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ORIGINAL ARTICLE
Atrial fibrillation

Management and prognosis of atrial fibrillation in diabetic patients: an EORP-AF General Pilot Registry report

Stefano Fumagalli[1]*, Salah A. Said[2], Cecile Laroche[3], Debbie Gabbai[1], Serena Boni[1], Niccolò Marchionni[1], Giuseppe Boriani[4], Aldo P. Maggioni[3,5], Agata Musialik-Lydka[6], Adam Sokal[7], Jens Petersen[8], Harry J.G.M. Crijns[9], and Gregory Y.H. Lip[10] on behalf of the EORP-AF General Pilot Registry Investigators[†]

[1]Department of Experimental and Clinical Medicine, Geriatric Intensive Care Unit, University of Florence and AOU Careggi, Viale Pieraccini 6, 50139 Florence, Italy; [2]Department of Cardiology, Hospital Group Twente, Hengelo, The Netherlands; [3]EURObservational Research Programme Department, European Society of Cardiology, Sophia Antipolis, France; [4]Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena Hospital, Modena, Italy; [5]Centro Studi ANMCO, Florence, Italy; [6]NZOZ "OPIFER", Zabrze, Poland; [7]1st Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center of Heart Diseases, Zabrze, Poland; [8]Sygehus Vendsyssel, Medicinsk afdeling, Hjørring, Denmark; [9]Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands; and [10]Institute of Cardiovascular Sciences, City Hospital, Birmingham, England, UK

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Aims Diabetes mellitus (DM) is one of the most important cardiovascular risk factors. The aim of this study was to evaluate clinical correlates of DM, including management and outcomes, in the EURObservational Research Programme (EORP)-Atrial Fibrillation (AF) General Pilot (EORP-AF) Registry of the European Society of Cardiology.

Methods and results We studied consecutive patients ($N = 3101$) enrolled in 70 centres of nine European countries between February 2012 and March 2013, and compared diabetics with non-diabetics during a 1-year follow-up. In the overall cohort, the prevalence of DM was 20.6%. Diabetics were older (71 ± 9 vs. 68 ± 12 years, $P < 0.0001$) and had more comorbidities, higher CHA_2DS_2-VASc score (4.6 ± 1.6 vs. 2.9 ± 1.7, $P < 0.0001$) and higher prevalence of permanent AF (21.5 vs. 16.0%, $P = 0.0022$). Quality of life amongst DM patients was significantly worse [atrial fibrillation quality of life questionnaire (AF-QoL) score 45.2 ± 19.2 vs. 49.3 ± 20.1, $P < 0.0001$]. Amongst diabetics, the use of electrical cardioversion (16.2 vs. 24.6%, $P < 0.0001$) and catheter ablation (3.3 vs. 8.6%, $P < 0.0001$) was lower, whilst oral anticoagulants were more often prescribed (84.3 vs. 78.9%, $P = 0.0027$). After one year, diabetic patients had significantly higher all-cause (11.9 vs. 4.9%, $P < 0.0001$), cardiovascular (6.2 vs. 1.9%, $P < 0.0001$), and non-cardiovascular mortality (2.3 vs. 1.1%, $P = 0.0356$).

Conclusion In AF patients, DM is associated with a higher prevalence of comorbidities and a worse quality of life. After one year, all-cause, cardiovascular, and non-cardiovascular mortality were significantly higher in diabetic subjects.

Keywords Atrial fibrillation • Diabetes mellitus • Elderly • Oral anticoagulants • Prognosis

Introduction

The incidence of diabetes mellitus (DM) is rapidly growing, paralleling social and cultural changes of Western society. In particular, the ageing process, urbanization, sedentariness, and changes in dietary habits seem to play a significant role in this epidemiological trend.[1] About 8.5% of all European adults are affected by DM.[2] In USA, the prevalence of DM in people >75 years is 14.9% and, with undiagnosed forms, could be as high as 28.3%.[3]

Approximately 20% of diabetic patients have atrial fibrillation (AF).[4] The Framingham Heart Study showed that the presence of DM favoured the development of incident AF, both in men and

* Corresponding author. Tel: +39 055 2758135, Fax: +39 055 7946297, Email: stefano.fumagalli@unifi.it;fumadue@tin.it

† Listed in the Supplementary material online, *Appendix 1*.

women.[5] Furthermore, AF and DM are associated with a higher risk of stroke and thromboembolism, and the presence of both seems additive to risk.[6,7] Indeed, DM is one of the risk factors used to compute the $CHADS_2$ and the CHA_2DS_2-VASc risk scores.[8,9]

Despite the growing body of evidence, many aspects of the interactions between AF and DM are still to be clarified. The aim of this study was to evaluate the differences in clinical characteristics, health-related quality of life (HRQL), management and in-hospital and 12-month prognosis between patients with and without DM enrolled in the EURObservational Research Programme-AF General Pilot (EORP-AF) Registry. We also investigated the independent predictors of mortality at the follow-up evaluation.

Methods

The EORP-AF Registry

The baseline features and the main results of the EORP-AF Registry have been previously published.[10,11] In brief, the EORP-AF Registry, established by the European Society of Cardiology (ESC), originates from the need to know how ESC participating countries manage AF patients, the degree of concordance of medical treatment with current guidelines, and what is the current long-term prognosis of the arrhythmia.[10,11]

Between February 2012 and March 2013, consecutive patients were enrolled in 70 centres in nine European Countries (i.e. Belgium, Denmark, Greece, Italy, Norway, Poland, Portugal, Romania, and The Netherlands). The Registry population comprised in- and outpatients with an AF documented by 12-lead electrocardiogram (ECG), 24-h Holter ECG, or other ECG recordings. The qualifying episode should have occurred in the last 12 months, independently of its presence at the time of enrollment. A primary or secondary diagnosis of AF was allowed. Each centre had to recruit at least 20 patients, with a total target Registry population of 3000 subjects. Follow-up visits were scheduled at 12, 24, and 36 months.[10,11] For the purpose of this study, we will present data at the 12-month evaluation only. Our landmark analysis, such as in the first follow-up EORP-AF Registry report,[11] was always centred on this time window in order to avoid attrition and to maintain an adequate sample size.

At baseline and at the follow-up, clinical data, HRQL evaluation, and drug therapy were collected in an electronic web-based chart. Hospital charts and other medical reports constituted the preferred source of information for the follow-up evaluation. Bleeding events were classified according to the criteria of the International Society on Thrombosis and Haemostasis.[12] Laboratory and instrumental data were obtained at baseline only. Health-related quality of life was assessed with a self-administered questionnaire (atrial fibrillation quality of life questionnaire (AF-QoL)) consisting of 18 items exploring psychological (7 items), physical (8 items), and sexual (3 items) domains. All questions refer to feelings perceived in the preceding month and can be answered on a five-point Likert scale (from 1 to 5), with lower scores indicating a greater negative impact of the arrhythmia on HRQL.[13]

The Ethical Committee of all participating centres approved the study protocol.

Statistical analysis

For the aim of this study, the EORP-AF Registry population was stratified into two groups according to the presence of DM.

Continuous variables are reported as mean ± standard deviation or as median and interquartile range. Between-group comparisons were made using a non-parametric test (the Kruskal–Wallis test). Categorical variables are reported as percentages (without missing values if applicable). Between-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 were used.

Plots of the Kaplan–Meier curves for death according to DM status (diabetic patients vs. non-diabetic patients) were performed. The survival distributions were compared using the log-rank test. The consistency of the influence of DM on mortality across specific subgroups of patients was tested with the Cochran–Mantel–Haenszel Statistics.

A stepwise multiple Cox regression analysis was used to determine the predictors of all causes of death including all the candidate variables (variables with $P < 0.10$ in univariate analysis). A significance level of 0.05 was required to allow variable entrance (SLENTRY = 0.05) and stay into the model (SLSTAY = 0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal.

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

Results

The EORP-AF Investigators enrolled 3 101 patients (mean age 69 ± 11 years, men 59.7%). Mean CHA_2DS_2-VASc and HAS-BLED scores were, respectively, 3.2 ± 1.8 and 1.4 ± 1.1. Atrial fibrillation was the main diagnosis in 60.2% of cases, and the prevalence of DM was 20.6% ($N = 638/3101$). Diabetic patients were older and as expected, had a higher prevalence of comorbidities (*Table 1*). Accordingly, mean CHA_2DS_2-VASc score was higher, with almost all diabetic subjects being in the high-risk group. When DM was present, AF was responsible for hospitalization or evaluation in the ambulatory or outpatient clinic in a lower proportion of cases (*Table 1*).

Patients with DM more often presented with permanent AF and had a lower prevalence of paroxysmal AF. Of presenting symptoms, dyspnoea, and chest pain were more commonly seen in diabetic subjects.

Health-related quality of life

Data on HRQL are available for 1877 patients (60.5% of the whole population). The presence of DM was associated to a worse HRQL, with lower AF-QoL scores in total, psychological, physical, and sexual activity domains (*Table 1*). The higher CHA_2DS_2-VASc score of diabetic individuals explained these differences. Indeed, at bivariate analysis, each point of increase of the CHA_2DS_2-VASc was associated with a mean reduction of the total AF-QoL score of 2.5 ± 0.3 points ($P < 0.0001$); in this model, DM lost its statistical significance ($P = 0.998$).

Rhythm- and rate-control strategies

While pharmacological cardioversion did not differ by group, external electrical cardioversion (ECV) and ablation procedures were significantly more common in non-DM subjects (*Table 2*).

In a symptomatic population, a rhythm-control strategy was the preferred option independent of the presence of DM (diabetic patients 68.1% vs. non-diabetic patients 68.2%, $P = 0.3556$). If symptoms were absent, sinus rhythm restoration was more frequently pursued in subjects without DM (29.5 vs. 42.9%, $P = 0.0002$).

Table 1 Clinical characteristics of patients by presence of diabetes[a]

	Diabetes		*P*-value
	No (*N* = 2463)	Yes (*N* = 638)	
Age (years)	68 ± 12	71 ± 9	<0.0001
Men	59.8	58.9	0.6757
CAD	32.6	50.1	<0.0001
CHF	43.9	60.5	<0.0001
EF	53.1 ± 13.2	49.3 ± 14.0	<0.0001
<30%	6.2	10.7	<0.0001
30–44%	15.5	20.5	
45–54%	20.0	24.5	
≥55%	58.3	44.3	
COPD	9.7	15.9	<0.0001
CRF	10.8	21.9	<0.0001
CVD			
Stroke	5.7	8.9	0.0033
TIA	3.7	5.6	0.0344
Haemorrhages	5.7	6.7	0.3074
Hypertension	67.0	84.6	<0.0001
Hyperthyroidism	2.9	3.3	0.5748
CHA_2DS_2-VASc (score)	2.9 ± 1.7	4.6 ± 1.6	<0.0001
Low risk	10.2	0	<0.0001
Moderate risk	12.6	1.3	
High risk	77.2	98.7	
HAS-BLED (score)	1.3 ± 1.0	1.7 ± 1.1	<0.0001
AF			
First episode	30.3	30.6	0.0022
Paroxysmal	27.8	21.6	
Persistent	21.4	20.8	
Persistent LS	4.5	5.4	
Permanent	16.0	21.5	
AF as main diagnosis	63.9	45.9	<0.0001
Symptoms	61.2	57.1	0.0548
Palpitations	74.1	71.4	0.3048
Dyspnoea	52.3	59.9	0.0093
Fatigue	45.8	50.3	0.1265
Non-wellbeing	34.2	38.5	0.1217
Dizziness	23.1	27.7	0.0650
Chest pain	22.4	28.0	0.0235
Fear/anxiety	20.8	17.3	0.1405
EHRA class			
I	38.8	42.9	0.0026
II	32.4	24.9	
III	23.2	26.5	
IV	5.6	5.6	
HR (bpm)	90 ± 30	91 ± 28	0.2476
SAP (mmHg)	131 ± 20	135 ± 22	<0.0001
DAP (mmHg)	79 ± 13	78 ± 13	0.5823
Hb (g/dL)	13.6 ± 1.8	13.0 ± 1.9	<0.0001
AF-QoL (score)			
Psychological domain	20.2 ± 8.0	19.1 ± 8.1	0.0106
Physical domain	21.2 ± 9.6	18.6 ± 9.1	<0.0001
Sexual activity domain	9.8 ± 4.2	9.3 ± 4.3	0.0252
Total score	49.3 ± 20.1	45.2 ± 19.2	<0.0001

AF, atrial fibrillation; AF-QoL, atrial fibrillation quality of life questionnaire; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CHA_2DS_2-VASc low/moderate/high risk, proportion of patients scoring 0/1 (only for men)/≥2; CHF, chronic heart failure; CRF, chronic renal failure; CVD, cerebrovascular disease; EF, left ventricular ejection fraction; EHRA, European Heart Rhythm Association; Haemorrhages, history of haemorrhages; Hb, haemoglobin concentration; HR, heart rate; Persistent LS, long-standing persistent atrial fibrillation; SAP/DAP, systolic/diastolic arterial pressure; SD, standard deviation; Symptoms, atrial fibrillation symptoms; TIA, transient ischaemic attack.
[a]Continuous variables are expressed as mean ± SD, categorical variables as percentages.

Table 2 Diagnostic and therapeutic procedures by presence of diabetes

	Diabetes		*P*-value
	No (*N* = 2463)	Yes (*N* = 638)	
Diagnostic procedures (%)			
Coronary angiography	12.9	20.6	<0.0001
Echocardiography	91.7	92.2	0.7395
EPS	4.5	2.8	0.0557
Exercise stress test	8.2	6.0	0.0636
Holter monitoring	17.4	15.0	0.1374
TOE	12.1	8.4	0.0092
Thyroid blood tests			
Pre-enrollment	53.9	52.5	0.8729
Baseline evaluation	40.2	42.3	0.7765
Programmed	22.2	30.8	0.2581
Therapies (%)			
AF ablation	8.6	3.3	<0.0001
AF surgery	0.3	0.5	0.7067
Electrical cardioversion	24.6	16.2	<0.0001
Pharmacological cardioversion	24.0	27.3	0.0892
ICD implantation	0.7	2.4	0.0004
Pacemaker implantation	4.9	3.8	0.2211

AF, atrial fibrillation; Echocardiography, transthoracic echocardiography; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator; TOE, transoesophageal echocardiography.

Accordingly, the use of Class IC antiarrhythmic drugs was more common in non-DM patients, while we did not find any difference in the use of Class III agents, beta-blockers, and non-dihydropyridine calcium antagonists (*Table 3*).

Given the higher prevalence of chronic heart failure (CHF), an implantable cardioverter-defibrillator was more frequently used in DM patients (*Table 2*).

Table 3 Antithrombotic and other medical therapy by presence of diabetes

	Diabetes		*P*-value
	No (*N* = 2463)	Yes (*N* = 638)	
Antithrombotic therapy (%)			
At least one antithrombotic	94.6	97.8	0.0007
Oral anticoagulants	78.9	84.3	0.0027
VKA	70.3	76.7	0.0015
Dabigatran	7.2	5.3	0.0963
Rivaroxaban	1.5	2.2	0.2206
Antiplatelet agents			
ASA	29.0	36.9	0.0001
Clopidogrel	8.5	14.6	<0.0001
ASA/clopidogrel	5.9	10.2	0.0001
Prasugrel	0.2	0.2	>0.999
Ticagrelor	0.2	0.2	>0.999
Other anticoagulants			
LMWH	4.1	7.4	0.0006
Fondaparinux	0.1	0	>0.999
Antiarrhythmic drugs (%)			
At least one antiarrhythmic	36.6	32.7	0.0648
Class IC	11.5	5.5	<0.0001
Flecainide	5.6	2.4	0.0007
Propafenone	5.9	3.1	0.0063
Class III	25.4	27.8	0.2119
Amiodarone	20.7	23.7	0.0951
Dronedarone	0.3	0.2	0.6957
Sotalol	4.4	3.9	0.5744
Other drugs			
ACE-inhibitors	41.5	49.5	0.0003
Angiotensin receptor blockers	20.8	25.6	0.0080
Anti-aldosterone agents	23.1	29.9	0.0004
Beta-blockers	69.0	71.0	0.3368
Digoxin	18.6	23.9	0.0029
Diuretics	46.7	65.3	<0.0001
DP Ca-antagonists	12.5	17.1	0.0022
Non-DP Ca-antagonists	5.9	7.1	0.2718
Oral antidiabetics	0.0	69.9	<0.0001
Insulin	0.0	27.3	<0.0001
Statins	45.5	64.0	<0.0001

ASA, acetylsalicylic acid; DP, dihydropyridine; LMWH, low molecular weight heparin; VKA, Vitamin K antagonists.

Antithrombotic and other drug therapy

Diabetic patients received oral antidiabetic agents and insulin in 69.9 and in 27.3% of cases, respectively. Drugs acting on the renin angiotensin system, anti-aldosterone agents, digitalis, diuretics, dihydropyridine calcium antagonists, and statins were commonly prescribed if DM was present (*Table 3*).

Overall, 95.3% of our subjects were prescribed an antithrombotic drug; the proportion was significantly higher in the case of DM because of a larger use of both oral anticoagulants and antiplatelet agents (*Table 3*). At discharge from hospital or at the end of the enrollment visit, the combined use of an anticoagulant with an antiplatelet agent was observed in 29.4% and 17.6% of diabetic and non-diabetic subjects, respectively ($P < 0.0001$). At the 1-year follow-up, the proportion of patients taking an oral anticoagulant was only slightly reduced from baseline (DM 82.9 vs. non-DM 75.3%, $P = 0.0004$). Therapy with antiplatelet agents alone (DM 34.7 vs. non-DM 26.5%, $P = 0.0003$) or in combination with an anticoagulant drug (DM 23.7 vs. non-DM 13.7%, $P < 0.0001$) followed the same trend.

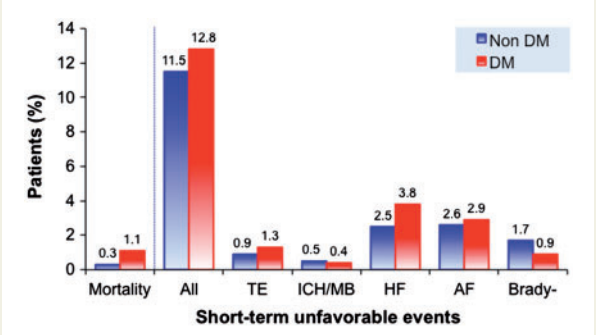

Figure 1 Incidence of in-hospital and acute (within 15 days from the enrollment) adverse events in the EORP-AF Registry by presence of diabetes mellitus. Only most frequent or severe occurrences are reported. AF, AF relapse; All, all unfavourable events other than mortality; Brady-, bradyarrhythmias; DM, diabetes mellitus; HF, heart failure; ICH/MB, intracerebral haemorrhage/major bleeding; Mortality, all-cause mortality; TE, thromboembolism.

In-hospital and acute adverse events

Patients were enrolled during their in-hospital stay in 64.0% of cases, with the remaining enrolled from outpatients and ambulatory settings. Overall mortality was 0.5% ($N = 10/1984$), higher, yet not statistically significant, in patients with DM ($P = 0.0507$) (*Figure 1*).

Major complications during hospitalization or in the 15 days following the enrollment occurred in 11.5% ($N = 177$) of non-diabetic and in 12.8% ($N = 57$) of diabetic patients ($P = 0.4391$), respectively. No differences between the DM and non-DM groups were observed in the incidence of cardio-embolic events, intra-cerebral haemorrhage or major bleeding, CHF, AF recurrence, bradyarrhythmias, and ventricular tachyarrhythmias (*Figure 1*).

Mortality and adverse events at follow-up

Follow-up data at 12 months were available for 84.7% of the whole population ($N = 2627/3101$). The composite of all thromboembolic events was higher in DM patients (5.6 vs. 3.5%, $P = 0.0439$). The incidence of stroke/transient ischaemic attack (TIA) (on the whole, 1.0%), and of peripheral or pulmonary embolism (on the whole, 0.1%) was low and not different between groups ($P = 0.5875$ and $P = 1.0000$, respectively). New coronary events were significantly higher if DM was present, whilst the incidence of major bleeding was low (on the whole, 1.1%) and not different in the two groups of subjects ($P = 0.2999$) (*Figure 2*).

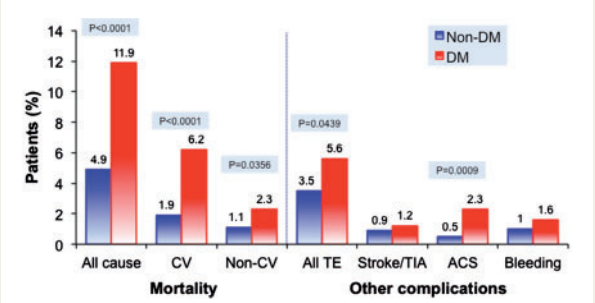

Figure 2 Distribution of main adverse events at the 12-month follow-up by presence of diabetes mellitus. ACS, acute coronary syndromes; CV, cardiovascular; DM, diabetes mellitus; TE, thromboembolic complications; TIA, transient ischaemic attack.

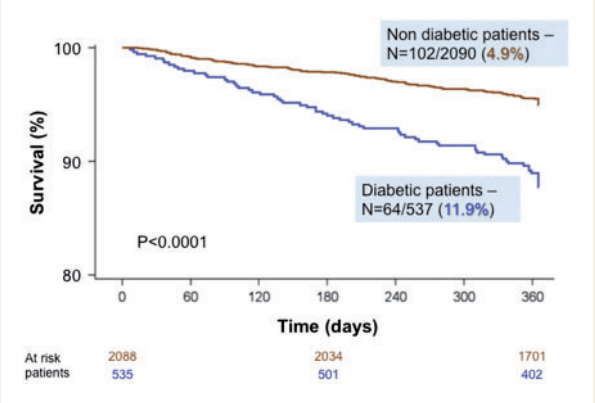

Figure 3 All-cause mortality during the 12-month follow-up in diabetic and non-diabetic patients (Kaplan–Meier analysis).

At the 12-month evaluation, 6.3% ($N = 166/2627$) of the enrolled population was dead. Overall mortality was significantly higher in DM patients and, on the Kaplan–Meier analysis, survival curves diverged immediately after the enrollment (*Figure 3*). Amongst DM patients, mortality for both cardiovascular and non-cardiovascular causes was also higher (*Figure 2*). The association between DM and mortality persisted also in the subgroup analysis. In particular, no differences in behaviour were observed among age (<75 vs. ≥75 years, $P < 0.001$), gender (men vs. women, $P < 0.001$), and CHA_2DS_2-VASC (low vs. moderate vs. high risk score, $P < 0.001$) strata.

Univariate and multivariate analysis of mortality

Univariate predictors of all-cause mortality were age and several important comorbidities, such as coronary artery disease (CAD), CHF, chronic obstructive pulmonary disease, chronic renal failure (CRF), malignant neoplasms, and TIA. Better HRQL was associated with reduced mortality ($P = 0.0068$). New minor bleeding and thromboembolic events during the follow-up identified the high-risk group. Improved survival was associated with AF as the main diagnosis and the presence of AF-related symptoms at the baseline evaluation. Among therapies, the use of oral anticoagulants and statins was higher in those who survived (*Table 4*).

Cox multivariate analysis (P for the whole model <0.0001) confirmed that DM, even after adjustment, was a significant independent predictor of all-cause mortality. Diabetic subjects had a risk of events nearly twofold higher than the non-DM AF population (hazard ratio (HR) 1.86, 95% confidence interval (CI) 1.31–2.62; $P = 0.0004$). The other clinical variables, independently associated with prognosis, were age, the presence of CHF, CRF, a previous TIA, and minor

Table 4 Clinical characteristics and 12-month survival (univariate analysis)

	Alive		*P*-value
	No (*N* = 166)	Yes (*N* = 2461)	
Age (years)[a]	79 (70–84)	69 (61–76)	<0.0001
Men (%)	60.2	60.5	0.9465
Bleeding			
Major (%)	3.6	1.6	0.0625
Minor (%)	13.3	4.1	<0.0001
CAD (%)	49.3	35.0	0.0004
CHF (%)	75.0	43.9	<0.0001
COPD (%)	23.3	10.6	<0.0001
CRF (%)	41.2	11.1	<0.0001
CVD (%)			
Stroke	5.5	6.1	0.7227
TIA	10.3	3.7	<0.0001
Hyperthyroidism (%)	3.7	3.0	0.6328
Malignant neoplasms (%)	10.6	4.9	0.0016
Thromboembolism (%)	23.0	12.1	<0.0001
AF (%)			
First episode	41.2	29.2	0.0006
Paroxysmal	17.0	27.5	
Persistent	21.2	26.3	
Permanent	20.6	17.1	
AF as main diagnosis (%)	25.3	63.1	<0.0001
AF symptoms (%)	38.6	60.3	<0.0001
EHRA Class			
I (%)	61.4	39.7	<0.0001
II (%)	15.7	32.3	
III (%)	18.1	23.0	
IV (%)	4.8	5.0	
Diuretics at discharge (%)	77.6	49.4	<0.0001
Oral anticoagulants at discharge (%)	75.3	81.6	0.0447
Oral antidiabetics at discharge (%)	23.0	13.5	0.0007
Statins at discharge (%)	41.2	49.3	0.0451

AF, atrial fibrillation; Bleeding/thromboembolism, events during the follow-up; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVD, cerebrovascular disease; EHRA, European Heart Rhythm Association; Persistent, persistent and long-standing persistent; TIA, transient ischaemic attack.
[a]Age is expressed as median value with interquartile range.

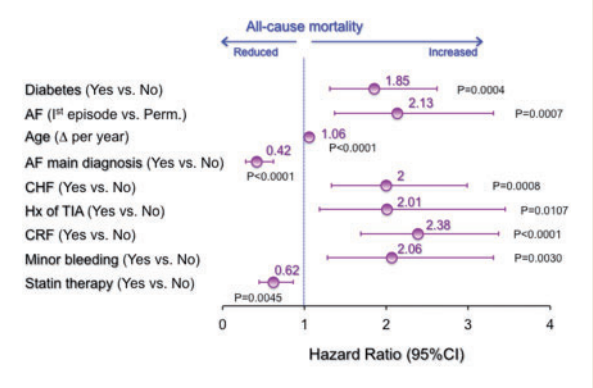

Figure 4 Predictors of 12-month all-cause mortality in the EORP-AF patients (Cox multivariate analysis model). Diabetes mellitus maintains statistical significance even after adjustment for confounders. AF, atrial fibrillation; CHF, chronic heart failure; CI, confidence interval; CRF, chronic renal failure; Perm., permanent; TIA, transient ischaemic attack.

bleeding. Patients with a first episode of arrhythmia were at higher risk than those with a permanent form, whilst AF as the main diagnosis and statin use identified the population with a lower mortality (*Figure 4*).

Discussion

In this ancillary analysis from the EORP-AF Pilot Registry, DM was present in 20.6% of the cohort, and was associated with older age, more comorbidities and higher cardio-embolic risk. AF patients with DM, because of their higher CHA_2DS_2-VASc score, had a worse HRQL. After 12 months, even after adjustment, all-cause, cardiovascular and non-cardiovascular mortality were significantly higher when DM was present.

The high proportion of diabetic individuals in the EORP-AF Registry is consistent with the contemporary age-dependent increase in the prevalence of both DM[3] and AF. Indeed, the arrhythmia can be found in 14.7% and 23.4% of subjects aged 75–84 and ≥85 years, respectively.[14] Furthermore, a large meta-analysis reported that DM associates with an about 40% higher risk of incident AF.[15]

Lack of glycaemic control, increased atrial fibrosis, augmented sympathetic activity and the associated changes in electrical properties of atrial tissue all contribute to the multifactorial link between the two conditions.[16]

Diabetes mellitus is a well-established risk factor for thromboembolic events.[8,9] Recently, the European Prevention of thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF) showed that insulin-dependent diabetics had a significantly higher risk of stroke or systemic embolism at 1-year follow-up compared to non-insulin dependent type 2 diabetics or non-diabetics.[17] Furthermore, analyses of the nationwide Danish registries showed that duration of DM history could be a significant predictor of stroke.[18] In the EORP-AF Registry, antithrombotic therapy was more often prescribed in diabetic patients. Oral anticoagulants, even in association with antiplatelet agents, were more frequently used than in non-DM, consistent with prior reports,[19] proving that guideline recommendations are followed. Interestingly, one study exploring the quality of anticoagulation in a wide cohort of older patients, found that the presence of DM contributed to a significant reduction of time in therapeutic range amongst warfarin users.[20]

In the EORP-AF Registry, the higher prevalence of CAD in diabetic patients explained a more frequent prescription of coronary angiography. Transoesophageal echocardiography was less often employed in subjects with DM, probably because of the lower use of ECV and AF ablation. The older age of the diabetic population could justify these findings. In a previous analysis of the EORP-AF Registry, we showed that both ECV and AF ablation were utilized more often in subjects <75 years than in those ≥75 years.[21] Indeed, AF in elderly individuals may be considered a marker of frailty.[22] In this case, the rate-control strategy would be the preferred therapeutic option.

Our study showed that diabetic patients, when compared with non-diabetics, were characterized by a worse HRQL. The total, and each single-domain score of the AF-QoL questionnaire, were significantly lower in DM subjects, and, at the follow-up, all-cause mortality was higher in those with a poor HRQL. The higher CHA_2DS_2-VASc score of the diabetic population largely explains these results. Indeed, in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), women had both a higher CHA_2DS_2-VASc score and a worse HRQL than men, and showed a progressively poorer psychological status with the increase of thromboembolic risk.[23]

One of the most important findings of this study is the strong association between DM and prognosis at the follow-up, with an all-cause mortality risk nearly two-fold higher in DM than in non-DM subjects. A similar, albeit quantitatively lower excess of all-cause mortality risk (HR 1.23, 95% CI 1.03–1.46), was observed in the Loire Valley Atrial Fibrillation Project, where no differences in the incidence of thromboembolic events and bleeding were evident according to the presence of DM.[24] The link between AF and prognosis, observed in our diabetic patients, is strengthened by the relation of DM with some of the comorbidities associated with 1-year mortality. Indeed, the prevalence of systolic CHF, CRF and a previous TIA was higher in diabetic subjects. It was already found that in patients with CHF, the presence of DM increased the risk of new hospitalizations and cardiovascular mortality during a follow-up of 9.9 months.[25] Furthermore, it was shown that CRF of any degree was associated with higher all-cause mortality in AF patients.[26]

Our results, based on a European experience, are enforced by those recently obtained by the ORBIT-AF Registry, in a wide, prospectively enrolled, USA population ($N = 9479$) stratified by metabolic status. Also in this case, diabetic patients presented a higher burden of comorbid conditions but, in contrast with what we found, they were younger than controls. As in the EORP-AF Pilot Registry, diabetic population was more likely to receive anticoagulant therapy and characterized by a higher mortality risk.[27] Interestingly, also ORBIT-AF diabetic patients, when compared to those without DM, showed a worse HRQL,[27] a finding that we proved closely correlated to clinical complexity, as expressed by the CHA_2DS_2-VASc score.

Limitations

This study is limited by its observational design and we cannot exclude the existence of differences in the evaluation and

management of patients—sometimes very complex—despite the efforts to make the clinical conduct of the registry homogeneous. We do not have data about the quality of anticoagulation control. When EORP-AF data were gathered, non-vitamin K oral anticoagulants had not yet been authorized in some countries. Regarding antidiabetic therapies, we could only differentiate between insulin and oral antidiabetics, with no possibility of further details on specific drugs. Also, no data about the degree of glucose control were present. Data about HRQL were available in only 60% of patients. This prevented us from evaluating the independent effect of the variable on mortality in a multivariate model. Despite these limitations, the EORP-AF Registry allowed to better define clinical characteristics, management and the poor prognosis amongst AF patients presenting with DM.

Conclusions

Diabetic patients represent a large part of AF population. DM is associated with a higher prevalence of comorbidities and a worse impact on quality of life. After one year, despite a greater prescription of antithrombotic therapy, the diabetic population had a significantly higher all-cause, cardiovascular, and non-cardiovascular mortality.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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