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Original article

Impact of diabetes on the management and outcomes in atrial fibrillation: an analysis from the ESC-EHRA EORP-AF Long-Term General Registry

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ABSTRACT

Background: The prevalence of atrial fibrillation(AF) and diabetes mellitus is rising to epidemic proportions. We aimed to assess the impact of diabetes on the management and outcomes of patients with AF.
Methods: The EORP-AF General Long-Term Registry is a prospective, observational registry from 250 centres across 27 European countries. Outcomes of interest were as follows: i)rhythm control interventions; ii)quality of life; iii)healthcare resource utilisation; and iv)major adverse events.
Results: Of 11,028 patients with AF, the median age was 71 (63–77) years and 2537 (23.0%) had diabetes. Median follow-up was 24 months. Diabetes was related to increased use of anticoagulation but less rhythm control interventions. Using multivariable analysis, at 2-year follow-up, patients with diabetes were associated with greater levels of anxiety ($p = 0.038$) compared to those without diabetes. Overall, diabetes was associated with worse health during follow-up, as indicated by Health Utility Score and Visual Analogue Scale. Healthcare resource utilisation was greater with diabetes in terms of length of hospital stay (8.1 (±8.2) vs. 6.1 (±6.7) days); cardiology and internal medicine/general practitioner visits; and emergency room admissions. Diabetes was an independent risk factor of major adverse cardiovascular event (MACE; HR 1.26 [95% CI, 1.04–1.52]), all-cause mortality (HR 1.28 [95% CI, 1.08–1.52]), and cardiovascular mortality (HR 1.41 [95% CI, 1.09–1.83]).
Conclusion: In this contemporary AF cohort, diabetes was present in 1 in 4 patients and it served as an independent risk factor for reduced quality of life, greater healthcare resource utilisation and excess MACE, all-cause mortality and cardiovascular mortality. There was increased use of anticoagulation therapy in diabetes but with less rhythm control interventions.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, frequently associated with other conditions such as diabetes mellitus [1,2], and confers major healthcare costs [3]. Given the increasing number of AF patients with multi-morbidity, these patients should be managed with a holistic or integrated management approach to AF patient care [4]. Such an approach has been associated with improved clinical outcomes [5,6].

The incidence of diabetes is rising to epidemic proportions, with recent estimates reporting that as many as 8.5% of adults in Europe are affected [7]. Of note, diabetes is an independent risk factor for

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developing AF [8], with approximately 20% of diabetic patients having AF [9,10]. amongst patients with AF, diabetes is a known risk factor for thromboembolic complications [1]. Furthermore, the presence of diabetes in patients with AF has previously been reported to be linked to reduced quality of life, higher symptom burden, and increased risk of cardiovascular hospitalisations and mortality [11,12]. However, much of the relationship between AF and diabetes on quality of life, greater healthcare resource utilisation and outcomes remains ill-defined in contemporary cohorts.

In this study, we aimed to assess the impact of diabetes on the management and outcomes of patients with AF from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry.

2. Methods

2.1. Study design and population

The EORP-AF General Long-Term Registry is a prospective, observational, large-scale multicentre registry from 250 centres across 27 participating European countries. Details of the study design has previously been published [13]. Briefly, adults with AF who presented to cardiology services between October 2013 and September 2016 were enroled. All patients had electrocardiographic confirmation of AF within 12 months prior to enrolment. For this study, we included patients with known diabetes status. Informed consent was obtained from each patient. Institutional review board approval of the study protocol was obtained for every institution, and the study was performed in accordance with the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

2.2. Data collection and definitions

Data on demographics, comorbidities, medication use and investigations were collected at study enrolment. Estimated glomerular filtration rate (eGFR) was assessed using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation. AF classification was based on recommendations from the European Society of Cardiology [14]. Severity of AF-related symptoms was established with the European Heart Rhythm Association (EHRA) classification [15]. Thromboembolic risk was defined according to the CHA_2DS_2-VASc score and bleeding risk according to the HAS-BLED score.

2.3. Quality of life evaluation

Quality of life was evaluated at baseline, and 1-year and 2-year follow-ups using the EQ-5D-5 L questionnaire. This generic, validated, easy to use instrument consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The descriptive system is comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 possible levels for each dimension (no problems, slight problems, moderate problems, severe problems and extreme problems), generating 5^5= 3125 unique health states. Based on the United Kingdom trade-off value set [16], we translated each of the levels into a single numeric value, with lower values corresponding to better health. Thereafter, the value of each dimension was combined into a 5-digit health state which was translated into a single index, termed the Health Utility Score (HUS), by subtracting the total of these values from 1. The best possible health in each dimension (=11,111) corresponded to a HUS of 1.0 (perfect health). A HUS of 0 was equivalent to death. The VAS was used for patients to self-rate their current health status, ranging from 0 (worst health imaginable) to 100 (best health imaginable).

2.4. Study outcomes

Study outcomes were compared between patients with and without diabetes. The outcomes of interest included: i) rhythm control interventions, ii) quality of life, iii) healthcare resource utilisation, and iv) adverse events. Rhythm control interventions evaluated during follow-up were electrical cardioversion, pharmacological cardioversion, catheter AF ablation and surgical AF ablation. Healthcare resource utilisation was based on the occurrence and number of cardiology and internal medicine/general practitioner (GP) visits, as well as emergency room (ER) admissions. Adverse events assessed were major adverse cardiovascular events (MACEs; composite of any thromboembolic event, acute coronary syndrome and cardiovascular [CV] mortality), all-cause mortality, CV mortality, non-CV mortality, any thromboembolic event, ischaemic stroke, acute coronary syndrome, major bleeding and intracranial haemorrhage. Subgroup analysis of patients with diabetes was performed to evaluate the effects of treatment (insulin vs. oral antidiabetics alone) on adverse events.

2.5. Statistical analysis

Continuous variables were described with mean and standard deviation (SD) or median and interquartile range (IQR), and tested for differences with Student's *t*-test and Mann-Whitney U test, respectively. Categorical variables were described as counts and/or percentages, and tested for differences with chi-squared test. A linear regression model was used to evaluate the effects of diabetes on quality of life, length of hospital stay and number of medical visits. The multivariable model was adjusted for CHA_2DS_2-VASc score, type of AF and EHRA classification. Additionally, quality of life during follow-up was adjusted for baseline values. A logistic regression model was used to evaluate the relationship between diabetes and occurrence of medical visits after adjustment for CHA_2DS_2-VASc score, type of AF and EHRA classification.

Differences in the cumulative risk of adverse events were assessed using Kaplan-Meier curves and survival distributions were compared using log-rank test. The association between diabetes and adverse events was investigated using Cox regression analysis. A multivariable model was performed to account for other risk factors of poor outcomes by adjusting for the following covariates: age, gender, estimated glomerular filtration rate, chronic obstructive pulmonary disease, coronary artery disease, heart failure, hypercholesterolaemia, hypertension, peripheral artery disease, previous haemorrhagic event, previous thromboembolism, sleep apnoea and use of anticoagulation.

Linear regression analyses were reported as Beta coefficient with 95% confidence interval (CI). Logistic regression analyses were reported as odds ratio (OR) with 95% CI. Cox regression analyses were reported as hazard ratio (HR) with 95% CI. A two-sided p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY).

3. Results

3.1. Baseline characteristics

For this analysis, we included a total of 11,028 patients with AF, comprising 99.4% of the original EORP-AF General Long-Term Registry cohort. The median age was 71 (63 - 77) years with 4487 (40.7%) women and there were 2537 (23.0%) patients with DM. Baseline characteristics of the groups are shown in Table 1. Patients with diabetes were older and more likely to be women. Furthermore, the presence of diabetes was associated with elevated body mass index and left atrial diameter, and reduced eGFR. amongst patients with diabetes, there was a greater prevalence of comorbidities such as chronic obstructive pulmonary disease, coronary artery disease, heart failure, hypercholesterolaemia, hypertension, peripheral artery disease, previous haemorrhagic event, previous thromboembolism, previous ischaemic

Table 1
Baseline Characteristics and Medication Use.

Baseline Characteristics	Diabetes (n = 2537)	No Diabetes (n = 8491)	p
Age (years), median (IQR)	72 (66 - 78)	70 (62 - 77)	<0.001
Women, n (%)	1091 (43.0%)	3396 (40.0%)	0.007
Heart rate, median (IQR)	80 (69 - 94)	78 (66 - 93)	0.006
sBP (mmHg), median (IQR)	133 (120 - 147)	130 (120 - 140)	<0.001
dBP (mmHg), median (IQR)	80 (70 - 88)	80 (70 - 87)	0.641
BMI (kg/m^2), median (IQR)	29.0 (26.0 - 32.9)	27.1 (24.5 - 30.5)	<0.001
eGFR (mL/min/1.73m^2), median (IQR)	62.6 (46.4 - 79.9)	71.7 (56.9 - 86.1)	<0.001
LA diameter (mm), median (IQR)	46 (41 - 50)	44 (40 - 50)	<0.001
LVEF (%), median (IQR)	55 (44 - 60)	56 (46 - 62)	<0.001
LVH, n (%)	711 (33.1%)	1385 (16.6%)	<0.001
AF classification, n (%)			<0.001
First-detected	343 (13.7%)	2243 (26.9%)	
Paroxysmal	591 (23.6%)	1729 (20.7%)	
Persistent	386 (15.4%)	369 (4.4%)	
Long-standing persistent	106 (4.2%)	2613 (31.3%)	
Permanent	1074 (43.0%)	1385 (16.6%)	
EHRA classification, n (%)			0.002
I	1200 (47.3%)	3807 (44.8%)	0.029
II	822 (32.4%)	3044 (35.9%)	0.001
III	444 (17.5%)	1468 (17.3%)	0.806
IV	71 (2.8%)	171 (2.0%)	0.018
Symptoms	1337 (52.7%)	4684 (55.2%)	0.029
Palpitations	770 (30.4%)	2937 (34.6%)	<0.001
Dyspnoea	813 (32.0%)	2548 (30.0%)	0.050
Fatigue	562 (22.2%)	1771 (20.9%)	0.161
Non-wellbeing	414 (16.3%)	1235 (14.5%)	0.028
Dizziness	272 (10.7%)	954 (11.2%)	0.469
Syncope	68 (2.7%)	226 (2.7%)	0.960
Chest pain	317 (12.5%)	903 (10.6%)	0.009
Fear/anxiety	167 (6.6%)	606 (7.1%)	0.336
Comorbidities, n (%)			
COPD	321 (12.8%)	652 (7.7%)	<0.001
Coronary artery disease	979 (41.4%)	2063 (25.7%)	<0.001
Heart failure	1278 (50.8%)	3040 (36.1%)	<0.001
Hypercholesterolaemia	1380 (56.7%)	2983 (36.7%)	<0.001
Hypertension	1850 (73.5%)	4947 (58.7%)	<0.001
Peripheral artery disease	317 (12.8%)	561 (6.7%)	<0.001
Previous haemorrhagic event	164 (6.5%)	405 (4.8%)	0.001
Previous thromboembolism	331 (13.2%)	937 (11.1%)	0.004
Previous ischaemic stroke	187 (7.5%)	489 (5.8%)	0.003
Sleep apnoea	175 (7.2%)	314 (3.8%)	<0.001
CHA_2DS_2-VASc, median (IQR)	4 (3 - 5)	3 (2 - 4)	<0.001
HAS-BLED, median (IQR)	2 (1 - 3)	1 (1 - 2)	<0.001
Medication Use, n (%)			
Anti-thrombotic	2426 (95.7%)	7896 (93.0%)	<0.001
Any antiplatelet	675 (26.6%)	1531 (18.0%)	<0.001
Acetylsalicylic acid	603 (23.8%)	1377 (16.2%)	<0.001
Clopidogrel	243 (9.6%)	452 (5.3%)	<0.001
Any anticoagulant	2253 (88.8%)	7313 (86.2%)	0.001
Vitamin K antagonist	1405 (55.4%)	4118 (48.5%)	<0.001
Any NOAC	792 (31.2%)	3063 (36.1%)	<0.001
Apixaban	218 (8.6%)	849 (10.0%)	0.036
Dabigatran	175 (6.9%)	685 (8.1%)	0.055
Edoxaban	24 (0.9%)	79 (0.9%)	0.941
Rivaroxaban	375 (14.8%)	1450 (17.1%)	0.007
Anti-arrhythmic drugs	573 (22.7%)	2461 (29.1%)	<0.001
Flecainide	37 (1.5%)	322 (3.8%)	<0.001
Propafenone	54 (2.1%)	335 (4.0%)	<0.001
Amiodarone	435 (17.2%)	1519 (18.0%)	0.411
Sotalol	44 (1.7%)	253 (3.0%)	0.001
Other treatments			
ACE inhibitor	1243 (49.3%)	3463 (40.9%)	<0.001
Aldosterone blocker	577 (22.9%)	1425 (16.9%)	<0.001
Angiotensin receptor blocker	606 (24.0%)	1480 (17.5%)	<0.001
Beta-blocker	1709 (68.3%)	5143 (61.5%)	<0.001
Dihydropyridine CCB	569 (22.6%)	1282 (15.2%)	<0.001
Digoxin	481 (19.1%)	1115 (13.2%)	<0.001
Diuretic	1657 (65.7%)	4008 (47.4%)	<0.001
Statin	1427 (56.5%)	3210 (38.0%)	<0.001

ACE, angiotensin converting enzyme; AF, atrial fibrillation; BMI, body mass index; CCB, calcium-channel blocker; COPD, chronic obstructive pulmonary disease; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; IQR, interquartile range; LA, left atrium; LVEF, left ventricle ejection fraction; LVH, left ventricular hypertrophy; NOAC, non-vitamin K oral anticoagulant; sBP, systolic blood pressure.

stroke and sleep apnoea. The median CHA_2DS_2-VASc and HAS-BLED scores were increased amongst patients with diabetes.

3.2. Baseline medication use

The use of medications at baseline are summarised in Table 1. Patients with diabetes were more likely to receive anticoagulation therapy (88.8% vs. 86.2%), particularly in the form of vitamin K antagonist (55.4% vs. 48.5%), and other treatments such as angiotensin converting enzyme inhibitor, aldosterone blocker, angiotensin receptor blocker, beta-blocker, dihydropyridine calcium-channel blocker, digoxin, diuretic and statin. Differences in the rates of anticoagulation therapy between the groups were attenuated by accounting for those with an indication for treatment according to current European Society of Cardiology guidelines, though variations in the choice of vitamin K antagonist vs. non-vitamin K antagonist oral anticoagulants persisted. Antiarrhythmic drugs were less frequently prescribed in patients with diabetes (22.7% vs. 29.1%).

3.3. Diagnostic investigations and rhythm control interventions

In terms of diagnostic investigations within 12 months prior to enrolment, trans-thoracic echocardiography (80.5% vs. 77.7%) and invasive coronary angiography (17.6% vs. 12.5%) were more commonly performed in patients with diabetes (**Supplementary Figure 1**). The presence of diabetes was associated with reduced trans-oesophageal echocardiography (10.2% vs. 12.4%), cardiac computed tomography (2.6% vs. 4.3%) and electrophysiology study (1.5% vs. 2.8%). The median follow-up duration was 24 (IQR 23 - 24 months). During this period, rhythm control interventions in the form of electrical cardioversion, pharmacological cardioversion and catheter AF ablation were undertaken less frequently amongst patients with diabetes (**Supplementary Table 1**).

3.4. Quality of life

At baseline, there were significant differences in all the quality of life indicators of the EQ-5D-5 L questionnaire between patients with and without diabetes (Table 2). These differences were not observed after adjustment for other confounders. At 1-year and 2-year follow-ups, there was reduced quality of life indicators amongst patients with diabetes compared to non-DM. Using multivariable analysis, at 1-year follow-up, patients with diabetes had a trend for worse mobility ($p = 0.051$), and were less able to attend to their self-care ($p = 0.002$) and usual activities ($p = 0.023$), and had greater levels of anxiety ($p = 0.023$) vs. those without diabetes. Using multivariable analysis, at 2-year follow-up, patients with diabetes had a trend to be less able to attend to their usual activities ($p = 0.052$) and had greater levels of anxiety ($p = 0.038$). Overall, diabetes was associated with worse HUS and VAS during follow-up.

3.5. Healthcare resource utilisation

After multivariable adjustment, the presence of diabetes was related to excess internal medicine/GP visits at 1-year follow-up ($p = 0.001$), ER admissions at 1-year follow-up ($p<0.001$) and internal medicine/GP visits at 2-year follow-up ($p = 0.005$) (Table 3). The mean length of stay was greater in the group with diabetes at 8.1 (± 8.2) vs. 6.1 (± 6.7) days in the group without diabetes, $p = 0.012$ following adjustment for other risk factors. After multivariable adjustment, diabetes was associated with more cardiology visits at 1-year and 2-year follow-ups ($p = 0.017$

Table 2
Baseline and Follow-Up Quality of Life Indicators for Diabetes vs. No Diabetes.

EQ-5D-5 L, mean ± SD	Diabetes	No Diabetes	p	Diabetes vs. No Diabetes Beta (95% CI) *	p
Baseline Descriptive indicators					
Mobility	0.057 ± 0.063	0.042 ± 0.060	<0.001	−0.016 (−0.055 to 0.001)	0.151
Self-care	0.023 ± 0.042	0.016 ± 0.036	<0.001	−0.016 (−0.003 to 0.001)	0.148
Usual activities	0.040 ± 0.048	0.031 ± 0.044	<0.001	−0.010 (−0.003 to 0.001)	0.371
Pain/ discomfort	0.053 ± 0.069	0.043 ± 0.065	<0.001	−0.004 (−0.004 to 0.003)	0.747
Anxiety	0.049 ± 0.071	0.044 ± 0.066	0.005	−0.005 (−0.004 to 0.003)	0.680
Health Utility Score	0.778 ± 0.214	0.823 ± 0.198	<0.001	0.012 (−0.005 to 0.016)	0.277
Visual analogue Scale	66 ± 20	69 ± 21	<0.001	0.005 (−0.925 to 1.397)	0.690
EQ-5D-5 L, mean ± SD	**Diabetes**	**No Diabetes**	**p**	**Diabetes vs. No Diabetes** Beta (95% CI)†	**p**
1-Year Follow-Up Descriptive indicators					
Mobility	0.057 ± 0.064	0.037 ± 0.054	<0.001	0.025 (0.000 to 0.007)	**0.051**
Self-care	0.024 ± 0.041	0.014 ± 0.032	<0.001	0.040 (0.001 to 0.005)	**0.002**
Usual activities	0.041 ± 0.047	0.027 ± 0.040	<0.001	0.030 (0.000 to 0.006)	**0.023**
Pain/ discomfort	0.052 ± 0.071	0.038 ± 0.060	<0.001	0.021 (−0.001 to 0.007)	0.117
Anxiety	0.047 ± 0.068	0.037 ± 0.059	<0.001	0.031 (0.001 to 0.009)	**0.023**
Health Utility Score	0.700 ± 0.317	0.793 ± 0.273	<0.001	−0.137 (−0.109 to −0.077)	**<0.001**
Visual analogue Scale	66 ± 20	71 ± 19	<0.001	−0.029 (−2.588 to −0.101)	**0.034**
2-Year Follow-Up Descriptive indicators					
Mobility	0.058 ± 0.066	0.040 ± 0.056	<0.001	0.015 (−0.002 to 0.006)	0.294
Self-care	0.026 ± 0.043	0.015 ± 0.034	<0.001	0.024 (0.000 to 0.005)	0.107
Usual activities	0.043 ± 0.048	0.029 ± 0.041	<0.001	0.029 (0.000 to 0.006)	**0.052**
Pain/ discomfort	0.051 ± 0.068	0.038 ± 0.061	<0.001	0.011 (−0.003 to 0.006)	0.487
Anxiety	0.045 ± 0.065	0.035 ± 0.057	<0.001	0.032 (0.000 to 0.009)	**0.038**
Health Utility Score	0.610 ± 0.374	0.722 ± 0.342	<0.001	−0.135 (−0.132 to −0.090)	**<0.001**
Visual analogue Scale	66 ± 20	72 ± 19	<0.001	−0.037 (−3.171 to −0.309)	**0.017**

*Adjusted for CHA_2DS_2-VASc score, type of atrial fibrillation and European Heart Rhythm Association classification.

† Adjusted for CHA_2DS_2-VASc score, type of atrial fibrillation, European Heart Rhythm Association classification and respective 5Q-5D-5 L scores at baseline. CI, confidence interval.

Table 3
Healthcare Resource Utilisation according to Diabetes vs. No Diabetes.

Any Visits or Admissions,%	Diabetes	No Diabetes	p	Diabetes vs. No Diabetes OR (95% CI)*	p
Cardiology visits 1Y	54.4	57.7	0.003	1.02 (0.93 - 1.13)	0.664
IM/GP visits 1Y	13.6	11.9	0.026	1.29 (1.11 - 1.49)	**0.001**
ER admissions 1Y	23.5	17.3	<0.001	1.29 (1.13 - 1.48)	**<0.001**
Cardiology visits 2Y	68.4	68.1	0.831	1.04 (0.92 - 1.19)	0.512
IM/GP visits 2Y	23.1	21.9	0.186	1.18 (1.05 - 1.33)	**0.005**
ER admissions 2Y	16.5	14.3	0.022	1.05 (0.89 - 1.24)	0.539
Number of Visits or Admissions, mean ± SD	**Diabetes**	**No Diabetes**	**p**	**Diabetes vs. No Diabetes** Beta (95% CI)*	**p**
Cardiology visits 1Y	1.4 ± 2.0	1.4 ± 1.9	0.407	0.025 (0.020 to 0.211)	**0.017**
IM/GP visits 1Y	0.7 ± 2.4	0.6 ± 2.0	0.012	0.031 (0.052 to 0.260)	**0.003**
ER admissions 1Y	1.7 ± 1.3	1.7 ± 1.4	0.649	0.037 (−0.056 to 0.281)	0.190
Cardiology visits 2Y	1.0 ± 1.0	1.0 ± 1.0	0.148	0.024 (0.007 to 0.089)	**0.022**
IM/GP visits 2Y	0.9 ± 2.6	0.8 ± 2.6	0.105	0.018 (−0.013 to 0.238)	0.079
ER admissions 2Y	1.5 ± 1.1	1.5 ± 1.2	0.984	0.000 (−0.176 to 0.174)	0.993

*Adjusted for CHA_2DS_2-VASc score, type of atrial fibrillation and European Heart Rhythm Association classification. 1Y, 1-year follow-up; 2Y, 2-year follow-up; CI, confidence interval; ER, emergency room; GP, general practitioner; IM, internal medicine; SD, standard deviation; OR, odds ratio.

and $p = 0.022$, respectively), and internal medicine/GP visits at 1-year follow-up ($p = 0.003$).

3.6. Adverse events

In the univariate model, patients with diabetes had significantly worse outcomes in terms of MACE (HR 1.58 [95% CI, 1.35 - 1.85]), all-cause mortality (HR 1.59 [95% CI, 1.38 - 1.84]), CV mortality (HR 1.79 [95% CI, 1.44 - 2.24]), non-CV mortality (HR 1.33 [95% CI, 1.00 - 1.77]) and acute coronary syndrome (HR 1.54 [95% CI, 1.16 - 2.04]) (Table 4). There was no statistical difference between the groups for any thromboembolic event, ischaemic stroke, major bleeding and intracranial haemorrhage.

Kaplan-Meier analyses are shown in Fig. 1. Using multivariable analysis, diabetes was independently associated with excess MACE (HR 1.26 [95% CI, 1.04 - 1.52]), all-cause mortality (HR 1.28 [95% CI, 1.08 - 1.52]) and CV mortality (HR 1.41 [95% CI, 1.09 - 1.83]), but not non-CV mortality, any thromboembolic event, ischaemic stroke, acute coronary syndrome, major bleeding and intracranial haemorrhage.

Table 4
Major Adverse Events at 2-Year Follow-Up by the Presence of Diabetes.

Major adverse events	Diabetes %	No Diabetes	Univariate HR (95% CI)	Multivariable* HR (95% CI)
MACE	10.2	6.6	**1.58 (1.35 - 1.85)**	**1.26 (1.04 - 1.52)**
All-cause mortality	11.9	7.6	**1.59 (1.38 - 1.84)**	**1.28 (1.08 - 1.52)**
CV mortality	5.0	2.9	**1.79 (1.44 - 2.24)**	**1.41 (1.09 - 1.83)**
Non-CV mortality	2.8	2.1	**1.33 (1.00 - 1.77)**	1.16 (0.84 - 1.60)
Any thromboembolic event	2.3	1.9	1.20 (0.87 - 1.65)	1.25 (0.85 - 1.83)
Ischaemic stroke	1.3	1.0	1.23 (0.80 - 1.90)	1.21 (0.72 - 2.04)
Acute coronary syndrome	3.1	2.1	**1.54 (1.16 - 2.04)**	1.06 (0.76 - 1.50)
Major bleeding	1.0	0.9	1.06 (0.65 - 1.74)	0.75 (0.43 - 1.33)
Intracranial haemorrhage	0.2	0.3	0.65 (0.25 - 1.69)	0.62 (0.23 - 1.72)

* Adjusted for age, gender, estimated glomerular filtration rate, chronic obstructive pulmonary disease, coronary artery disease, heart failure, hypercholesterolaemia, hypertension, peripheral artery disease, previous haemorrhagic event, previous thromboembolism, sleep apnoea and use of anticoagulation. MACE represents a composite of any thromboembolic event, acute coronary syndrome and CV mortality. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

Subgroup analysis of patients with diabetes who were treated with either insulin or oral anti-diabetics alone found higher rates of MACE, all-cause mortality, CV mortality and acute coronary syndrome amongst insulin users (**Supplementary Table 2**). However, these effects were attenuated after adjusting for confounders with no statistical differences between the groups for any of the adverse outcomes.

4. Discussion

In this large cohort study of AF patients who were prospectively recruited from 250 centres across 27 participating European countries, our principal findings are as follows: (i) 1 in 4 patients with AF had diabetes, and they were older with greater burden of comorbidities as compared to patients without diabetes; (ii) the presence of diabetes was associated with increased use of anticoagulation but less rhythm control interventions whether in the form of anti-arrhythmic drugs, cardioversion or AF ablation; (iii) diabetes was linked to reduced quality of life, particularly in that patients were less able to attend to their usual activities and had greater levels of anxiety; (iv) healthcare resource utilisation was higher amongst those with diabetes in terms of outpatient visits, ER admissions and length of in-hospital stay; and (v) diabetes was an independent risk factor of MACE, all-cause mortality, and CV mortality over a 2-year follow-up period.

Similar to the previous studies, we found a high incidence of diabetes amongst AF patients (23%); driven by an age-dependant increase in both diabetes and AF [9,10,17]. Consequently, as these patients were overburdened with multi-morbidity, they were exposed to an elevated risk of thromboembolic events as compared to patients without diabetes. In response, there was greater use of anticoagulation therapy in diabetes patients, despite their excess risk of major bleeding. Vitamin K antagonist was more frequently prescribed in patients with diabetes; this was likely related to the severity of renal impairment in this group rather than the presence of diabetes per se, as both non-vitamin K antagonist oral anticoagulants and vitamin K antagonist have been shown to be effective amongst these patients. Of note, a recent study showed that patients with diabetes had poorer time-in-therapeutic range (TTR) than patients without diabetes, and that lower TTR was associated with a higher risk of adverse events [18]. This highlights the need for closer monitoring in patients with diabetes. Furthermore, AF is commonly asymptomatic and improved diagnosis focuses on better monitoring [19,20]. The importance of proper evaluation and characterisation of AF patients, including assessment of comorbidities such as diabetes, has been emphasised [21].

Rhythm control interventions during follow-up were less commonly pursued in patients with diabetes likely as a result of their older age and the perceived lower success rate. This is in keeping with the European Society of Cardiology guidelines where a rhythm control strategy is recommended for symptomatic, preferably younger patients to improve the quality of life [4]. Although patients with AF universally have impaired quality of life [22], we found that the coexistence of diabetes was related to poorer quality of life indicators in terms of mobility, self-care, usual activities, pain/discomfort and anxiety; resulting in a worse overall health. At 2-year follow-up, the presence of diabetes was an independent risk factor for poor health due to limitations in usual

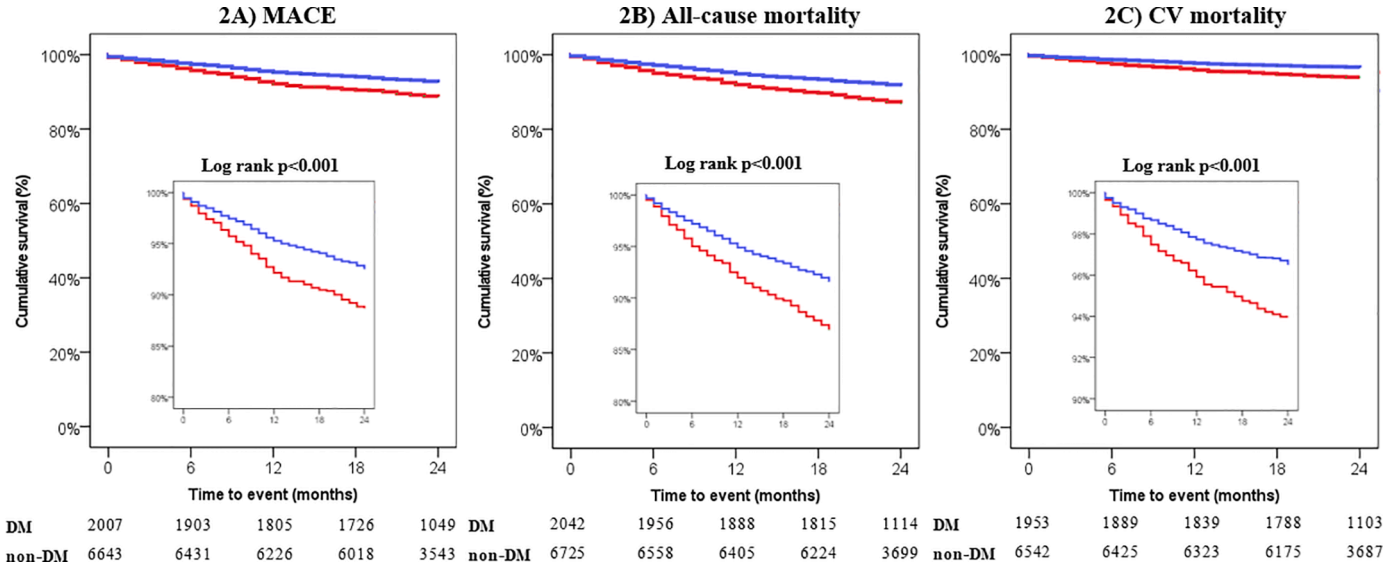

Fig. 1. Kaplan-Meier analysis of MACE, all-cause mortality and CV mortality over 24 months of follow-up in atrial fibrillation patients with and without diabetes. Diabetes = red line, No diabetes = blue line. MACE represents a composite of any thromboembolic event, acute coronary syndrome and CV mortality. CV, cardiovascular; DM, diabetes mellitus; MACE, major adverse cardiovascular event.

activities and greater levels of anxiety.

Consistent with other registries, we found that hospital re-admissions were common in AF patients [11,23], with an excess number of ER admissions and outpatients clinic visits (IM/GP and cardiology type) amongst those with diabetes. This finding may be partly driven by the higher prevalence of other comorbidities (such as chronic obstructive pulmonary disease, heart failure and coronary artery disease) amongst these patients. Likewise, a recent study of 20,172 patients with AF from the Chinese Atrial Fibrillation Registry showed that diabetes was a risk factor for hospitalisation [24]. Other risk factors reported by Dong et al. were concomitant heart failure, coronary artery disease, ischaemic stroke/transient ischaemic attack, chronic obstructive pulmonary disease and renal failure. Notably, the number of AF-related hospitalisations is acknowledged as a significant healthcare burden that is predicted to rise over the next 2 decades [3]. Overall, a multidisciplinary approach to the management of comorbidities is crucial to improve quality of life and reduce the hospitalisation rate in patients with AF and diabetes [25].

Herein, we demonstrated that amongst AF patients, diabetes was an independent risk factor of MACE, all-cause mortality and CV mortality (but not non-CV mortality, any thromboembolic event, ischaemic stroke, acute coronary syndrome and major bleeding). Similarly, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) study showed that patients with diabetes and AF had an increased risk of CV events (coronary events, stroke and heart failure), all-cause mortality and CV mortality, as compared to the non-AF group [26]. A study of 9749 patients with AF from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry found that diabetes was an associated with increased all-cause mortality and CV mortality, after accounting for other risk factors [11]. These high-risk patients may benefit from SGLT2 (sodium-glucose cotransporter 2) inhibitors which have been shown to reduce adverse events [27], potentially through their mechanistic effects on interstitial myocardial fibrosis and aortic stiffness [28].

4.1. Limitations

The primary limitations of this study are its observational design and the potential for residual confounders. Furthermore, as patients were enroled from cardiology practices in Europe, the results may not be generalisable to the wider population. As we did not account for new cases of diabetes during the follow-up period, the true prevalence of diabetes may have been underestimated [29]. The inclusion of patients who may have developed diabetes following enrolment in the group without diabetes may have reduced the detrimental effects of diabetes observed in our study. Regarding antidiabetic therapies, we had limited information on the type of oral medications or insulin that were prescribed. Moreover, we lacked data on the quality of glucose control, and type or duration of diabetes. The former was potentially important as poor glucose control, indicated by increasing levels of haemoglobin A1c, have been associated with a higher risk of thromboembolic events [30].

5. Conclusions

In this contemporary European cohort of AF patients, diabetes was present in 1 in 4 patients and it served as independent risk factor for reduced quality of life, greater healthcare resource utilisation and excess MACE, all-cause mortality and CV mortality over a 2-year follow-up period. There was increased use of anticoagulation therapy amongst patients with AF and diabetes but they were less likely to receive rhythm control interventions.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Contributorship statement

WYD and GYHL contributed to the design of the study; WYD analysed and interpreted the data, and drafted the manuscript; GB, FM, CBL, TSP, LF and GYHL revised the manuscript critically for important intellectual content.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.04.026.

Appendix

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