-up

	Odds ratio	95% confidence interval	*P*-value
Age (per year)	1.06	1.04–1.08	<0.0001
Other main reason for admission vs. AF	1.92	1.39–2.66	<0.0001
First detected AF vs. permanent AF	1.67	1.14–2.45	0.0083
None vs. regular physical activity	2.71	1.63–4.51	0.0001
Chronic heart failure	2.18	1.57–3.04	<0.0001
Chronic kidney disease	2.35	1.67–3.31	<0.0001
Diabetes	1.67	1.21–2.30	0.0018
Malignancy	1.85	1.10–3.11	0.0208
Calcium-channel blockers	0.41	0.24–0.71	0.0013
ACE inhibitors	0.63	0.47–0.86	0.0031

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; TIA, transient ischaemic attack.

Discussion

During the 2-year follow-up of the EORP-AF Pilot General Registry, our data are consistent with those previously reported for the 1-year follow-up analysis.[5] The vast majority of AF patients persist to remain asymptomatic, while those still experiencing symptoms had differential patterns according to different AF subtype. Persistence with OAC use was still high (79.5%), with the use of NOACs increasing.

Rate control was the most common approach used in the overall population, with even lower rates of both pharmacological and electrical cardioversion procedures, as well as for catheter ablation. Mortality rates were consistently high (5.0%), with more than a half due to cardiac or vascular causes. Hospital readmissions were common, even if slightly reduced compared with that reported for the 1-year follow-up. Different to that reported during the 1-year follow-up, any other cardiovascular reason for admission than AF was independently directly associated with increased mortality.

Asymptomatic AF was still common, being reported up to 40% of patients.[8] Of importance, being asymptomatic was not associated with a lower thromboembolic risk[8] and is frequently associated with stroke occurrence.[9] The ESC guidelines still recommend opportunistic screening for AF in all patients aged 65 or more,[2] but increasing evidence suggests that we should reconsider much wider systematic screening.[9] Indeed, even a single screening point could identify many new AF patients,[10] especially with more recent approaches using new technology devices that are both feasible and cost-effective in identifying new 'high-risk' AF patients.[11]

Our data show how the persistence of OAC therapy use is still high, even after 2 years of follow-up, with almost 80% of patients still being treated and almost 85% of these being at high thromboembolic risk. Even if prior data about OAC use showed lower figures, our

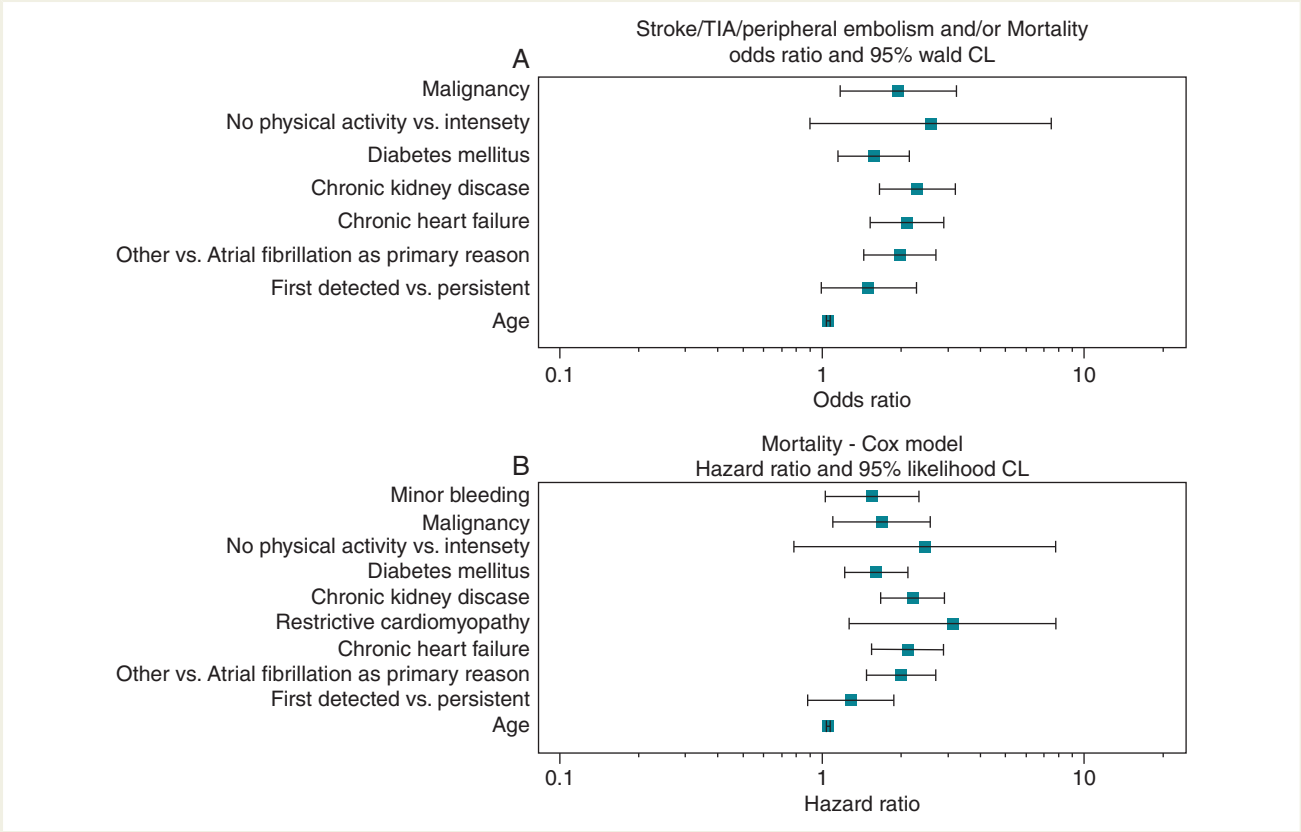


Figure 5 Forest plots for multivariate predictors of composite outcome and all-cause death. (*A*) Stroke/transient ischaemic attack/peripheral embolism and/or mortality. (*B*) All-cause mortality.

Table 5 Cox Regression analysis for clinical factors associated with death occurrence by 2-year follow-up

	Hazard ratio	95% confidence interval	*P*-value
Age (per year)	1.06	1.04–1.07	<0.0001
Other main reason for admission vs. AF	2.01	1.48–2.75	<0.0001
First detected AF vs. permanent AF	1.83	1.30–2.57	0.0005
None vs. regular physical activity	2.88	1.67–4.96	0.0001
Chronic heart failure	2.25	1.63–3.11	<0.0001
Chronic kidney disease	2.23	1.68–2.95	<0.0001
Diabetes	1.66	1.26–2.19	0.0003
Malignancy	1.56	1.01–2.39	0.0430
Heparin	1.60	1.04–2.47	0.0327
Statins	0.68	0.52–0.89	0.0053
Calcium-channel blockers	0.46	0.26–0.79	0.0050
ACE inhibitors	0.66	0.25–0.87	0.0032

ACE, angiotensin-converting enzyme; AF, atrial fibrillation.

data seem to confirm other reports from different AF cohorts. Indeed, the GLORIA-AF Phase II study reported that 80% of patients from Europe were treated with at least one OAC drug.[4] In this 2-year follow-up report, we describe an increasing use for NOACs, but more than a half of the patients were still treated with VKA. This is in contrast to data from GLORIA-AF, which reported that 47.7% of patients were prescribed with NOACs.[4] This difference could be easily explained by the fact that our patients were enrolled during the early period following the introduction of NOACs, and many patients well managed with VKA would not be automatically changed to NOACs.[12] Also, many countries participating in the EORP-AF Pilot Registry have some limitations on NOAC usage due to costs. Of note, reassuring real-world efficacy and safety data on NOACs are progressively available,[13–18] reinforcing the evidence for their effectiveness and safety out with the setting of randomized clinical trials.[19] Thus, we could foresee that the proportion of patients treated with NOACs will progressively increase among European patients, and data from the EORP-AF Long-Term Registry will provide further insights into NOAC use in European countries.

Persistence with OAC therapy, particularly related to NOACs, is of pivotal importance in preventing thromboembolism.[20–23] Also, appropriate OAC prescription according to thromboembolic risk strata is central in reducing the occurrence of both thromboembolic events and death among AF patients. Data from EORP-AF 1-year

follow-up analysis found that ESC guideline-adherent treatment was associated with significantly better outcomes.[6] Specifically, inappropriately prescribed OAC therapy is associated with a higher risk for the composite outcome of 'all-cause death and any TE', with undertreatment or overtreatment conferring a 60% excess relative risk for this composite outcome.

Our data emphasize the high risk of mortality and hospitalizations of AF patients over a long-term follow-up, consistent with the 1-year follow-up data[7] and other previous reports.[24] Different from the previous follow-up report, AF per se does not seem to be the main determinant of death. Moreover, the association between the use of calcium-channel blockers, ACE inhibitors, and statins and the lower mortality, as well as the different co-morbid conditions as predictors of increased mortality, seems to suggest how the overall clinical status (and appropriate treatments) would be the major factor in determining mortality risk among AF patients, perhaps beyond what would be expected from stroke risk strata and OAC therapy use.

Together with recent observations about the higher risk for cardiovascular events associated with the presence of polypharmacy (defined as the contemporary use of five or more drugs) and the poorer clinical status of such patients,[25] these data suggest the need for additional steps towards a more comprehensive clinical evaluation and medical management of AF patients to reduce mortality, going beyond stroke risk assessment and OAC prescription.

Limitations

The most important limitation of our study is its observational nature, and given its modest size, it was not powered to detect differences in some endpoints. Moreover, our study is based on cardiologist-managed patients. Another major limitation is the high number of patients lost to follow-up that may hamper the discriminatory ability of some analyses, potentially reducing generalizability of the results. Finally, data on anticoagulation control are not currently available for this cohort and cannot be considered in this analysis.

Conclusions

In this 2-year follow-up report from EORP-AF, mortality rates with AF are still high (particularly from cardiovascular causes), despite the high prevalent use of OAC. Improved management strategies to reduce major adverse outcomes in AF patients are needed.

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Catheter ablation for atrial fibrillation in a patient with unilateral left pulmonary artery agenesis: an enlarged right pulmonary vein caused arrhythmogenicity of atrial fibrillation

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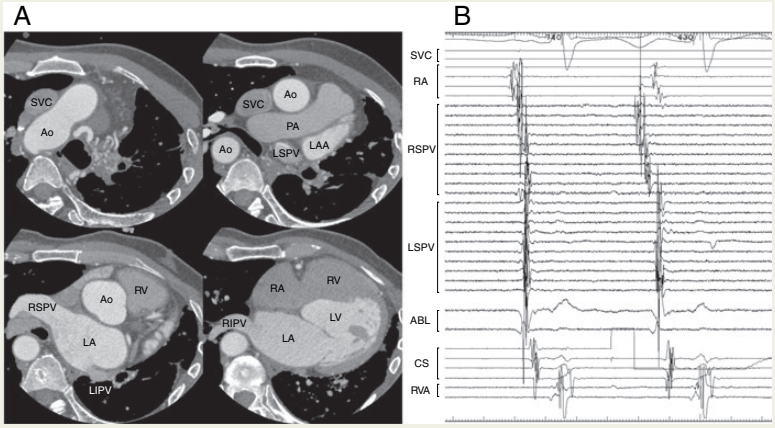
A 55-year-old male with persistent atrial fibrillation (AF) was admitted to our hospital for catheter ablation (CA). Enhanced computerized tomography before CA demonstrated a left shrunken lung and absence of the left main pulmonary artery (*Panel A*). Collateral flow via the coronary and bronchial arteries fed to the peripheral left pulmonary artery. The left pulmonary veins (PVs) were relatively small, and the right superior and inferior PVs were enlarged because of increased pulmonary blood flow (right superior: 31.1 × 15.8 mm, right inferior: 30.3 × 17.7 mm, left superior: 16.5 × 11.8 mm, left inferior: 9.2 × 11.0 mm).



Pulmonary vein potentials in the smallest (left inferior) PV were not prominent compared with the other three PVs. Premature atrial contractions from the enlarged right superior and inferior PVs were reproducibly induced (*Panel B*). We considered that repetitive premature atrial contractions represented arrhythmogenicity in the enlarged right PVs. We performed extensive PV isolation and linear ablation of the cavo-tricuspid isthmus. Enlarged right PVs were easily isolated. There were no complications and no recurrence of atrial arrhythmias.

In the present report, we demonstrate efficacy of CA for AF in a case of left UPAA, which led to arrhythmogenicity owing to the increased size of right PVs because of uneven blood flow.

The full-length version of this report can be viewed at: http://www.escardio.org/Guidelines-&-Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports.