Features of Clinical Complexity in European Patients With Atrial Fibrillation: A Report From a European Observational Prospective AF Registry

Marco Proietti, MD, PhD[a,b,c,#], Giulio F. Romiti, MD[a,d,#], Bernadette Corica, MD[a,d], Davide A. Mei, MD[a,e], Niccolò Bonini, MD[a,e,f], Marco Vitolo, MD[a,e,f], Jacopo F. Imberti, MD[a,e,f], Giuseppe Boriani, MD, PhD[e,†], and Gregory Y.H. Lip, MD[a,g,†*]

From the [a] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom, [b] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [c] Division of Subacute Care, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy, [d] Department of Translational and Precision Medicine, Sapienza—University of Rome, Rome, Italy, [e] Department of Biomedical, Metabolic and Neural Sciences, Cardiology Division, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy, [f] Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy and [g] Department of Clinical Medicine, Danish Center for Clinical Health Services Research, Aalborg University, Aalborg, Denmark.

Abstract: There is increasing concern regarding impact of clinical complexity in patients with atrial fibrillation (AF). We explored the impact of different clinical complexity features in AF patients. We analyzed patients from a prospective, observational, multicenter Europe-wide AF registry. Features of clinical complexity among patients with CHA_2DS_2-VASc $\geq$2 were: (1) history of bleeding; (2) frailty; (3) chronic kidney disease (CKD); (4) $\geq$2 features. A total of

# These authors contributed equally.
† Joint senior authors.
*Corresponding author: Gregory Y.H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, 6 West Derby St, Liverpool L7 8TX, United Kingdom. E-mail: gregory.lip@liverpool.ac.uk

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10,169 patients were analyzed. Of these, 141 (1.4%) had history of bleeding, 954 (9.4%) were frail, 1767 (17.4%) had CKD and 1253 (12.3%) had ≥2 features. All features of clinical complexity were less treated with OAC. History of bleeding (HR 1.94, 95% CI 1.32-2.85), frailty (HR 1.38, 95% CI 1.11-1.71), CKD (HR 1.50, 95% 1.28-1.75) and ≥2 features (HR 2.08, 95% CI 1.73-2.51) were associated with outcomes. Presence of features of clinical complexity is associated with lower use of OAC and higher risk of outcomes. (Curr Probl Cardiol 2023;48:101752.)

Introduction

In the last decade, clinical research about atrial fibrillation (AF) has moved from the mere evaluation of thromboembolic risk and analysis of the impact of oral anticoagulation (OAC) to the more comprehensive evaluation of patients' clinical profile, with particular attention to the role of chronic comorbidities.[1-3] Such approach focused on complex features such as multimorbidity, frailty and polypharmacy, all of which influence clinical management and increase the risk of adverse outcomes in patients with AF.[4-8] All these factors-complicating the clinical management of patients and being associated with worse quality of life and increased risk of major adverse outcomes[9,10]-entail the so-called phenotype of "clinical complexity."[11,12]

In observational data, clinical complexity defined as the presence of either multimorbidity, frailty or polypharmacy was found associated with an increased risk for major adverse outcomes.[12] If multimorbidity, frailty and polypharmacy can represent the main "domains" of clinical complexity.[13,14] In the prospective global GLORIA-AF registry, the presence of a clinical history of bleeding, presence of frailty or chronic kidney disease (CKD), as well as the coexistence of ≥2 of these, was associated with an increased thromboembolic risk (CHA_2DS_2-VASc score ≥2) and a higher risk of major adverse outcomes, but a lower odds of receiving OAC and a higher risk of OAC discontinuations, compared to those AF patients with CHA_2DS_2-VASc ≥2 but without any features of clinical complexity.[13]

Recently the Atrial Fibrillation Better Care' (ABC) pathway, has been proposed to streamline the implementation of holistic integrated management,[14] showing a significant effectiveness in reducing all AF-related major adverse outcomes.[15] Currently no data exist about the impact of

adherence to ABC pathway in patients with specific features of clinical complexity.

The aim of this study in a large prospective European AF cohort was to examine the associations of the specific features of clinical complexity, with the following: (1) use of OAC and other antithrombotic drugs; (2) quality of life indicators; (3) the use of healthcare resources; (4) the risk of major adverse outcomes; and (5) the impact of adherence to ABC pathway on the risk of major adverse outcomes in patients with specific features of clinical complexity.

Methods

Data to perform these analyses were derived from a large prospective, observational, multicenter European AF registry. The study enrolled consecutive AF inpatients and outpatients in 250 practices, across 27 countries. Details on study design, baseline characteristics and follow-up are reported elsewhere.[16,17]

Briefly, all patients enrolled had documented AF within 12 months before enrolment. All patients were aged ≥18 years and provided written informed consent. Enrolment was undertaken from October 2013 to September 2016, with planned 1-and 2-year follow-up. Institutional review board approved the study protocol for each country; the study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.[16,17]

Study Procedures

Symptomatic status was defined according to the EHRA score,[18] while thromboembolic and bleeding risk were assessed according to CHA_2DS_2-VASc and HAS-BLED scores, computed according to the original schemes.[18] We defined high thromboembolic risk when CHA_2DS_2-VASc was ≥2 in males and ≥3 in females, and high bleeding risk when HAS-BLED was ≥3. Use of OAC and other antithrombotic drugs was defined at baseline, at the end of enrolment. All data were entered into a centralized electronic case report form (eCRF). Adherence to the ABC pathway was defined as per a previously published study on the same cohort[19] and was evaluated at baseline. The ABC pathway has been proposed to streamline integrated care in AF patients based on the following pillars: (1) Avoid stroke with Anticoagulation; (2) Better symptom management, with patient-centered symptom-directed decisions on rate or rhythm

control; and (3) Cardiovascular comorbidities and risk factor optimization (including lifestyle changes).[14]

Features of Clinical Complexity

Consistent with a previously published analysis,[13] we defined at baseline the presence of the features of clinical complexity, among those subjects with CHA_2DS_2-VASc $\geq$2, as follows:

- History of bleeding: a clinical history of a previous clinically significant bleeding, as reported by investigators in the study eCRF;
- Frailty: according to a 40-items frailty index built as per the cumulative deficit model, as defined in a previous analysis9, presence of frailty was defined as a frailty index $\geq$0.25;
- CKD: presence of CKD was defined based on clinical history, as reported by investigators, or according to a glomerular filtration rate $<$60 mL/min/1.73 m2 evaluated according to CKD-EPI formula.

All patients were assigned uniquely to 1 group, according to the presence of the characteristics described above; those with 2 or more characteristics were included in the "$\geq$2 features" group, while those patients who did not present with any of the features of clinical complexity were included in either the "CHA_2DS_2-VASc $\geq$2" or CHA_2DS_2-VASc $<$2 groups. Reference group for all the analyses was the "CHA_2DS_2-VASc $\geq$2" group (ie, patients with CHA_2DS_2-VASc $\geq$2 but without clinical complexity features).

Domains of Clinical Complexity

Multimorbidity was defined as the number of comorbidities reported at baseline by the study investigators, when a patient presented at least 2 conditions among the list of 12 examined at baseline. Frailty, as reported above, was evaluated according to a 40-items frailty index.[20,21] Polypharmacy was defined according to the number of drugs prescribed at baseline, as the presence of $\geq$5 different drugs taken by a patient.[22]

Follow-Up and Major Adverse Outcomes

All patients discharged alive after the baseline evaluation entered the follow-up. During follow-up all incident major clinical events were recorded by each investigator and entered in the eCRF at 1-and 2-years follow-up visits. We considered as *primary outcome* the occurrence of a

net clinical outcome (NCO) composed of all-cause death, major adverse cardiovascular events (MACEs) (defined as any thromboembolic events, any acute coronary syndrome and cardiovascular death) and major bleeding (defined as intracranial hemorrhage and major extracranial hemorrhage).

As *secondary outcomes* we also considered the components of NCO, as follows: (1) a composite outcome of all-cause death and MACE; (2) all-cause death; (3) MACE; and (4) Major Bleeding. Evaluation of major adverse outcomes was performed by each investigator and not adjudicated centrally. Follow-up was censored at the end of observation or at occurrence of all-cause death, whichever occurred first. Detailed methods regarding the analysis of quality-of-life indicators and use of healthcare resources are reported in Supplementary Materials.

Statistical Analyses

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range [IQR] and differences across the groups were evaluated according to One-Way ANOVA and Kruskal-Wallis One-Way ANOVA, respectively according to the number of groups. Categorical variables were expressed as counts and percentages and differences across groups were evaluated according to the chi-square test.

Linear and logistic regression models were compiled to examine the association between the features of clinical complexity and the various dependent variables. Regression models were adjusted according to different possible multivariate models: (1) *Model 1:* age, sex, type of AF, EHRA score; (2) *Model 2*: age, sex, type of AF, EHRA score, number of comorbidities, number of drugs. All results from regression models were reported as odds ratio (OR) and 95% confidence interval (CI).

Differences in survival according to features of clinical complexity for the primary outcome were analyzed with Log-Rank test and Kaplan-Meier curves were drafted accordingly. Association between the features of clinical complexity and occurrence of major adverse outcomes was examined according to a Cox regression analysis. Two different multivariate models were performed and reported, with different covariate adjustment: (1) Model 1: age, sex, type of AF, EHRA score; Model 2: age, sex, type of AF, EHRA score, number of comorbidities, number of drugs. All results from the Cox regression models were reported as hazard ratio (HR) and 95% CI.

A secondary analysis was performed to evaluate the possible impact of ABC pathway adherence on the primary outcome according to the presence of the features of clinical complexity. The rate of outcome and incidence rate (IR) (events per 100 patients-years) were reported, and 95% CI were calculated according to the exact method.[23] IR ratio (IRR) and 95% CI was then calculated for adherence vs nonadherence to ABC pathway.

A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS statistical software version 28.0.1.0 (IBM, NY) for MacOS 13.2.1, Stata/MP 17.0 (StataCorp, TX) for MacOS 13.2.1, and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) for Windows.

Results

Among the 11,096 patients originally enrolled in the registry, a total of 10,169 (91.6%) had available data to be included in this analysis. Median [IQR] age was 70 [62-77] years, with 4,099 (40.3%) females: 2,002 (19.7%) were at low risk and 8,167 (80.3%) patients with CHA_2DS_2-VASc $\geq$2. Of the latter subgroup, 4052 (39.8%) had no features of clinical complexity, 141 (1.4%) had a clinical history of bleeding, 954 (9.4%) were frail, 1767 (17.4%) had CKD and 1253 (12,3%) had $\geq$2 features of clinical complexity. Baseline characteristics are reported in Table A1.

In the study cohort, 4115 (40.5%) patients had at least 1 feature of clinical complexity. Patients with CKD and with $\geq$2 features of clinical complexity were the oldest, while the frail subgroup was youngest among those with features of clinical complexity ($P < 0.001$). AF patients with $\geq$2 features of clinical complexity were those less likely admitted for AF as primary reason ($P < 0.001$), while those with history of bleeding were more likely permanent AF ($P < 0.001$) (Table A1).

Patients with $\geq$2 features had the highest thromboembolic and bleeding risk, as well as the highest burden of comorbidities (all $P < 0.001$). Frail patients as well as those with $\geq$2 features had the highest frailty index and polypharmacy (all $P < 0.001$). Adherence to ABC pathway was significantly lower in frail patients and in those with $\geq$2 complexity features ($P < 0.001$) (Table A1).

Features and Domains of Clinical Complexity

In Table A1 we show the associations between the features of clinical complexity with multimorbidity, frailty and polypharmacy. After

adjustments according to multivariate model 1, the low-risk group (vs patients with CHA_2DS_2-VASc ≥ 2) was inversely associated with number of comorbidities, frailty index and number of drugs, as well as with presence of both multimorbidity and polypharmacy. Conversely, frail patients, those with CKD and those with ≥ 2 features were all associated with the 3 domains of clinical complexity. Finally, the history of bleeding group was associated with a progressively higher frailty index (Table A2).

Use of Antithrombotic Drugs

In Table 1 we report the use of antithrombotic drugs according to features of clinical complexity. Use of antiplatelet drugs was lowest in the low-risk patients, and highest in those with ≥ 2 features, with increasing higher rate in patients with CKD, history of bleeding and frail patients. Multivariate model 2 showed that only having ≥ 2 features was associated with higher likelihood of being prescribed with antiplatelet drugs (Table 1).

All complexity groups were also associated with lower OAC prescription, being lowest in those with ≥ 2 features. Patients with CKD, those with ≥ 2 features and frail patients were less prescribed with non-vitamin K antagonist oral anticoagulants (NOACs). The final multivariate model found that all the features of complexity were inversely associated with OAC prescription, with history of bleeding associated with a higher prescription of NOACs, while frailty was associated with lower prescription (Table 1). Patients with history of bleeding were more likely not treated with any antithrombotic, and more prescribed with only antiplatelet drugs as were AF patients with those ≥ 2 features of clinical complexity. After full adjustment all the features of clinical complexity were inversely associated with OAC use, especially in those patients with ≥ 2 features (Table 1).

Quality of Life Analysis

At baseline (Table 2), both health utility score (HUS) and visual analog scale (VAS) mean (SD) values were highest in patients with low risk, while were progressively lower in patients with history of bleeding, CKD, frail ones, and those with ≥ 2 features (both $P < 0.001$). On univariate linear regression analysis, the low-risk group was associated with higher HUS values, compared to CHA_2DS_2-VASc ≥ 2 group, while history of CKD, having ≥ 2 complexity features and being frail were

TABLE 1. Use of antithrombotic drugs and association with features of clinical complexity

	Low risk	CHA_2DS_2-VASc ≥2	Hx bleeding	Frailty	CKD	≥2 Features
Any antiplatelet drug, n (%)*	250 (12.5)	704 (17.4)	30 (21.3)	261 (27.4)	364 (20.6)	421 (33.7)
Univariate, OR [95% CI]	0.68 [0.58-0.79]	Ref.	1.28 [0.85-1.94]	1.80 [1.52-2.11]	1.23 [1.07-1.42]	2.41 [2.09-2.78]
Multivariate 1, OR [95% CI]	0.61 [0.51-0.73]	Ref.	1.38 [0.91-2.10]	2.13 [1.78-2.53]	1.27 [1.09-1.47]	2.82 [2.42-3.29]
Multivariate 2, OR [95% CI]	1.06 [0.87-1.28]	Ref.	1.39 [0.90-2.15]	1.12 [0.92-1.37]	1.11 [0.95-1.29]	1.36 [1.13-1.64]
Any OAC, n (%)*	1524 (76.2)	3662 (90.4)	110 (78.0)	829 (87.0)	1559 (88.3)	986 (78.7)
Univariate, OR [95% CI]	0.34 [0.29-0.39]	Ref.	0.38 [0.25-0.57]	0.71 [0.57-0.88]	0.80 [0.67-0.96]	0.39 [0.33-0.47]
Multivariate 1, OR [95% CI]	0.43 [0.36-0.51]	Ref.	0.30 [0.20-0.46]	0.60 [0.48-0.75]	0.71 [0.59-0.85]	0.29 [0.24-0.35]
Multivariate 2, OR [95% CI]	0.62 [0.50-0.76]	Ref.	0.28 [0.17-0.45]	0.52 [0.39-0.68]	0.70 [0.57-0.85]	0.25 [0.20-0.32]
Type of OAC, n (%)*						
VKA	750 (49.2)	2080 (56.8)	55 (50.0)	567 (68.4)	921 (59.1)	663 (67.2)
NOAC	774 (50.8)	1582 (43.2)	55 (50.0)	262 (31.6)	638 (40.9)	323 (32.8)
Univariate, OR [95% CI]						
NOAC (vs VKA)	1.36 [1.20-1.53]	Ref.	1.32 [0.90-1.92]	0.61 [0.52-0.71]	0.91 [0.81-1.03]	0.64 [0.55-0.74]
Multivariate 1, OR [95% CI]						
NOAC (vs VKA)	1.22 [1.05-1.40]	Ref.	1.62 [1.09-2.39]	0.56 [0.47-0.67]	0.90 [0.79-1.02]	0.67 [0.57-0.78]
Multivariate 2, OR [95% CI]						
NOAC (vs VKA)	0.90 [0.77-1.05]	Ref.	1.64 [1.10-2.43]	0.80 [0.67-0.97]	0.98 [0.86-1.28]	1.06 [0.88-1.28]
Antithrombotic pattern, n (%)*						
None	337 (16.9)	159 (3.9)	13 (9.2)	50 (5.2)	78 (4.4)	97 (7.7)
Only antiplatelet	139 (7.0)	230 (5.7)	18 (12.8)	74 (7.8)	129 (7.3)	170 (13.6)
Only VKA	681 (34.1)	1761 (43.5)	45 (31.9)	426 (44.7)	740 (41.9)	463 (37.0)
Only NOAC	732 (36.6)	1,425 (35.2)	53 (37.6)	216 (22.7)	584 (33.1)	271 (21.6)
OAC & antiplatelet	111 (5.6)	474 (11.7)	12 (8.5)	187 (19.6)	235 (13.3)	251 (20.0)
Univariate, OR [95% CI]						
None	-	Ref.	-	-	-	-
Only antiplatelet	0.28 [0.21-0.38]		0.96 [0.46-2.01]	1.02 [0.68-1.54]	1.14 [0.81-1.62]	1.21 [0.88-1.67]
Only VKA	0.18 [0.15-0.22]		0.31 [0.16-0.59]	0.77 [0.55-1.07]	0.86 [0.64-1.14]	0.43 [0.33-0.57]

(*continued on next page*)

TABLE 1. (*continued*)

	Low risk	CHA_2DS_2-VASc $\geq$2	Hx bleeding	Frailty	CKD	$\geq$2 Features
Only NOAC	0.24 [0.20-0.30]		0.45 [0.24-0.85]	0.48 [0.34-0.68]	0.83 [0.63-1.11]	0.31 [0.23-0.41]
OAC & antiplatelet	0.11 [0.08-0.15]		0.31 [0.14-0.69]	1.25 [0.87-1.80]	1.01 [0.74-1.38]	0.87 [0.65-1.17]
Multivariate 1, OR [95% CI]						
None	-	Ref.	-	-	-	-
Only antiplatelet	0.41 [0.30-0.58]		0.94 [0.44-1.99]	1.13 [0.74-1.47]	0.91 [0.63-1.30]	1.04 [0.74-1.47]
Only VKA	0.30 [0.23-0.38]		0.22 [0.12-0.43]	0.69 [0.49-0.98]	0.66 [0.49-0.98]	0.28 [0.21-0.38]
Only NOAC	0.34 [0.26-0.44]		0.42 [0.22-0.79]	0.40 [0.28-0.58]	0.66 [0.49-0.89]	0.22 [0.16-0.29]
OAC & antiplatelet	0.14 [0.10-0.20]		0.25 [0.11-0.57]	1.25 [0.86-1.82]	0.85 [0.61-1.17]	0.69 [0.50-0.95]
Multivariate 2, OR [95% CI]						
None	-	Ref.	-	-	-	-
Only antiplatelet	0.73 [0.50-1.06]		0.87 [0.38-2.01]	0.61 [0.36-1.01]	0.83 [0.56-1.21]	0.43 [0.27-0.67]
Only VKA	0.57 [0.42-0.77]		0.19 [0.09-0.41]	0.43 [0.27-0.67]	0.63 [0.45-0.87]	0.14 [0.09-0.21]
Only NOAC	0.50 [0.37-0.68]		0.36 [0.17-0.77]	0.34 [0.21-0.53]	0.67 [0.48-0.93]	0.16 [0.11-0.24]
OAC & antiplatelet	0.50 [0.35-0.73]		0.19 [0.08-0.50]	0.38 [0.23-0.62]	0.67 [0.47-0.97]	0.15 [0.10-0.24]

CI, Confidence Interval; CKD, Chronic Kidney Disease; NOAC, Non-Vitamin K Antagonist Oral Anticoagulant; OAC, Oral Anticoagulant; OR, Odds Ratio; VKA, Vitamin K Antagonist.

*all rates comparisons across groups were significant at $P < 0.001$; Model 1 is adjusted for age, sex, EHRA score, type of AF; Model 2 is adjusted for age, sex, EHRA score, type of AF, number of comorbidities, number of drugs.

TABLE 2. Quality of life indicators at baseline and association with features of complexity

	Low risk	CHA_2DS_2-VASc ≥2	Hx bleeding	Frailty	CKD	≥2 Features
Health utility score, mean (SD)*	0.88 (0.16)	0.85 (0.17)	0.84 (0.18)	0.67 (0.24)	0.81 (0.18)	0.67 (0.25)
Univariate, OR [95% CI] (each 0.100)	1.26 [1.13-1.40]	Ref.	0.84 [0.61-1.17]	0.16 [0.14-0.19]	0.67 [0.60-0.75]	0.16 [0.14-0.18]
Multivariate 1, OR [95% CI] (each 0.100)	0.86 [0.76-0.98]	Ref.	0.86 [0.63-1.19]	0.19 [0.16-0.22]	0.78 [0.70-0.88]	0.20 [0.18-0.23]
Multivariate 2, OR [95% CI] (each 0.100)	0.78 [0.68-0.89]	Ref.	0.88 [0.64-1.22]	0.21 [0.18-0.25]	0.81 [0.72-0.91]	0.23 [0.20-0.27]
Visual analog scale, mean (SD)*	72.9 (20.2)	71.2 (19.1)	67.1 (20.0)	60.7 (21.7)	68.1 (18.4)	59.7 (22.7)
Univariate, OR [95% CI] (each 10)	1.18 [1.05-1.33]	Ref.	0.66 [0.46-0.97]	0.35 [0.30-0.41]	0.74 [0.65-0.84]	0.32 [0.27-0.37]
Multivariate 1, OR [95% CI] (each 10)	0.94 [0.82-1.08]	Ref.	0.67 [0.46-0.97]	0.43 [0.36-0.51]	0.82 [0.71-0.93]	0.41 [0.35-0.48]
Multivariate 2, OR [95% CI] (each 10)	0.74 [0.64-0.86]	Ref.	0.66 [0.45-0.95]	0.54 [0.45-0.65]	0.87 [0.76-1.00]	0.56 [0.47-0.67]

CI, Confidence Interval; CKD, Chronic Kidney Disease; OR, Odds Ratio.

*both indicators mean (SD) values are different across the groups at $P < 0.001$; Model 1 is adjusted for age, sex, EHRA score, type of AF; Model 2 is adjusted for age, sex, EHRA score, type of AF, number of comorbidities, number of drugs.

associated with lower values. The magnitude of the association was progressively mitigated in multivariate model 1 and model 2, reversing the association for the low risk group and confirming the inverse association between the other 3 groups (Table 2). Similar evidence was found for VAS, with progressively greater inverse association for history of CKD, history of bleeding, having ≥2 features and being frail (Table 2).

Use of Healthcare Resources

Data about use of healthcare resources are shown in Table 3. Statistically significant differences were found in the occurrence of internal medicine/general practitioner visits and emergency room admissions both a 1 year and 2 years follow-up, with patients presenting ≥2 features of clinical complexity reporting the higher use for both health-care resources at both follow-up points. No difference was found for cardiology visits.

Logistic regression analysis showed that after adjustment for the full Model 2, compared to CHA_2DS_2-VASc ≥2 without features of clinical complexity, only reporting ≥2 features was associated with a higher likelihood of emergency room admissions both a 1 year and 2 years of follow-up (Table 3), with several associations being mitigated compared to Model 1. Among the other features, multivariate Model 2 mitigated several associations found with Model 1 (Table 3), only showing that CKD group was associated with emergency room admissions at 1 year of follow-up and both frailty and CKD groups were associated with higher occurrence of emergency room admissions at 2 years of follow-up (Table 3).

Regarding hospital admissions, all 3 outcomes considered were similarly higher for all the 4 features of clinical complexity, compared to low risk and only CHA_2DS_2-VASc ≥2 groups. Multivariate Model 2 showed significant association for all the 4 groups, compared to those CHA_2DS_2-VASc ≥2, with both any and CV hospitalization. No significant association was found with non-cv hospitalization (Table 3).

Follow-Up and Risk of Outcomes

Across a mean (SD) follow-up time of 1.74 (0.62) years, there were 1558 (17.1%) net clinical outcome (NCO) events. Rates of primary outcome, as well as for all the secondary ones, were higher for all groups of features of clinical complexity, being highest in patients reporting ≥2 features of clinical complexity (Table 4). Kaplan-Meier curves for the

TABLE 3. Use of health-care resources and association† with features of clinical complexity

	Low risk	CHA_2DS_2-VASc ≥2	Hx bleeding	Frailty	CKD	≥2 Features
Cardiology visits 1Y, n (%)*	1292 (74.7)	2483 (72.7)	89 (74.2)	557 (76.7)	1035 (73.4)	672 (75.4)$_{0.198}$
Univariate, OR [95% CI]	1.09 [0.96-1.25]	Ref.	1.08 [0.71-1.63]	1.24 [1.02-1.49]	1.03 [0.90-1.19]	1.15 [0.97-1.36]
Multivariate 1, OR [95% CI]	0.82 [0.70-0.96]	Ref.	1.15 [0.76-1.75]	1.04 [0.86-1.27]	1.15 [0.99-1.33]	1.16 [0.97-1.39]
Multivariate 2, OR [95% CI]	0.88 [0.75-1.05]	Ref.	1.12 [0.74-1.71]	0.95 [0.77-1.18]	1.13 [0.97-1.31]	1.07 [0.87-1.31]
IM/GP Visits 1Y, n (%)*	639 (45.0)	1276 (49.5)	37 (39.8)	355 (55.2)	596 (50.4)	438 (56.4)
Univariate, OR [95% CI]	0.80 [0.70-0.90]	Ref.	0.67 [0.44-1.03]	1.26 [1.06-1.50]	1.04 [0.90-1.19]	1.32 [1.13-1.55]
Multivariate 1, OR [95% CI]	0.69 [0.60-0.81]	Ref.	0.72 [0.47-1.10]	1.13 [0.94-1.35]	1.10 [0.95-1.27]	1.31 [1.10-1.55]
Multivariate 2, OR [95% CI]	0.84 [0.71-0.99]	Ref.	0.73 [0.48-1.13]	0.85 [0.70-1.04]	1.04 [0.90-1.20]	0.89 [0.73-1.08]
ER admissions 1Y, n (%)*	270 (16.0)	522 (16.0)	19 (16.4)	160 (22.2)	295 (21.2)	240 (27.6)
Univariate, OR [95% CI]	0.99 [0.85-1.16]	Ref.	1.03 [0.62-1.69]	1.49 [1.22-1.82]	1.41 [1.20-1.65]	2.00 [1.68-2.38]
Multivariate 1, OR [95% CI]	0.96 [0.79-1.15]	Ref.	1.15 [0.69-1.90]	1.25 [1.02-1.54]	1.40 [1.18-1.65]	1.82 [1.51-2.19]
Multivariate 2, OR [95% CI]	1.18 [0.97-1.44]	Ref.	1.12 [0.67-1.87]	0.99 [0.79-1.24]	1.31 [1.10-1.55]	1.34 [1.07-1.67]
Cardiology visits 2Y, n (%)*	1031 (67.4)	2064 (68.6)	63 (59.4)	456 (71.9)	816 (67.3)	481 (69.1)$_{0.100}$
Univariate, OR [95% CI]	0.94 [0.83-1.08]	Ref.	0.67 [0.45-1.00]	1.17 [0.97-1.42]	0.94 [0.82-1.08]	1.02 [0.86-1.22]
Multivariate 1, OR [95% CI]	0.83 [0.71-0.97]	Ref.	0.68 [0.46-1.01]	1.02 [0.84-1.25]	0.99 [0.86-1.15]	0.97 [0.80-1.17]
Multivariate 2, OR [95% CI]	0.89 [0.75-1.05]	Ref.	0.69 [0.46-1.03]	0.94 [0.76-1.17]	0.99 [0.85-1.15]	0.91 [0.73-1.12]
IM/GP visits 2Y, n (%)*	624 (47.7)	1,143 (47.6)	32 (36.0)	306 (53.0)	501 (47.2)	363 (56.9)
Univariate, OR [95% CI]	0.99 [0.86-1.13]	Ref.	0.62 [0.40-0.96]	1.24 [1.04-1.49]	0.98 [0.85-1.14]	1.45 [1.22-1.73]
Multivariate 1, OR [95% CI]	0.84 [0.72-0.99]	Ref.	0.64 [0.41-0.99]	1.31 [1.08-1.58]	1.09 [0.93-1.27]	1.65 [1.37-1.98]
Multivariate 2, OR [95% CI]	1.06 [0.89-1.25]	Ref.	0.65 [0.42-1.02]	0.99 [0.80-1.22]	1.03 [0.88-1.20]	1.19 [0.96-1.47]
ER Admissions 2Y, n (%)*	181 (12.1)	369 (12.9)	18 (17.0)	123 (20.0)	220 (18.7)	140 (20.6)
Univariate, OR [95% CI]	0.90 [0.74-1.09]	Ref.	1.38 [0.82-2.31]	1.68 [1.34-2.11]	1.55 [1.29-1.86]	1.75 [1.41-2.17]
Multivariate 1, OR [95% CI]	0.84 [0.67-1.05]	Ref.	1.49 [0.88-2.51]	1.49 [1.17-1.99]	1.58 [1.30-1.91]	1.66 [1.32-2.08]
Multivariate 2, OR [95% CI]	1.00 [0.79-1.26]	Ref.	1.55 [0.92-2.61]	1.29 [1.00-1.67]	1.55 [1.27-1.88]	1.42 [1.09-1.84]
Any Hospitalization, n (%)*	656 (34.8)	1,272 (33.9)	61 (46.6)	383 (44.4)	690 (42.0)	536 (46.9)
Univariate, OR [95% CI]	1.04 [0.93-1.17]	Ref.	1.70 [1.20-2.41]	1.55 [1.34-1.80]	1.41 [1.25-1.59]	1.72 [1.50-1.96
Multivariate 1, OR [95% CI]	0.87 [0.76-1.00]	Ref.	1.92 [1.34-2.73]	1.34 [1.15-1.57]	1.49 [1.31-1.69]	1.69 [1.47-1.95]

(*continued on next page*)

TABLE 3. (*continued*)

	Low risk	CHA_2DS_2-VASc $\geq$2	Hx bleeding	Frailty	CKD	$\geq$2 Features
Multivariate 2, OR [95% CI]	1.05 [0.90-1.21]	Ref.	1.86 [1.30-2.67]	1.10 [0.93-1.31]	1.41 [1.24-1.60]	1.35 [1.14-1.60]
CV Hospitalization, n (%)*	431 (22.9)	805 (21.5)	40 (30.5)	271 (31.4)	428 (26.0)	358 (31.3)
Univariate, OR [95% CI]	1.06 [0.93-1.21]	Ref.	1.61 [1.10-2.35]	1.67 [1.42-1.97]	1.29 [1.12-1.47]	1.67 [1.44-1.93]
Multivariate 1, OR [95% CI]	0.79 [0.68-0.92]	Ref.	1.83 [1.24-2.69]	1.48 [1.25-1.76]	1.45 [1.26-1.67]	1.77 [1.52-2.07]
Multivariate 2, OR [95% CI]	0.95 [0.81-1.12]	Ref.	1.79 [1.21-2.65]	1.20 [1.00-1.45]	1.36 [1.18-1.57]	1.38 [1.15-1.67]
Non-CV Hospitalization, n (%)*	153 (8.1)	395 (10.5)	19 (14.5)	109 (12.6)	227 (13.8)	182 (15.9)
Univariate, OR [95% CI]	0.74 [0.61-0.90]	Ref.	1.44 [0.88-2.37]	1.23 [0.98-1.54]	1.36 [1.14-1.62]	1.61 [1.33-1.94]
Multivariate 1, OR [95% CI]	0.88 [0.70-1.09]	Ref.	1.50 [0.91-2.47]	1.16 [0.91-1.46]	1.22 [1.02-1.47]	1.42 [1.16-1.74]
Multivariate 2, OR [95% CI]	1.03 [0.81-1.30]	Ref.	1.35 [0.80-2.28]	0.99 [0.77-1.28]	1.15 [0.96-1.39]	1.10 [0.86-1.40]

1Y, One Year Follow-Up; 2Y, Two Years of Follow-Up; AF, Atrial Fibrillation; CI, Confidence Interval; CKD, Chronic Kidney Disease; CV, Cardiovascular; ER, Emergency Room; IM, Internal Medicine; GP, General Practitioner; OR, Odds Ratio.

*all rates comparisons across groups were significant at $P < 0.001$ except where reported in the subscripts reported in last column, Italic characters entail not significant comparisons; †Logistic Regression Models; Model 1 is adjusted for age, sex, EHRA score, type of AF; Model 2 is adjusted for age, sex, EHRA score, type of AF, number of comorbidities, number of drugs.

TABLE 4. Adverse clinical events and association with features of clinical complexity

	Low risk	CHA_2DS_2-VASc ≥2	Hx bleeding	Frailty	CKD	≥2 Features
NCO, n (%)*	108 (6.0)	470 (12.9)	31 (24.2)	184 (22.3)	357 (22.5)	408 (36.5)
Univariate, HR [95% CI]	0.46 [0.37-0.57]	Ref.	2.04 [1.39-3.00]	1.72 [1.43-2.08]	1.91 [1.65-2.21]	3.52 [3.06-4.06]
Multivariate 1, HR [95% CI]	0.67 [0.52-0.85]	Ref.	1.88 [1.28-2.76]	1.87 [1.54-2.28]	1.62 [1.39-1.88]	3.15 [2.70-3.66]
Multivariate 2, HR [95% CI]	0.81 [0.63-1.04]	Ref.	1.94 [1.32-2.85]	1.38 [1.11-1.71]	1.50 [1.28-1.75]	2.08 [1.73-2.51]
Composite Event, n (%)*	93 (5.1)	426 (11.7)	24 (18.6)	174 (21.1)	324 (20.4)	378 (33.9)
Univariate, HR [95% CI]	0.44 [0.34-0.56]	Ref.	1.66 [1.07-2.58]	1.79 [1.47-2.18]	1.90 [1.63-2.22]	3.59 [3.10-4.17]
Multivariate 1, HR [95% CI]	0.66 [0.51-0.86]	Ref.	1.52 [0.98-2.36]	1.95 [1.59-2.40]	1.58 [1.34-1.85]	3.15 [2.69-3.70]
Multivariate 2, HR [95% CI]	0.82 [0.63-1.07]	Ref.	1.56 [1.00-2.42]	1.42 [1.13-1.78]	1.45 [1.23-1.71]	2.02 [1.66-2.46]
All-Cause Death, n (%)*	40 (2.1)	243 (6.3)	14 (10.2)	87 (9.9)	231 (14.0)	294 (25.1)
Univariate, HR [95% CI]	0.32 [0.23-0.45]	Ref.	1.63 [0.95-2.79]	1.60 [1.25-2.04]	2.27 [1.25-2.04]	4.53 [3.82-5.37]
Multivariate 1, HR [95% CI]	0.64 [0.45-0.92]	Ref.	1.41 [0.82-2.43]	1.83 [1.42-2.35]	1.70 [1.41-2.05]	3.66 [3.05-4.40]
Multivariate 2, HR [95% CI]	0.83 [0.58-1.19]	Ref.	1.45 [0.85-2.49]	1.23 [0.94-1.63]	1.55 [1.28-1.87]	2.18 [1.74-2.73]
MACEs, n (%)*	67 (3.6)	268 (7.1)	17 (13.0)	131 (15.0)	197 (11.9)	230 (19.7)
Univariate, HR [95% CI]	0.53 [0.39-0.72]	Ref.	2.01 [1.17-3.45]	2.17 [1.69-2.78]	1.90 [1.54-2.34]	3.51 [2.87-4.29]
Multivariate 1, HR [95% CI]	0.60 [0.43-0.83]	Ref.	1.91 [1.11-3.29]	2.36 [1.82-3.06]	1.79 [1.44-2.23]	3.48 [2.81-4.32]
Multivariate 2, HR [95% CI]	0.77 [0.55-1.09]	Ref.	1.97 [1.14-3.39]	1.59 [1.20-2.11]	1.62 [1.30-2.02]	2.06 [1.58-2.68]
Major Bleeding, n (%)*	20 (1.1)	54 (1.4)	10 (7.5)	21 (2.4)	45 (2.8)	56 (4.8)
Univariate, HR [95% CI]	0.73 [0.44-1.22]	Ref.	5.41 [2.76-10.62]	1.74 [1.05-2.89]	1.99 [1.34-2.96]	3.85 [2.65-5.60]
Multivariate 1, HR [95% CI]	0.82 [0.47-1.45]	Ref.	5.17 [2.62-10.19]	1.88 [1.11-3.17]	1.86 [1.23-2.81]	3.78 [2.53-5.63]
Multivariate 2, HR [95% CI]	0.91 [0.51-1.65]	Ref.	5.27 [2.67-10.40]	1.48 [0.83-2.62]	1.77 [1.17-2.67]	2.81 [1.72-4.57]

CI, Confidence Interval; CKD, Chronic Kidney Disease; HR, Hazard Ratio; MACEs, Major Adverse Cardiovascular Events; NCO, Net Clinical Outcome.
*all rates comparisons across groups were significant at $P < 0.001$; Model 1 is adjusted for age, sex, EHRA score, type of AF; Model 2 is adjusted for age, sex, EHRA score, type of AF, number of comorbidities, number of drugs.

primary outcome showed a significantly higher cumulative risk for patients with ≥2 features of clinical complexity, and lower for both patients with CHA_2DS_2-VASc ≥2 without features of clinical complexity and low risk ones (Log-rank: 562.393, $P < 0.001$) (Figure A1).

After full adjustment with Model 2, when compared to CHA_2DS_2-VASc ≥2 without features of clinical complexity, all the 4 groups of clinical complexity were associated with a higher risk of NCO, with the highest magnitude for patients with history of bleeding and those reporting ≥2 features. Similar results were reported for all the exploratory secondary outcomes, except for all-cause death for which patients with history of bleeding and frail ones showed no significant association (Table 4).

ABC Pathway Adherence, Features of Clinical Complexity and Outcomes

As a secondary exploratory analysis, we examined for each group the incidence rate of the primary outcome according to ABC pathway adherence. NCO incidence rate ratio was statistically significantly favorable for ABC pathway adherence in all groups of features of clinical complexity except for frailty. In the low risk and CHA_2DS_2VASc ≥2 groups despite not being statistically significant, point estimates suggest a potential benefit (Table 5).

Discussion

In this large cohort of European AF patients, our principal findings are as follows: (1) features of perceived clinical complexity are common, representing more than 40% of patients, and that such patients present a higher burden of thromboembolic and bleeding risks, multimorbidity, frailty and polypharmacy, and are more likely symptomatic; (2) Features of clinical complexity were associated to a lower use of OAC and with a differential use of NOACs according to the domains of complexity; (3) Clinical complexity was associated with a lower quality of life, and increasing use of healthcare resources; (4) As expected, features of clinical complexity are associated with a higher risk of major adverse outcomes, even after adjustment for main domains of clinical complexity. Patients reporting ≥2 features of clinical complexity reported the highest risks, even though the risk of major bleeding is predominantly influenced by the clinical history of previous bleeding; (5) Adherence to ABC pathway was associated with a lower incidence of primary outcome of NCO

TABLE 5. Net Clinical outcome occurrence according to adherence to ABC pathway and features of clinical complexity

	ABC nonadherent* *N (%)*	**IR (95% CI)** *events per 100 pts-yrs*	**ABC adherent*** *N (%)*	**IR (95% CI)** *events per 100 pts-yrs*	**IRR (95% CI)**	***P***
Low risk	60 (6.0) *0.545*	3.08 (2.35-3.97)	22 (5.2) *0.545*	2.63 (1.65-3.98)	0.85 (0.52-1.39)	0.526
CHA_2DS_2-VASc ≥2	203 (14.3) *0.161*	7.83 (6.79-8.99)	106 (12.3) *0.161*	6.53 (5.35-7.90)	0.83 (0.66-1.05)	0.128
Hx bleeding	20 (31.3) **0.042**	18.60 (11.36-28.73)	3 (11.5) **0.042**	5.66 (1.17-16.55)	0.40 (0.09-1.02)	0.042
Frailty	91 (21.3) *0.537*	12.11 (9.75-14.87)	13 (25.0) *0.537*	15.02 (8.00-25.69)	1.24 (0.69-2.22)	0.467
CKD	163 (26.1) **<0.001**	15.31 (13.05-17.85)	57 (16.5) **<0.001**	9.19 (6.96-11.91)	0.60 (0.44-0.81)	<0.001
≥2 Features	226 (38.5) **0.016**	26.19 (22.88-29.83)	26 (26.0) **0.016**	15.29 (9.99-22.41)	0.58 (0.39-0.88)	0.009

ABC, Atrial Fibrillation Better Care; CI, Confidence Interval; CKD, Chronic Kidney Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; pts-yrs, patients-years. *values reported in subscripts represent *P* values for NCO rates comparison according to each feature of clinical complexity, with Italic characters depicting nonsignificant differences and Bold characters depicting significant differences.

in AF patients with history of bleeding, CKD and those presenting ≥2 features of clinical complexity.

In recent years much attention has been given to the concept of clinical complexity in patients with AF. The major domains of clinical complexity (ie, multimorbidity, frailty, and polypharmacy) have been associated with AF, being highly prevalent and influencing both the clinical management of patients and the risks of major adverse outcomes, showing a higher risk for all of them.[5,8,9,24] A progressively higher burden of complexity (ie, higher number of comorbidities, higher frailty index, and higher number of drugs taken at baseline) is associated with a more conservative approach (lower prescription of OAC, lower use of antiarrhythmic strategy), lower quality of life, higher use of health-care resources and a progressively higher risk for adverse outcomes.[5,8,9,24]

The occurrence of these various phenomena confers a so-called "clinical complexity" phenotype.[25] While these dimensions all relate to specific areas of complexity entailing a differential impact in clinical management and patients' course,[26] the inter-relationships between each other and the potential unpredictability of these linkages underlies the concept of clinical complexity.[27] While there has been limited evidence in the cardiovascular medicine field for implementation of the clinical complexity concepts, this has recently been explored in AF.[12,13]

In a previous analysis from this same cohort, clinical complexity has been defined as the presence of either one of multimorbidity, frailty or polypharmacy.[12] The presence of such defined clinical complexity was associated to an increase in risk of all adverse outcomes related to AF, which ranged from a 50% relative increase in risk for MACE to a 2-fold increase in risk for all-cause death.[12] In the present analysis, we provide additional observations that clinical management adherent to the ABC pathway was associated with a significant risk reduction for all the outcomes considered in these clinically complex patients.[12] Indeed, the significant reduction of incidence rate for outcomes in patients managed adherent to the ABC pathway, adds more knowledge to this area in relation to clinical complexity. The use of a clinical strategy adherent to the ABC pathway is associated with a reduction of risk for all-cause death, cardiovascular death, stroke, and major bleeding,[15] leading to the ABC pathway being recommended by guidelines.[18,28] That ABC pathway has also been associated with significant risk reduction in multimorbid, frail, polypharmacy and the overall clinically complex AF patients,[12,29] but the data presented in this paper enlighten how the beneficial impact of ABC pathway adherence is evident in patients with specific features of clinical complexity.

In the prospective global "Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation" (GLORIA-AF) Registry, clinical complexity was explored, whereby higher clinical complexity (ie, history of bleeding, frail elderly, CKD) and their interaction with high thromboembolic risk (CHA_2DS_2-VASc $\geq$2) were analyzed, with data regarding prescription and discontinuation of OAC, as well as the risk of adverse outcomes.[13] The concurrent presence of at least 2 of the 3 features considered was associated with a lower prescription of OAC, with higher odds of OAC discontinuation, as well as a higher risk of adverse outcomes.[13] The magnitude of association was greater in those patients reporting $\geq$2 features of perceived complexity.

In the present paper in a European cohort, we confirm and extend the previous observations. First, all the 3 features examined were associated with multimorbidity, frailty and polypharmacy. Moreover, the higher biological complexity (as entailed by the presence of frailty which denotes biological ageing) as well as the higher burden of features of clinical complexity (ie, the presence of $\geq$2 features), in the context of high thromboembolic risk, showed the highest magnitude in association with all the 3 domains of clinical complexity. Second, features of clinical complexity significantly influence the management of patients, quality of life and the use of healthcare resources. Indeed, each feature was found associated with lower chance of being prescribed with OAC-based strategies, with a worse quality of life and with a higher use of healthcare resources, particularly those hospital-based (admission to emergency rooms and hospitalizations). Our data on the association of clinical complexity with impaired quality of life and higher use of healthcare resources, particularly those hospital-based (ie, emergency room admissions and hospitalizations), represents the first report on this specific association, emphasizing the specific detrimental impact of these features of clinical complexity.

Our paper confirms the previous evidence about the association between the features of clinical complexity and the risk of major adverse outcomes, also extending the previous knowledge.[13] Indeed, the differences regarding the associations of frailty with outcomes in different studies may lie in the more accurate definition of frailty, compared to the previous paper that only provided a proxy of frailty,[13] which is based on a standardized method. Notably, our results also underlined how the clinical history of bleeding is prominent in determining the risk of future bleeding events compared to the other features of clinical complexity.

Conclusions

Presence of features of clinical complexity is associated with a lower use of OAC, lower quality of life and higher use of healthcare resources. Features of clinical complexity are associated with a higher risk of adverse outcomes, especially in those with a higher burden of complexity features.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101752.

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