Clinical Complexity Domains, Anticoagulation, and Outcomes in Patients with Atrial Fibrillation: A Report from the GLORIA-AF Registry Phase II and III

Giulio Francesco Romiti[1,2,*] Marco Proietti[2,3,4,*] Niccolò Bonini[2,5] Wern Yew Ding[1] Giuseppe Boriani[5] Menno V. Huisman[6,*] Gregory Y. H. Lip[1,7,**] and on behalf of the GLORIA-AF Investigators[***]

[1] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[2] Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
[3] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[4] Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy
[5] Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy
[6] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands
[7] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Address for correspondence 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).

Thromb Haemost 2022;122:2030–2041.

Abstract

Background Clinical complexity is common in atrial fibrillation (AF) patients. We assessed the impact of clinical complexity on oral anticoagulant (OAC) treatment patterns and major adverse outcomes in a contemporary cohort of AF patients.

Methods The GLORIA-AF Phase II and III Registry enrolled newly diagnosed AF patients with at least one stroke risk factor. Among patients with CHA_2DS_2-VASc score ≥ 2, we defined four domains of perceived clinical complexity: frail elderly (age ≥ 75 years and body mass index $< 23\ kg/m^2$), chronic kidney disease (CKD, creatinine clearance < 60 mL/min), history of bleeding, and those with ≥ 2 of the above conditions. We evaluated the associations between clinical complexity domains and antithrombotic treatment prescription, risk of OAC discontinuation, and major adverse outcomes.

Results Among the 29,625 patients included (mean age 69.6 ± 10.7 years, 44.2% females), 9,504 (32.1%) presented with at least one complexity criterion. Clinical complexity was associated with lower OAC prescription, with stronger associations in frail elderly (odds ratio [OR]: 0.47, 95% confidence interval [CI]: 0.36–0.62) and those

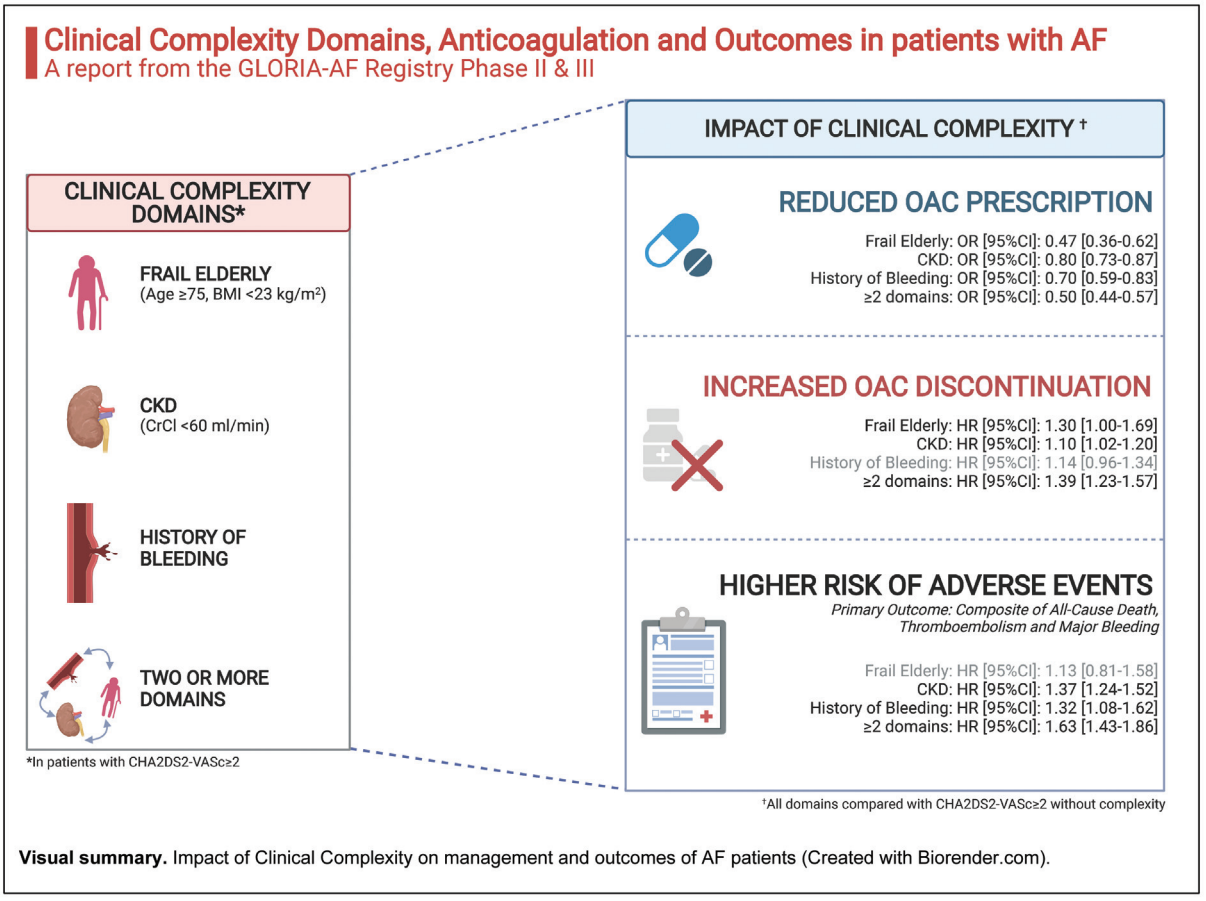
Keywords
- atrial fibrillation
- clinical complexity
- oral anticoagulants
- persistence
- outcomes

* *Joint first authors.*
** *Profs. Lip and Huisman are co-chairs of the GLORIA-AF Registry programme.*
*** *The list of investigators is given in Supplementary Appendix [available in the online version].*
Note: The review process for this paper was fully handled by Christian Weber, Editor-in-Chief.

received
August 11, 2022
accepted
August 18, 2022
published online
August 29, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0042-1756355.
ISSN 0340-6245.



Visual summary. Impact of Clinical Complexity on management and outcomes of AF patients (Created with Biorender.com).

with ≥2 complexity domains (OR: 0.50, 95% CI: 0.44–0.57). Risk of OAC discontinuation was higher among frail elderly (hazard ratio [HR]: 1.30, 95% CI: 1.00–1.69), CKD (HR: 1.10, 95% CI: 1.02–1.20), and those with ≥2 complexity domains (HR: 1.39, 95% CI: 1.23–1.57). Clinical complexity was associated with higher risk of the primary outcome of all-cause death, thromboembolism, and major bleeding, with the highest magnitude in those with ≥2 criteria (HR: 1.63, 95% CI: 1.43–1.86).

Conclusion In AF patients, clinical complexity influences OAC treatment management, and increases the risk of poor clinical outcomes. These patients require additional efforts, such as integrated care approach, to improve their management and prognosis.

Introduction

The prevalence and incidence of atrial fibrillation (AF) are increasing and are projected to rise significantly over the next decades, especially in the elderly[1,2]; consistently, the number of individuals at high thromboembolic risk who need treatment with oral anticoagulants (OACs) for effective stroke prevention is continuously rising. Since their introduction, the non-vitamin K antagonist OACs (NOACs; also referred to as direct OACs) represented a safer and effective alternative to vitamin K antagonist (VKA) for stroke prevention in AF patients,[3] and this was reflected by the increasing uptake of NOACs in clinical practice.[4–7]

However, OAC undertreatment remains a concern in AF patients,[8,9] being also associated with worse outcomes,[10] especially in high-risk patients. Indeed, with the progressive aging of the AF population, a significant proportion of patients are burdened by concomitant comorbidities and conditions that increase both thromboembolic and bleeding risks, entailing the so-called "clinical complexity" that influences treatment choices and poses significant challenges in the management of AF.[11] Frailty, chronic kidney disease (CKD), and history of bleeding represent three of the most common conditions that are known to increase the risk of adverse outcomes (including bleeding) in AF patients,[12–16]

and are often perceived as major barriers to OAC prescription.[17] Furthermore, these conditions often coexist, leading to further challenges in the management of these patients.

Given the need for appropriate stroke prevention, as recommended by international guidelines,[18,19] and the concomitant high risk for hemorrhagic events, these patients currently present a significant unmet need for safe anticoagulation and thromboembolic risk prevention.

In this analysis, we used data from the phases II and III of the Global Registry on Long-Term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) to analyze the following: (1) the prevalence of perceived clinical complexity domains (as defined by either frail elderly, CKD, history of bleeding, and their combination); (2) patterns of OAC prescription and discontinuation across different groups of clinically complex patients; and (3) association of clinical complexity with major adverse outcomes.

Methods

The GLORIA-AF is a global, multicenter prospective registry structured in three phases, which aims to evaluate the long-term safety and effectiveness of dabigatran in real-world patients with AF. Complete details on the design of the GLORIA-AF study have been previously reported,[20,21] as well as the primary papers comparing dabigatran versus VKA and other NOACs.[22,23] Briefly, patients with new-onset nonvalvular AF and CHA_2DS_2-VASc score $\geq$1 were consecutively enrolled between 2011 and 2016 (2011–2014 for phase II, and 2014–2016 for phase III). Patients enrolled in phase II who initiated dabigatran were prospectively followed up for 2 years, while all patients enrolled in phase III (irrespective of the antithrombotic treatment) were followed up for 3 years.

Inclusion Criteria and Procedures

Full details on inclusion and exclusion criteria were described elsewhere.[23] Patients aged 18 years or older, with a recent diagnosis of AF (<3 months, except in Latin America where <4.5 months cut-off was used) and a CHA_2DS_2-VASc score $\geq$1, who provided written informed consent were considered eligible for inclusion. The protocol of the study was approved by the European Medicines Agency, and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Local institutional review boards gave ethical approval at each participating site.

At baseline, data on age, sex, type of AF (either paroxysmal, persistent, or permanent), comorbidities, and CHA_2DS_2-VASc and HAS-BLED risk scores were collected, along with data on symptoms (according to the European Heart Rhythm Association classification) and concurrent medications received.

For the purpose of this analysis, we included only patients with complete data on the clinical complexity domains evaluated (frail elderly, history of bleeding, CKD).

Clinical Complexity Domains Definition

We defined four main domains of perceived clinical complexity:

- Frail elderly: patients with CHA_2DS_2-VASc $\geq$2, age $\geq$75 years, and body mass index (BMI) <23 kg/m^2, consistently with a previous BMI cut-off identified in the elderly.[24]
- History of bleeding: patients with CHA_2DS_2-VASc $\geq$2 and previous history of bleeding, as reported in the case report form by the investigators.
- CKD: patients with CHA_2DS_2-VASc $\geq$2 and a creatinine clearance (calculated according to the Cockcroft–Gault formula) <60 mL/min.
- Two or more domains: patients who presented with two or three of the above-defined complexity domains.

Each subject was included in only one of the clinical complexity groups (e.g., a patient with both CKD and history of bleeding was included only in the "Two or more domains" group). The remaining patients, not having any of the complexity domain defined above, were classified according to the CHA_2DS_2-VASc score (either $\geq$2 or <2). Reference group for all the analyses was composed of patients with CHA_2DS_2-VASc score of $\geq$2, without any complexity criteria.

Follow-Up, Persistence, and Major Adverse Outcomes

Details on follow-up and outcomes for phase II and phase III were reported elsewhere.[23,25] During follow-up, data regarding treatment discontinuation and major adverse outcomes were collected, until study withdrawal, death, or end of study. Nonpersistence was defined as either discontinuation or study termination. Discontinuation was defined as either switching to another antithrombotic regimen (including switching to a different OAC) or interruption of the treatment received at baseline for 30 days or more (to exclude temporary interruptions due to invasive procedures or surgery). Dose adjustments were not considered as discontinuation events. For the purpose of our analysis, we only evaluated discontinuation for patients who were prescribed with OAC (either VKA or NOAC) at baseline.

We also evaluated the risk of major adverse outcomes according to the clinical complexity domains. We defined our *primary outcome* as the net clinical outcome of all-cause death, thromboembolism (including stroke, transient ischemic attack [TIA], and extracranial thromboembolism) and major bleeding (defined according to the International Society of Thrombosis and Haemostasis classification, i.e., a bleeding associated with a reduction in hemoglobin of at least 20 g/L or leading to at least 2 units of blood or packed cells transfusion, or a symptomatic bleeding in a critical organ, or life-threatening/fatal bleeding). As secondary outcomes, we also investigated the composite of all-cause death and major adverse cardiovascular events (MACE, defined as the composite of cardiovascular death, stroke, and myocardial infarction), as well as all-cause death, cardiovascular death, MACEs, thromboembolism, and major bleeding.

Statistical Analysis

Baseline characteristics were reported as mean and standard deviation or median and interquartile range (IQR] for normally and nonnormally distributed continuous variables, and compared respectively with parametric and nonparametric

tests. Categorical variables were reported using frequencies and percentages and were compared using a chi-square test.

Logistic regression analyses were used to evaluate the association between clinical complexity domains and prescription of OAC, while multivariable Cox-regression analyses were performed to evaluate the association between clinical complexity and OAC discontinuation; results were reported as odds ratio (OR) and 95% confidence intervals (CIs), and hazard ratio (HR) and 95% CI, respectively.

For each analysis, three models were evaluated: model 1 was adjusted for age, sex and type of AF; model 2 was adjusted for the same variables included in model 1 plus the CHA_2DS_2-VASc score; model 3 was adjusted for the same variables included in model 1 plus hypertension, diabetes mellitus, coronary artery disease, heart failure, history of stroke/TIA, and peripheral artery disease. Model 3 was considered as the final primary model of the analysis.

The association between clinical complexity domains and the risk of major outcomes was evaluated using a multivariable Cox-regression analysis adjusted for age, sex, type of AF, use of OAC, and baseline comorbidities (hypertension, diabetes mellitus, coronary artery disease, heart failure, peripheral artery disease, and history of stroke/TIA). A sensitivity analysis was also performed, adjusting the model for CHA_2DS_2-VASc instead of baseline comorbidities. Survival curves were used to represent cumulative hazard of patients for the primary net clinical outcome, and survival distributions were compared using a log-rank test.

A two-sided $p < 0.05$ was considered statistically significant. All the analyses were performed using R 4.0.3 (R Core Team 2020, Vienna, Austria).

Results

From the 36,617 patients originally enrolled in the GLORIA-AF Phase II and III Registry, 29,625 (80.9%; mean age 69.6 ± 10.7 years, 44.2% females) with complete data on clinical complexity domain were included in this analysis. Of these, 2,152 (7.3%) had two or more complexity criteria; 342 (1.2%) were frail elderly; 6,062 (20.5%) had CKD; and 948 (3.2%) had history of bleeding. Finally, 14,920 (50.4%) patients had a CHA_2DS_2-VASc score of ≥ 2 without any other complexity criteria, and 5,201 (17.6%) had a CHA_2DS_2-VASc score <2. A graphical representation of the complexity criteria distribution is reported in ►**Supplementary Fig. S1** (available in the online version), while baseline characteristics according to the clinical complexity group are reported in ►**Table 1**. Patients with at least one complexity criterion were older, more likely affected by comorbidities and thromboembolic risk factors, and presented with higher median CHA_2DS_2-VASc and HAS-BLED scores, compared to those who did not present any of the complexity criteria.

Antithrombotic Prescription Patterns

A graphical representation of the antithrombotic prescription patterns according to the complexity domain is reported in ►**Supplementary Fig. S2** (**Supplementary Material** [available in the online version]). Compared to patients with a CHA_2DS_2-VASc score ≥ 2 and without any complexity criteria, a lower proportion of patients in each complexity domain was prescribed with NOACs, with the lowest figures observed for patients with CKD (52.1%); consistently, these patients most frequently received a VKA (31.6 vs. 26.2% with a CHA_2DS_2-VASc score ≥ 2 without complexity). Rates of patients prescribed with antiplatelet drugs or not receiving any antithrombotics were higher in frail elderly patients (24.0%), in those with a history of bleeding (19.7%), and in those with two or more complexity criteria (22.1%), compared to those with CHA_2DS_2-VASc ≥ 2 without complexity (15.0%) or CKD (16.4%).

The results of the logistic regression showed that all the complexity domains were associated with a lower odds of being prescribed with OAC when compared to patients with a CHA_2DS_2-VASc score ≥ 2 and without complexity, regardless of the adjustment performed (►**Table 2**). In the final model 3, the lowest odds of OAC prescription were observed among frail elderly patients (OR: 0.47, 95% CI: 0.36–0.62) and those with two or more complexity criteria (OR: 0.50, 95% CI: 0.44–0.57).

When we analyzed the probability of receiving NOACs over VKA in patients who were prescribed OAC at baseline, patients with CKD (OR: 0.73, 95% CI: 0.67–0.79) and patients with two or more complexity criteria (OR: 0.80, 95% CI: 0.71–0.90) showed lower odds of receiving NOAC, compared to patients with a CHA_2DS_2-VASc score ≥ 2 and no complexity criteria (►**Table 2**).

OAC Persistence and Discontinuation

Among the 24,009 patients prescribed with OAC at baseline, 18,053 (75.2%) had follow-up data on OAC persistence at follow-up. Rates of OAC discontinuation at 6 months, 1 year, and 2 years of follow-up among patients who were prescribed OAC at baseline are reported in ►**Supplementary Fig. S3** (**Supplementary Material** [available in the online version]). Compared to patients with a CHA_2DS_2-VASc score ≥ 2 and no complexity, lower rates of OAC persistence were observed in all complexity domains, and particularly among those with history of bleeding (2-years persistence: 47.5%), those frail elderly (46.5%), and those with two or more complexity criteria (43.7%). When we analyzed data according to the type of OAC prescribed, we found similar results for NOAC, while among VKA users the rate of discontinuation was higher among frail elderly patients (39.5%) and in those with history of bleeding (36.8%), compared to patients with a CHA_2DS_2-VASc score ≥ 2 (34.0%) (►**Supplementary Fig. S4**, **Supplementary Material** [available in the online version]).

The results of the Cox-regression analyses for the risk of OAC discontinuation adjusted for age, sex, type of AF, and CHA_2DS_2-VASc score are reported in ►**Table 3**, with all the models providing broadly consistent results. In the final model 3, the risk of OAC discontinuation was significantly higher in frail elderly patients (HR: 1.30, 95% CI: 1.00–1.69), those with CKD (HR: 1.10, 95% CI: 1.02–1.20), and in those with two or more complexity criteria (HR: 1.39, 95% CI: 1.23–1.57) compared to patients with a CHA_2DS_2-VASc score ≥ 2

Table 1 Baseline characteristics of the included patients

	Clinical complexity domain						
	CHA_2DS_2-VASc $\geq 2^a$ ($n = 14,920$)	CHA_2DS_2-VASc <2 ($n = 5,201$)	CKD ($n = 6,062$)	Frail elderly ($n = 342$)	History of bleeding ($n = 948$)	Two or more criteria ($n = 2,152$)	*p*-Value
Age, mean ± SD	68.9 ± 8.9	58.1 ± 9.0	77.1 ± 7.3	79.0 ± 3.5	70.5 ± 8.5	80.7 ± 5.0	<0.001
Female sex	6,897 (46.2)	828 (15.9)	3,532 (58.3)	168 (49.1)	393 (41.5)	1,270 (59.0)	<0.001
BMI, median [IQR]	29.1 [26.0–33.2]	27.3 [24.4–31.1]	26.2 [24.2–28.9]	21.8 [20.8–22.5]	29.3 [26.1–32.9]	21.7 [20.2–22.8]	<0.001
SBP, median [IQR]	130 [120–143]	128 [118–140]	130 [120–144]	130 [119–145]	130 [120–141]	130 [118–142]	<0.001
DBP, median [IQR]	80 [70–86]	80 [70–87]	76 [69–82]	75 [67–81]	77 [70–84]	73 [65–80]	<0.001
Region							<0.001
North America	3,733 (25.0)	1,187 (22.8)	1,202 (19.8)	64 (18.7)	271 (28.6)	407 (18.9)	
Europe	7,629 (51.2)	2,096 (40.3)	3,158 (52.1)	164 (48.0)	501 (52.8)	1,027 (47.7)	
Latin America	723 (4.8)	303 (5.8)	454 (7.5)	9 (2.6)	48 (5.1)	103 (4.8)	
Africa/Middle East	275 (1.8)	61 (1.2)	108 (1.8)	3 (0.9)	10 (1.1)	19 (0.9)	
Asia	2,560 (17.2)	1,554 (29.9)	1,140 (18.8)	102 (29.8)	118 (12.4)	596 (27.7)	
AF type							<0.001
Paroxysmal	8,226 (55.1)	3,057 (58.8)	3,213 (53.0)	209 (61.1)	531 (56.0)	1,175 (54.6)	
Persistent	5,297 (35.5)	1,859 (35.7)	2,104 (34.7)	111 (32.5)	319 (33.6)	697 (32.4)	
Permanent	1,397 (9.4)	285 (5.5)	745 (12.3)	22 (6.4)	98 (10.3)	280 (13.0)	
Symptoms							<0.001
EHRA I	4,785 (36.7)	1,447 (31.4)	2,058 (39.1)	111 (35.6)	336 (40.9)	772 (41.0)	
EHRA II	5,297 (40.6)	2,183 (47.4)	2,029 (38.5)	132 (42.3)	297 (36.1)	737 (39.1)	
EHRA III	2,318 (17.8)	772 (16.8)	923 (17.5)	53 (17.0)	140 (17.0)	280 (14.9)	
EHRA IV	644 (4.9)	199 (4.3)	256 (4.9)	16 (5.1)	49 (6.0)	94 (5.0)	
Medical history							
Hypertension	11,916 (80.0)	2523 (48.7)	4909 (81.0)	201 (58.9)	763 (80.8)	1565 (72.8)	<0.001
CHF	3,585 (24.2)	561 (10.9)	1,803 (30.0)	64 (19.0)	221 (23.6)	560 (26.3)	<0.001
CAD	3,013 (20.6)	413 (8.1)	1,528 (25.8)	59 (17.6)	246 (26.8)	508 (24.2)	<0.001
Diabetes	4,315 (28.9)	181 (3.5)	1,601 (26.4)	47 (13.7)	266 (28.1)	379 (17.6)	<0.001
PAD	457 (3.1)	17 (0.3)	251 (4.2)	17 (5.0)	54 (5.8)	99 (4.6)	<0.001
Previous TE events	2413 (16.2)	0 (0.0)	1,208 (19.9)	66 (19.3)	249 (26.3)	507 (23.6)	<0.001
Previous bleeding	0 (0.0)	172 (3.4)	0 (0.0)	0 (0.0)	948 (100.0)	618 (28.7)	<0.001

Table 1 (*Continued*)

	Clinical complexity domain						
	CHA_2DS_2-VASc ≥ 2[a] ($n = 14,920$)	CHA_2DS_2-VASc <2 ($n = 5,201$)	CKD ($n = 6,062$)	Frail elderly ($n = 342$)	History of bleeding ($n = 948$)	Two or more criteria ($n = 2,152$)	*p*-Value
COPD	995 (6.7)	163 (3.2)	431 (7.1)	27 (7.9)	72 (7.6)	205 (9.6)	<0.001
Dementia	46 (0.3)	2 (0.0)	80 (1.3)	3 (0.9)	8 (0.8)	35 (1.6)	<0.001
History of cancer	1,393 (9.4)	274 (5.3)	682 (11.3)	53 (15.6)	139 (14.8)	347 (16.3)	<0.001
Scores							
CHA2DS2-VASc, median [IQR]	3 [2–4]	1 [1–1]	4 [3–5]	4 [3–5]	3 [2–4]	4 [3–5]	<0.001
HAS-BLED, median [IQR]	1 [1–2]	1 [0–1]	1 [1–2]	2 [1–2]	2 [2–3]	2 [1–3]	<0.001
HAS-BLED ≥ 3	1127 (8.2)	73 (1.6)	736 (13.1)	40 (12.8)	417 (47.3)	519 (26.2)	<0.001
Antithrombotic treatment							<0.001
Antiplatelets	1,442 (9.7)	957 (18.4)	647 (10.7)	44 (12.9)	101 (10.7)	304 (14.1)	
NOAC	8,777 (58.8)	2,447 (47.1)	3,156 (52.1)	180 (52.6)	519 (54.7)	1,085 (50.4)	
VKA	3,904 (26.2)	1,115 (21.4)	1,913 (31.6)	80 (23.4)	243 (25.6)	590 (27.4)	
None	793 (5.3)	681 (13.1)	344 (5.7)	38 (11.1)	85 (9.0)	173 (8.0)	
Other treatments							
ACEi	5,189 (34.8)	1,093 (21.0)	1,885 (31.1)	71 (20.8)	352 (37.1)	539 (25.0)	<0.001
ARB	3,876 (26.0)	831 (16.0)	1,638 (27.0)	59 (17.3)	255 (26.9)	494 (23.0)	<0.001
Statins	7,244 (48.6)	1,344 (25.8)	2,949 (48.6)	121 (35.4)	533 (56.2)	949 (44.1)	<0.001
Beta-blockers	9,777 (65.5)	2,980 (57.3)	3,851 (63.5)	190 (55.6)	640 (67.5)	1,232 (57.2)	<0.001

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin-II receptor blockers; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EHRA, European Heart Rhythm Association; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation; TE, thromboembolism; VKA, vitamin K antagonist.

[a]Patients with CHA_2DS_2-VASc ≥ 2 and without any other complexity criteria.

Table 2 Association between clinical complexity domains and OAC prescription

	Clinical complexity domain					
	CHA_2DS_2-VASc ≥ 2[a] ($n = 14,920$)	CHA_2DS_2-VASc <2 ($n = 5,201$)	CKD ($n = 6,062$)	Frail elderly ($n = 342$)	History of bleeding ($n = 948$)	Two or more criteria ($n = 2,152$)
OAC prescription, OR (95% CI)						
Model 1	Ref.	**0.46 (0.42–0.50)**	**0.77 (0.70–0.84)**	**0.47 (0.36–0.61)**	**0.69 (0.58–0.82)**	**0.48 (0.43–0.55)**
Model 2	Ref.	**0.43 (0.39–0.47)**	**0.78 (0.71–0.86)**	**0.48 (0.37–0.62)**	**0.70 (0.59–0.83)**	**0.49 (0.44–0.56)**
Model 3	Ref.	**0.45 (0.41–0.49)**	**0.80 (0.73–0.87)**	**0.47 (0.36–0.62)**	**0.70 (0.59–0.83)**	**0.50 (0.44–0.57)**
NOAC vs. VKA prescription[b], OR (95% CI)						
Model 1	Ref.	1.02 (0.93–1.12)	**0.71 (0.66–0.77)**	0.94 (0.72–1.23)	0.95 (0.81–1.11)	**0.79 (0.70–0.88)**
Model 2	Ref.	0.95 (0.86–1.05)	**0.72 (0.67–0.78)**	0.94 (0.72–1.23)	0.95 (0.82–1.12)	**0.80 (0.71–0.90)**
Model 3	Ref.	0.97 (0.87–1.07)	**0.73 (0.67–0.79)**	0.91 (0.69–1.19)	0.97 (0.83–1.15)	**0.80 (0.71–0.90)**

Abbreviations: CI, confidence intervals; CKD, chronic kidney disease; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; VKA, vitamin K antagonist.
Note: Model 1 = adjusted for age, sex and type of AF; Model 2 = adjusted for variables in model 1 and CHA2DS2-VASc score; Model 3 = adjusted for variables in model 1 and hypertension, diabetes, coronary artery disease, congestive heart failure, history of stroke/transient ischemic attack, and peripheral artery disease. Bold values depict results significant at a $p<0.05$ level.
[a]Patients with CHA_2DS_2-VASc ≥ 2 and without any other complexity criteria.
[b]Among patients prescribed with OAC at baseline.

Table 3 Association between clinical complexity domains and OAC discontinuation

	Clinical complexity domain					
	CHA_2DS_2-VASc ≥ 2[a] ($n = 9,705$)	CHA_2DS_2-VASc <2 ($n = 2,730$)	CKD ($n = 3,660$)	Frail elderly ($n = 202$)	History of bleeding ($n = 564$)	Two or more criteria ($n = 1,192$)
OAC discontinuation, HR (95% CI)						
Model 1	Ref.	**1.43 (1.31–1.55)**	**1.11 (1.02–1.20)**	1.27 (0.98–1.64)	1.16 (0.99–1.36)	**1.40 (1.24–1.57)**
Model 2	Ref.	**1.40 (1.28–1.54)**	**1.11 (1.03–1.21)**	1.27 (0.98–1.64)	1.16 (0.99–1.36)	**1.40 (1.25–1.58)**
Model 3	Ref.	**1.45 (1.32–1.59)**	**1.10 (1.02–1.20)**	**1.30 (1.00–1.69)**	1.14 (0.96–1.34)	**1.39 (1.23–1.57)**
VKA discontinuation, HR (95% CI)						
Model 1	Ref.	1.14 (0.96–1.35)	0.99 (0.85–1.15)	1.25 (0.74–2.09)	1.15 (0.83–1.58)	1.08 (0.85–1.37)
Model 2	Ref.	1.13 (0.93–1.37)	0.99 (0.85–1.16)	1.25 (0.74–2.09)	1.15 (0.83–1.58)	1.08 (0.85–1.37)
Model 3	Ref.	1.09 (0.90–1.32)	1.02 (0.88–1.20)	1.30 (0.77–2.19)	0.98 (0.68–1.41)	1.06 (0.83–1.35)
NOAC discontinuation, HR (95% CI)						
Model 1	Ref.	**1.53 (1.39–1.68)**	**1.13 (1.02–1.24)**	1.28 (0.95–1.72)	1.18 (0.98–1.41)	**1.50 (1.31–1.72)**
Model 2	Ref.	**1.49 (1.34–1.66)**	**1.13 (1.03–1.25)**	1.28 (0.95–1.72)	1.18 (0.98–1.42)	**1.51 (1.32–1.73)**
Model 3	Ref.	**1.57 (1.41–1.75)**	**1.11 (1.01–1.23)**	1.29 (0.96–1.75)	1.19 (0.99–1.43)	**1.51 (1.31–1.73)**

Abbreviations: CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.
Note: Model 1 = adjusted for age, sex and type of AF; Model 2 = adjusted for variables in model 1 and CHA2DS2-VASc score; Model 3 = adjusted for variables in model 1 and hypertension, diabetes, coronary artery disease, congestive heart failure, history of stroke/transient ischemic attack, and peripheral artery disease. Bold values depict results significant at a $p<0.05$ level.
[a]Patients with CHA_2DS_2-VASc ≥ 2 and without any other complexity criteria.

without complexity features. A similar, nonstatistically significant trend was observed also for patients with history of bleeding (HR: 1.14, 95% CI: 0.96–1.34).

When we analyzed the risk of discontinuation separately for patients prescribed with NOACs or VKA at baseline, frail elderly patients showed a trend towards higher risk of VKA discontinuation. Among NOAC users, patients with at least two or more complexity criteria (HR: 1.51, 95% CI: 1.31–1.73) and those with CKD (HR: 1.11, 95% CI: 1.01–1.23) showed a higher risk of NOAC discontinuation when compared to patients with a CHA_2DS_2-VASc score ≥ 2; similarly, nonstatistically significant trends were observed for the other complexity groups (►**Table 3**).

Risk of Major Adverse Outcomes

Overall, 21,090 patients (71.2%) with complete follow-up on the primary composite outcome were evaluated for the risk of adverse events. No significant differences in terms of age,

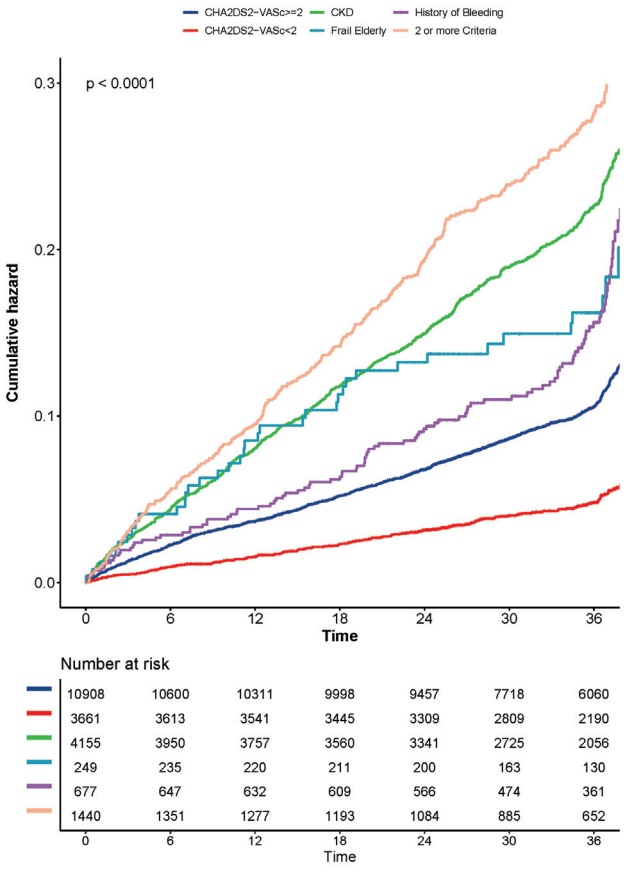


Fig. 1 Survival curves for the primary outcome of all-cause death, thromboembolism, and major bleeding according to clinical complexity domains. CKD, chronic kidney disease.

sex, and median CHA_2DS_2-VASc scores were observed between patients included and excluded from the longitudinal survival analysis.

During a median follow-up of 36.2 (IQR: 26.3–37.6) months, a total of 2,722 primary composite events occurred. Survival curves for the cumulative incidence of primary outcome according to clinical complexity domains are reported in ►**Fig. 1**, while the results of the analysis on the risk of major adverse outcomes are reported in ►**Table 4**.

The risk of the primary net clinical outcome of all-cause death, thromboembolism, and major bleeding was significantly increased across all the complexity groups except for frail elderly, with the highest magnitude observed among those with at least two complexity criteria (HR: 1.63, 95% CI 1.43–1.86). The analysis of secondary outcomes showed that those with two or more complexity criteria were at higher risk of all the outcomes investigated. Patients with CKD showed a significant higher risk of MACE, all-cause death, cardiovascular death, and thromboembolism, while patients with previous bleeding showed an increased risk of major bleeding events (HR: 1.80, 95% CI: 1.27–2.56). Consistent results were observed in the sensitivity analysis adjusted for CHA_2DS_2-VASc score instead of baseline comorbidities (►**Supplementary Table S1**, **Supplementary Material** [available in the online version]) and when restricting the analysis among those treated with OAC at baseline (►**Supplementary Table S2**, **Supplementary Material** [available in the online version]).

Discussion

In this retrospective analysis from a large, global cohort of newly diagnosed AF patients, our principal findings are as follows: (1) clinical complexity (as encompassed by frail elderly, CKD, history of bleeding, or the combinations of two or more of these conditions) is common among AF patients, being found in up to 32% of subjects included in this study; (2) clinical complexity domains influence treatment patterns, reducing the odds for OAC prescription, and also impacting the choice between NOACs and VKA; (3) OAC persistence is heterogeneously impacted by clinical complexity, with frail elderly, those with CKD, and those with two or more complexity criteria being at higher risk for OAC discontinuation; and (4) the risk of major outcomes is increased in clinically complex patients, with the highest magnitude observed in those who present two or more complexity criteria (**Visual Summary**).

Over the last decades, an increase in the burden of comorbidities and risk factors has been witnessed among AF patients, who are also becoming older with an overall high risk of thromboembolism and major adverse events.[26] Most often, clinical conditions do not occur isolated, but coexist in AF patients, leading to an unpredictable interplay and synergistic detrimental effects on patient prognosis and outcomes. These patients, who are often referred to as "clinically complex," need effective and safe anticoagulation to tackle thromboembolic risk; however, some of the conditions which are often found in these individuals are among the most important barriers to the implementation of OAC, due to the perceived high risk of bleeding.[27]

In this study, we found that up to 32% of AF patients present both high thromboembolic risk (as encompassed by a CHA_2DS_2-VASc score $\geq$2) and at least one condition that entails clinical complexity among CKD, frail elderly, and history of bleeding, with one-third of them presenting with a combination of two or more. Furthermore, these patients showed lower rates of OAC prescription and higher rates of discontinuation. This was particularly evident among those with two or more conditions: compared to patients with CHA_2DS_2-VASc score $\geq$2 and without any complexity feature, they showed a 50% lower odds of receiving OAC, and a 39% higher risk of discontinuing OAC during follow-up. Nevertheless, our study also showed that clinically complex AF patients have a poor prognosis, especially when the burden of clinical complexity is increased. The evidence provided is further strengthened by the observation of consistent results, irrespective of the model used to adjust the regression analyses. This further underlines the independent impact of complexity features in influencing the clinical history of AF patients.

Taken together, these findings suggest that the overall management of clinical complexity in AF patients is largely unsatisfactory and needs further improvements. Indeed, despite the introduction of NOACs, there is still a significant

Table 4 Number of events and risk of adverse outcomes according to clinical complexity domains

Clinical complexity domain						
Outcome	**CHA_2DS_2-VASc ≥ 2[a] ($n = 10,908$)**	**CHA_2DS_2-VASc <2 ($n = 3,661$)**	**CKD ($n = 4,155$)**	**Frail elderly ($n = 249$)**	**History of bleeding ($n = 677$)**	**Two or more criteria ($n = 1,440$)**
	n (%) HR (95% CI)	*n (%) HR (95% CI)*	*n (%) HR (95% CI)*	*n (%) HR (95% CI)*	*n (%) HR (95% CI)*	*n (%) HR (95% CI)*
Primary outcome						
Composite of all-cause death, thrombo-embolism and major bleeding	1,166 (10.7) Ref.	189 (5.2) 0.93 (0.78–1.11)	**858 (20.6) 1.37 (1.24–1.52)**	41 (16.5) 1.13 (0.81–1.58)	**111 (16.4) 1.32 (1.08–1.62)**	**357 (24.8) 1.63 (1.43–1.86)**
Secondary outcomes						
Composite of all-cause death and MACE	968 (8.9) Ref.	153 (4.2) 0.93 (0.77–1.14)	**774 (18.6) 1.44 (1.29–1.61)**	36 (14.5) 1.22 (0.86–1.73)	84 (12.4) 1.16 (0.91–1.46)	**319 (22.2) 1.72 (1.49–1.99)**
All-cause death	692 (6.3) Ref.	99 (2.7) 0.95 (0.74–1.21)	**626 (15.1) 1.49 (1.31–1.69)**	29 (11.6) 1.29 (0.87–1.91)	60 (8.9) 1.17 (0.89–1.54)	**270 (18.8) 1.84 (1.57–2.16)**
MACE	544 (5.1) Ref.	87 (2.4) 0.88 (0.68–1.15)	**427 (10.5) 1.53 (1.32–1.77)**	10 (4.1) 0.66 (0.34–1.28)	47 (7.0) 1.15 (0.84–1.57)	**158 (11.4) 1.68 (1.38–2.06)**
Cardiovascular death	229 (2.1) Ref.	30 (0.8) 0.83 (0.54–1.28)	**251 (6.2) 1.90 (1.55–2.34)**	2 (0.8) 0.31 (0.08–1.27)	20 (3.0) 1.25 (0.79–1.98)	**97 (7.0) 2.15 (1.64–2.82)**
Thromboembolism	347 (3.2) Ref.	63 (1.7) 1.03 (0.75–1.41)	**218 (5.2) 1.25 (1.03–1.52)**	9 (3.6) 0.85 (0.42–1.73)	29 (4.3) 1.06 (0.71–1.58)	**88 (6.1) 1.32 (1.01–1.71)**
Major bleeding	341 (3.1) Ref.	60 (1.6) 0.90 (0.64–1.27)	193 (4.6) 1.16 (0.94–1.42)	6 (2.4) 0.62 (0.26–1.52)	**38 (5.6) 1.80 (1.27–2.56)**	**85 (5.9) 1.46 (1.11–1.93)**

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events.
Note: Bold values depict results significant at a $p<0.05$ level.
[a]Patients with CHA_2DS_2-VASc ≥ 2 and without any other complexity criteria.

proportion of AF patients who are untreated and, even when prescribed with OAC, show a greater susceptibility to discontinue anticoagulation during follow-up. Consistently, we found that those with a higher burden of clinical complexity are at a higher risk of both suboptimal treatment and adverse outcomes, underlining how these patients currently present a critical unmet need and are not experiencing sufficient improvements in their management and prognosis.

Our results have important clinical implications. First, we found that clinical complexity entails a heterogeneous spectrum of medical conditions that are often closely intertwined. Indeed, more than 80% of elderly frail patients included in this analysis presented with at least another complexity criteria, underlining how complexity does not occur alone but more likely reflect the build-up of several risk factors and conditions. Second, we showed how clinical complexity is closely associated with significant undertreatment and lower persistence of OAC in clinical practice, which were only partially improved by the introduction of NOACs in clinical practice.[28] These data are in line with previous evidence that showed how frail patients are less likely to receive appropriate anticoagulation,[29,30] with little changes after the introduction of NOACs.[29] Renal disease has been also described as a main driver of OAC underuse as well as major outcomes among AF patients,[31,32] and history of bleeding represent a common concern when prescribing antithrombotic. Undertreatment and lower persistence, therefore, may reflect the lack of data regarding safety of anticoagulants in frail complex patients,[33,34] which were consistently under-represented in randomized controlled trials, even if NOACs have already been proved to be a safer alternative compared to VKA.[3]

On the other hand, we show how clinical complexity can impact prognosis, although with some differences among different domains, and how the concurrence of more than one condition can entail a worse prognosis. In fact, while the observation of an increased risk of adverse outcomes is consistent with the well-known association between multimorbidity and impaired survival in AF patients,[35,36] the combination of different complexity domains showed a synergistic detrimental effect on the risk of major outcomes, with the highest increase in outcomes risk observed for those with two or more complexity criteria. However, our sensitivity analysis showed a consistent risk of adverse events also among those treated with OAC at baseline, suggesting that clinically complex patients may need further interventions to improve prognosis, beyond the antithrombotic risk prevention attained with OAC.

Taken together, our findings lead to several considerations. On one side, there is an urgent need for further evidence on the efficacy and safety of current antithrombotic strategies, and research on novel antithrombotic approaches, in clinically complex patients who may be at higher risk of both bleeding and thromboembolism. Recently, the ELDERCARE-AF randomized controlled trials showed the benefit of a low-dose edoxaban regimen in elderly Japanese patients who were deemed inappropriate candidates for OAC treatment at the standard approved dose for thromboembolic prevention, with reduction in stroke and systemic embolism without a significant increase in major bleeding, compared to placebo[37]; the ongoing FRAIL-AF randomized trial, on the other side, is comparing the safety of switching to NOAC-based regimens in the frail AF elderly, and will provide more answers on the suitability of the existing strategies in this clinical scenario.[38] Furthermore, novel antithrombotic strategies with anti-XIa inhibitors may provide safe anticoagulation options in patients at high bleeding risk.[39]

On the other side, a more comprehensive and integrated approach is needed for the management of clinically complex AF patients. Indeed, recent international guidelines have already advocated for improved characterization and evaluation[40] and the implementation of an integrated approach for the treatment of AF patients.[18,19] Specifically, the "Atrial fibrillation Better Care" (ABC) pathway represents a model of such a holistic or integrated care approach to AF patient management, which includes in the "A" criterion the Anticoagulation to avoid stroke and thromboembolism, but expands further to consider also "B," better symptom control, and "C," cardiovascular and comorbidity optimization.[41] This approach has been repeatedly proved effective,[42–44] and its efficacy has also been shown in clinically complex and multimorbidity patients.[45,46]

Strengths and Limitations

Our study provides an up-to-date outlook on current patterns of antithrombotic prescription and persistence using data from a large, multinational cohort of newly diagnosed AF patients, thus being a solid representation of current practice in clinically complex patients. The large sample size from a global registry allows us to study the determinants of clinical complexity, and their interplay in influencing prescription and persistence of OAC, as well as their impact on major adverse outcomes.

Nevertheless, our study has some limitations. First, our definition of frail elderly was based on surrogate markers and may be incomplete or not completely able to capture the overall spectrum of frailty of the patients included. Second, we analyzed three of the most commonly perceived determinants of clinical complexity, although others may also have a role in influencing treatment patterns and the risk of outcomes, including socio-economic determinants and other clinical conditions which we did not analyze. Third, some patients were excluded from this analysis due to lack of data necessary to be classified across the complexity domains. However, the vast majority of the subjects enrolled were included in the analysis. Finally, although we provided covariate-adjusted regression analyses to evaluate the impact of clinical complexity on OAC use and risk of outcomes, we cannot exclude the contribution of unaccounted confounders, and therefore caution should be exerted when interpreting our results.

Conclusion

Clinical complexity is common among AF patients, has a significant impact on OAC treatment management, and

increases the risk of clinical outcomes. These patients require additional efforts, such as an integrated care models and tailored treatments, to improve their management and prognosis.

What is known about this topic?

- Clinical complexity is commonly found among atrial fibrillation (AF) patients, with detrimental effects on quality of care and prognosis.
- Among the determinants of clinical complexity, chronic kidney disease, frail elderly, and history of bleeding are among those more influential on OAC prescription and persistence, as well as clinical outcomes.

What does this paper add?

- Clinical complexity is associated with lower OAC prescription, despite the high thromboembolic risk.
- OAC persistence at follow-up is lower in clinically complex patients, especially in those with two or more complexity domains.
- The risk of major outcomes, including thromboembolism and major bleeding, was heterogeneously influenced by clinical complexity, with the highest risk observed in those with multiple complexity features.

Note

This publication is based on research using data from data contributors of Boehringer Ingelheim that have been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Author Contributions

G.F.R., M.P., and G.Y.H.L. conceived the study and interpreted study results; G.F.R. run the analyses; G.F.R. and M. P. drafted the first version of the manuscript; N.B., W.Y.D., G.B., M.V.H. and G.Y.H.L. provided important intellectual contribution in the finalization of the manuscript. All authors approved the final version of the manuscript.

Funding

This study was funded by Boehringer Ingelheim GmbH. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflict of Interest

G.Y.H.L.: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. G.Y.H.L. is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No. 899871. M.V.H. has been receiving research grants from the Dutch Healthcare Fund, Dutch Heart Foundation, BMS-Pfizer, Bayer Healthcare, and Boehringer Ingelheim, and consulting fees from BMS-Pfizer, Bayer Healthcare, and Boehringer Ingelheim. G.F.R. has been part-funded by an educational grant from Anthos. All other authors have nothing to declare.

Acknowledgments

We thank Dr. Christine Teutsch as medical study lead of GLORIA-AF for the help provided.

References

1 Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34(35):2746–2751
2 Burdett P, Lip GYH. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. Eur Heart J Qual Care Clin Outcomes 2022;8(02):187–194
3 López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017; 359:j5058
4 Gadsbøll K, Staerk L, Fosbøl EL, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J 2017;38(12):899–906
5 Hohnloser SH, Basic E, Nabauer M. Changes in oral anticoagulation therapy over one year in 51,000 atrial fibrillation patients at risk for stroke: a practice-derived study. Thromb Haemost 2019; 119(06):882–893
6 Lee SR, Choi EK, Kwon S, et al. Effectiveness and safety of direct oral anticoagulants in relation to temporal changes in their use. Circ Cardiovasc Qual Outcomes 2020;13(03):e005894
7 Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One 2017;12(12):e0189495
8 Xia X, Wang L, Lin T, et al. Barriers to prescribing oral anticoagulants to inpatients aged 80 years and older with nonvalvular atrial fibrillation: a cross-sectional study. BMC Geriatr 2022;22(01):263
9 Maura G, Billionnet C, Drouin J, Weill A, Neumann A, Pariente A. Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016. BMJ Open 2019;9(04):e026645
10 Sussman M, Barnes GD, Guo JD, et al. The burden of undertreatment and non-treatment among patients with non-valvular atrial fibrillation and elevated stroke risk: a systematic review. Curr Med Res Opin 2022;38(01):7–18
11 Kotalczyk A, Mazurek M, Kalarus Z, Potpara TS, Lip GYH. Stroke prevention strategies in high-risk patients with atrial fibrillation. Nat Rev Cardiol 2021;18(04):276–290
12 Ohta M, Hayashi K, Mori Y, et al. Impact of frailty on bleeding events related to anticoagulation therapy in patients with atrial fibrillation. Circ J 2021;85(03):235–242
13 Olesen JB, Lip GYH, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367 (07):625–635
14 Staerk L, Lip GYH, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. BMJ 2015;351:h5876
15 Ding WY, Gupta D, Wong CF, Lip GYH. Pathophysiology of atrial fibrillation and chronic kidney disease. Cardiovasc Res 2021;117 (04):1046–1059

16 Proietti M, Romiti GF, Raparelli V, et al. Frailty prevalence and impact on outcomes in patients with atrial fibrillation: a systematic review and meta-analysis of 1,187,000 patients. Ageing Res Rev 2022;79:101652
17 Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing 2011;40(06):675–683
18 Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42(05):373–498
19 Chao TF, Joung B, Takahashi Y, et al. 2021 Focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. Thromb Haemost 2022;122(01):20–47
20 Huisman MV, Lip GYH, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. Am Heart J 2014;167(03):329–334
21 Ding WY, Calvert P, Gupta D, Huisman MV, Lip GYH; GLORIA-AF Investigators. Impact of early ablation of atrial fibrillation on long-term outcomes: results from phase II/III of the GLORIA-AF registry. Clin Res Cardiol 2022;111(09):1057–1068
22 Lip GYH, Kotalczyk A, Teutsch C, et al; GLORIA-AF Investigators. Comparative effectiveness and safety of non-vitamin K antagonists for atrial fibrillation in clinical practice: GLORIA-AF Registry. Clin Res Cardiol 2022;111(05):560–573
23 Huisman MV, Teutsch C, Lu S, et al; GLORIA-AF Investigators. Dabigatran versus vitamin K antagonists for atrial fibrillation in clinical practice: final outcomes from Phase III of the GLORIA-AF registry. Clin Res Cardiol 2022;111(05):548–559
24 Winter JE, MacInnis RJ, Wattanapenpaiboon N, Nowson CA. BMI and all-cause mortality in older adults: a meta-analysis. Am J Clin Nutr 2014;99(04):875–890
25 Mazurek M, Teutsch C, Diener HC, et al; GLORIA-AF Investigators. Safety and effectiveness of dabigatran at 2 years: final outcomes from Phase II of the GLORIA-AF registry program. Am Heart J 2019;218:123–127
26 Proietti M, Laroche C, Nieuwlaat R, et al; EORP-AF General Pilot Registry Euro Heart Survey on AF Investigators. Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: a comparison between EORP-AF pilot and EHS-AF registries. Eur J Intern Med 2018; 55:28–34
27 Kakkar AK, Mueller I, Bassand JP, et al; GARFIELD Registry Investigators. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 2013;8(05):e63479
28 Ozaki AF, Choi AS, Le QT, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2020;13(03):e005969
29 Orlandi M, Dover DC, Sandhu RK, Hawkins NM, Kaul P, McAlister FA. The introduction of direct oral anticoagulants has not resolved treatment gaps for frail patients with nonvalvular atrial fibrillation. Can J Cardiol 2022;38(01):77–84
30 Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. Age Ageing 2019;48(02): 196–203
31 Park S, Je NK. Underutilization of anticoagulants in patients with nonvalvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants. International Journal of Arrhythmia 2022;23(01):1
32 Ding WY, Potpara TS, Blomström-Lundqvist C, et al; ESC-EHRA EORP-AF Long-Term General Registry Investigators. Impact of renal impairment on atrial fibrillation: ESC-EHRA EORP-AF Long-Term General Registry. Eur J Clin Invest 2022;52(06): e13745
33 Proietti M, Camera M, Gallieni M, et al. Use and prescription of direct oral anticoagulants in older and frail patients with atrial fibrillation: a multidisciplinary consensus document. J Pers Med 2022;12(03):469
34 Grymonprez M, Steurbaut S, De Backer TL, Petrovic M, Lahousse L. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-analysis. Front Pharmacol 2020;11:583311
35 Proietti M, Marzona I, Vannini T, et al. Long-term relationship between atrial fibrillation, multimorbidity and oral anticoagulant drug use. Mayo Clin Proc 2019;94(12):2427–2436
36 Jani BD, Nicholl BI, McQueenie R, et al. Multimorbidity and comorbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. Europace 2018;20(FI_3):f329–f336
37 Okumura K, Lip GYH, Akao M, et al. Edoxaban for the management of elderly Japanese patients with atrial fibrillation ineligible for standard oral anticoagulant therapies: rationale and design of the ELDERCARE-AF study. Am Heart J 2017;194:99–106
38 Joosten LPT, van Doorn S, Hoes AW, et al. Safety of switching from vitamin K antagonist to non-vitamin K antagonist oral anticoagulant in frail elderly with atrial fibrillation: rationale and design of the FRAIL-AF randomised controlled trial. BMJ Open 2019;9(12): e032488
39 Piccini JP, Caso V, Connolly SJ, et al; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet 2022;399(10333):1383–1390
40 Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): a novel approach to in-depth characterization (rather than classification) of atrial fibrillation. Thromb Haemost 2021;121(03): 270–278
41 Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017;14(11):627–628
42 Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. Am J Med 2018;131(11):1359–1366.e6
43 Romiti GF, Pastori D, Rivera-Caravaca JM, et al. Adherence to the 'Atrial Fibrillation Better Care' pathway in patients with atrial fibrillation: impact on clinical outcomes-a systematic review and meta-analysis of 285,000 patients. Thromb Haemost 2022;122 (03):406–414
44 Guo Y, Lane DA, Wang L, et al; mAF-App II Trial Investigators. Mobile health technology to improve care for patients with atrial fibrillation. J Am Coll Cardiol 2020;75(13):1523–1534
45 Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Comprehensive management with the abc (Atrial fibrillation better care) pathway in clinically complex patients with atrial fibrillation: a post hoc ancillary analysis from the affirm trial. J Am Heart Assoc 2020;9(10):e014932
46 Yao Y, Guo Y, Lip GYHmAF-App II Trial investigators. The effects of implementing a mobile health-technology supported pathway on atrial fibrillation-related adverse events among patients with multimorbidity: the mAFA-II randomized clinical trial. JAMA Netw Open 2021;4(12):e2140071