Management of anticoagulation in atrial fibrillation patients in Italy: insight from the *Atrial Fibrillation-Survey on Anticoagulated Patients Register* (AF-START)

Daniela Poli,[1] Walter Ageno,[2] Emilia Antonucci,[3] Salvatore Bradamante,[4] Eugenio Bucherini,[5] Paolo Chiarugi,[6] Antonio Chistolini,[7] Benilde Cosmi,[8] Anna Falanga,[9] Antonio Insana,[10] Domenico Lione,[11] Rosa Maria Lombardi,[12] Giuseppe Malcangi,[13] Rossella Marcucci,[1] Giuliana Martini,[14] Lucilla Masciocco,[15] Carmelo Paparo,[16] Daniele Pastori,[17] Simona Pedrini,[18] Vittorio Pengo,[19] Pasquale Pignatelli,[17] Andrea Toma,[20] Sophie Testa,[21] Gualtiero Palareti[3]

[1]Center of Atherothrombotic Disease, Careggi University Hospital, Florence; [2]Short Stay Observation and Short Recovery Unit, Department of Internal Medicine, Circolo Hospital and Macchi Foundation, ASST Sette Laghi, Varese; [3]Arianna Anticoagulazione Foundation, Bologna; [4]Transfusion Center, Hemostasis and Thrombosis Center, Annunziata Hospital, Taranto; [5]Vascular Medicine and Angiology SS, AUSL Romagna, Ravenna; [6]Clinical Chemical Analysis Organizational Unit, Pisana University Hospital, Pisa; 7Department of Translational and Precision Medicine, Sapienza University of Rome; [8]Division of Angiology and Blood Coagulation, S. Orsola-Malpighi University Hospital, Bologna; [9]Thrombosis, Hemostasis Immunohematology and Transfusion Medicine Center, ASST Papa Giovanni XXIII, Bergamo; [10]SC Chemical-Clinical Analysis and Microbiology Laboratory, Ordine Mauriziano Hospital, Turin; [11]Complex Operating Unit of Clinical Pathology, A. Perrino Hospital, Brindisi; [12]Internal Medicine Organization Unit, Hemostasis and Thrombosis Center, University Hospital of Parma; [13]Hemophilia and Thrombosis Center, Polyclinic of Bari; [14]Hemostasis Center, Civilian Hospitals of Brescia; [15]Complex Operating Unit of Internal Medicine, Lastaria Hospital, Lucera (FG); [16]Analysis Laboratory, Maggiore Chieri Hospital, Turin; [17]Department of Clinical Internal Medicine, Anesthesiology and Cardiovascular Sciences, Thrombosis Center, Sapienza University of Rome; [18]Laboratory Service, Poliambulanza Foundation Hospital, Brescia; [19]Department of Cardio-Thoracic-Vascular Sciences, University Hospital of Padua; [20]Complex Operating Unit of Clinical Pathology, Oral Anticoagulant Therapy Outpatient Clinic, L. Cazzavillan Civilian Hospital, Arzignano (VI); [21]Department of Laboratory Medicine, Hemostasis and Thrombosis Center, ASST Cremona, Italy

Correspondence: Daniela Poli, Center of Atherothrombotic Disease, Careggi University Hospital, Florence, Italy.
Tel.: +39.055.7945453.
E-mail: polida@aou-careggi.toscana.it

Citation: Poli D, Ageno W, Antonucci E, et al. Management of anticoagulation in atrial fibrillation patients in Italy: insight from the Atrial Fibrillation-Survey on Anticoagulated Patients Register (AF-START). Bleeding, Thrombosis, and Vascular Biology 2023;2:84.

Key words: atrial fibrillation, anticoagulation, bleeding event, stroke.

Contributions: DP, study conception, statistical analysis, and writing of the initial draft of the manuscript; WA, GP, critical review of the draft; EA, statistical analysis; SB, EB, AC, BC, AF, AI, DL, RML, GM, RM, GM, LM, DP, CP, SP, CP, VP, PP, AP, ST, data collection. All the authors read and commented on the paper and approved its submission.

Conflict of interest: the authors declare no potential conflict of interest.

Informed consent: the manuscript does not contain any individual person's data in any form. Written informed consent was obtained from each patient before enrollment.

Funding: Arianna Anticoagulation Foundation supported the START Register. The Foundation had no role in the study design, collection, analysis, and interpretation of data, in writing the report, and in the decision to submit the paper for publication.

Availability of data and materials: data and materials are available by the authors according to the Italian law on personal data protection.

Received: 12 May 2023.
Accepted: 22 June 2023.

Bleeding, Thrombosis and Vascular Biology 2023; 2:84
doi:10.4081/btvb.2023.84

ABSTRACT

The survey on anticoagulated patients register (START-Register) is an independent, prospective, inception-cohort observational study aimed at providing information on patients on vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) in Italy. In this study, we describe the cohort of atrial fibrillation (AF) patients in the START-Register and report outcomes and changes in anticoagulant prescription from 2011 to 2021. The study included 11,078 AF patients, enrolled in 47 Italian centers distributed all over the Country; the median age was 77 years (range 18-99 years); 6,029 (54.3%) were men; 5,135 (46.4%) were on VKAs, and 5,943 (53.6%) were on DOACs. Warfarin was the most prescribed VKA (98.4%), and apixaban

was the most prescribed DOAC (31.6%). Among DOAC users, 4,022 (67.7%) patients were naive to anticoagulation, and 2,562 (43.1%) patients were treated with a reduced dose. DOAC patients were significantly older than VKA patients (median age 79 years *vs* 76 years respectively, P<0.001), but no gender difference was detected. The mean CHA_2DS_2VASc score was higher in DOAC users than in VKA users (3.7 *vs* 3.6; P=0.03). The mean HAS-BLED score was not different between the two groups. During follow-up, 542 bleeding events were recorded [2.44 per 100 patient-years (pt-yrs)]; 240 were major (1.08 per 100 pt-yrs), and 301 were clinically relevant non-major bleedings (1.34 per 100 pt-yrs). 146 thrombotic events were recorded during follow-up (0.66 per 100 pt-yrs). The total mortality rate was 3.5 per 100 pt-yrs; the mortality rate was 4.54 per 100 pt-yrs among patients on VKAs and 2.31 per 100 pt-yrs among patients on DOACs. During the last 10 years, in Italy, AF patient management has changed with the large spread of DOACs all over the Country. DOAC patients are frequently treated with reduced doses and show a lower mortality rate in comparison to patients on VKAs.

Introduction

Atrial fibrillation (AF) is associated with a fivefold increased risk of stroke.[1,2] AF-related strokes are more severe and have higher mortality and disability than strokes occurring in patients without AF.[3,4] Adequate stroke prevention with oral anticoagulants is recommended for most patients.[5] However, the bleeding risk associated with anticoagulation and the complex management required for patients on treatment with vitamin K antagonists (VKAs) resulted in a limited adherence to these indications leading to the underuse of anticoagulant treatment.[6] The introduction of direct oral anticoagulants (DOACs) changed the landscape of anticoagulation, due to their ease of use and lower bleeding risk with respect to warfarin demonstrated in registrative studies.[7] Collecting data from large cohorts of patients to assess clinical practice patterns and the safety and effectiveness of treatment strategies has been a goal of clinical research in the last 20 years, and several prospective registries have been implemented.[8-12] In Italy, the marketing of DOACs started during the summer of 2013, and the reimbursement of these drugs required a specific prescription by specialists, such as cardiologists or internists. The possibility of prescription was extended to general practitioners only in 2020. Therefore, the use of DOACs was limited in the first years after marketing because of the Italian health policy. The AF survey on anticoagulated patients register (START-Register) was designed to provide information on AF patients and anticoagulant treatment with VKAs or DOACs in Italy; to describe prescription patterns and to evaluate the risks and benefits of the various anticoagulant drugs. Two cohorts were enrolled, cohort 1 completed data collection in 2015, and cohort 2 in 2021. Data on the AF START-Register cohort 1 were previously published.[13,14] In this study, we describe the characteristics of patients of the whole cohort of the AF START-Register (cohorts 1 and 2) and report outcome events that occurred during treatment and changes in anticoagulant prescription in the Register from 2011 to 2021.

Materials and Methods

The START-Register is an observational, multicenter, prospective cohort study that includes patients over 18 years old who start anticoagulation therapy, regardless of the drug and the indication for treatment. The START-Register aims to collect data on the incidence of adverse events in patients taking anticoagulants, as well as their determinants. The study design and protocol were approved by the Ethical Committee of the S. Orsola-Malpighi University Polyclinic Hospital (Bologna, Italy) in October 2011 (N.142/2010/0/0ss) (NCT02219984). The START-Register procedures and data collection have been previously described.[15]

Participating centers were required to enroll patients consecutively, without any *a priori* exclusion criteria other than short life expectancy or geographical inaccessibility, and to follow up with patients for at least one year.

Baseline demographic data and patients' clinical characteristics, associated diseases, clinical indication for treatment, and use of concomitant drugs were collected in a web-based case report form. Naive patients were enrolled in the study within the first month of treatment with an oral anticoagulant, either VKAs or DOACs. The patients who shifted to DOACs from VKAs were enrolled when VKA treatment was stopped and DOAC treatment was started. Also in these patients, the enrollment started within the first month after the prescription of DOACs. Serum creatinine levels were measured by local hospital laboratories, and creatinine clearance (CrCl) was calculated using the Cockroft-Gault formula.[16] Renal failure was defined by an estimated CrCl <30 mL/min.

Patients with non-valvular AF are stratified for stroke risk according to the CHA_2DS_2VASc score,[17] while baseline bleeding risk is evaluated by using the HAS-BLED score.[18] Participating centers are required to regularly follow up with enrolled patients and to provide detailed clinical reports of any relevant clinical outcome.

Major bleeding and clinically relevant non-major bleeding (CRNMB) were defined according to the classification proposed by the International Society on Thrombosis and Haemostasis.[19,20] Stroke diagnosis requires the abrupt onset of focal neurological symptoms lasting at least 24 hours and supported by congruent ischemic lesions at computed tomography or magnetic resonance imaging scan. Systemic embolism is defined by symptoms consistent with an acute loss of blood flow to a peripheral artery, which is supported by objective evidence of embolism.

Statistical analysis

A descriptive analysis was performed. Continuous variables are expressed as median and interquartile range or as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages. Differences between continuous values were assessed using the unpaired t-test, and categorical variables were compared using the Chi-square test or Fisher exact test, as appropriate. The incidence of bleeding events, thrombotic events, and death was calculated by dividing the number of events by the person's time at risk. The incidence rate ratio together with the 95% confidence interval was calculated. P<0.05 were considered statistically significant. The data were analyzed with the use of SPSS software for Windows, V.26 (IBM, Armonk, New York, USA) and Stata V.14 statistical software package (StataCorp, College Station, Texas, USA).

Results

The study included 11,078 AF patients, enrolled in 47 Italian centers. Participating centers are distributed all over the country: 66.9% in northern Italy, 23.6% in central Italy, and 9.5% in southern Italy. Patients were followed for a median time of 1.5 years (range 0.1-9.7 years). Figure 1 reports VKAs and DOACs prescription patterns over time. No difference in the DOAC prescription rates was found in terms of the geographical distribution of the participating centers.

The characteristics of patients are reported in Table 1. The median age was 77 (range 18-99 years), and 6029 (54.3%) were males. 5135 patients (46.4%) were on VKA treatment, whereas 5943 patients (53.6%) were on DOACs.

Warfarin was the most prescribed VKA (98.4% of cases), and apixaban was the most prescribed DOAC (31.6% of cases). Among DOAC users, 4022 (67.7%) patients were naive to anticoagulation, and 2562 (43.1%) patients were treated with a reduced dose.

DOAC patients were significantly older than VKA patients (median age 79 years *vs* 76 years respectively, P<0.001), but no gender differences were detected. The median follow-up period was 1.9 years for patients on VKAs and 1.3 years for patients on DOACs (P<0.001).

Patients on DOACs had paroxysmal AF, hypertension, thrombocytopenia, history of previous bleeding, and dementia and required bed rest more frequently than patients on VKAs. VKA patients had history of heart failure, coronary artery disease, peripheral occlusive arterial disease, and renal failure more frequently (Table 1). Similarly, VKA patients received concomitant antiplatelet drugs more frequently than DOAC patients (13.8% *vs* 10.1%; P<0.001). The mean CHA_2DS_2VASc score was higher in DOAC than in VKA users (3.7 *vs* 3.6; P=0.03), and the proportion of patients with a CHA_2DS_2VASc score ≤2 was significantly higher among VKA patients (24.4%) than DOAC patients (18.8%) (P<0.001). Instead, the mean HAS-BLED score was not different between the two groups (0.9 and 0.8, respectively).

During follow-up, 542 bleeding events were recorded [2.44 per 100 patient-years (pt-yrs)]; 240 were major (1.08 per 100 pt-yrs), and 301 were CRNMB (1.34 per 100 pt-yrs) (Table 2). Major bleeding was fatal in 25 cases (10.4%). Major bleedings were recorded in 119 patients on VKAs (rate 0.99 per 100 pt-yrs), and in 121 patients on DOACs (rate 1.19 per 100 pt-yrs).

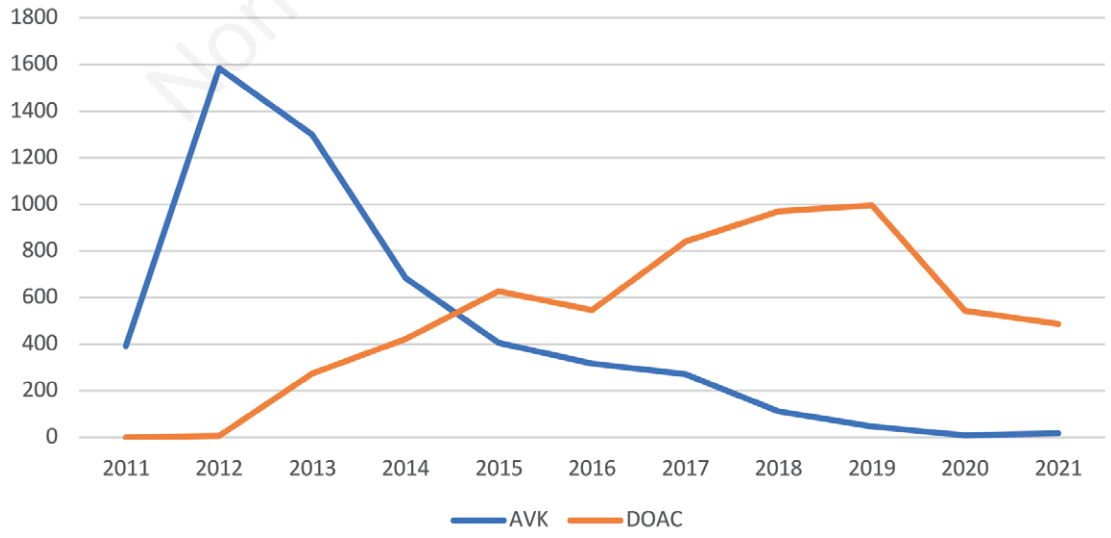
During follow-up, 146 thrombotic events were recorded (0.66 per 100 pt-yrs): 59 cases among patients on VKAs (rate 0.49 per 100 pt-yrs), and 87 cases among patients on DOACs (rate 0.86 per 100 pt-yrs). 783 patients died (rate 3.5 per 100 pt-yrs): 550 among patients on VKAs (rate 4.54 per 100 pt-yrs), and 231 among patients on DOACs (rate 2.28 per 100 pt-yrs). The causes of death were: bleeding in 25 cases (3.2%), and stroke in 10 cases (1.3%).

Discussion

We present here data from AF patients included in the whole cohort of the AF START-Register. During 10 years of observation, we observed a progressive decline in warfarin prescription and a progressive increase in DOAC prescription, with DOACs being prescribed to more than 95% of patients enrolled during 2021, the last year of observation. This finding is in agreement with what was reported in the majority of Western countries.[21,22]

Patients included in the AF START-Register are older than patients included in the Garfield AF, ORBIT AF,[23] and PREFER AF study,[10] with more than two-thirds of patients over 75 years of age, in comparison to less than 50% in the other studies. However, stroke risk, calculated by CHA_2DS_2VASc score, and bleeding risk, calculated by HAS-BLED score, are similar to those of patients included in the other studies.[10,23]

In our study, VKA patients had more frequently history of coronary artery disease and peripheral obstructive arterial dis-



AVK, vitamin K antagonist; DOAC, direct oral anticoagulant.

Figure 1. Enrollment of patients on vitamin K antagonists or direct oral anticoagulants.

ease. As a consequence, in these patients, a higher rate of concomitant antiplatelet treatment in comparison to patients on DOACs was found. Similarly, renal failure was more frequent in VKA patients than in DOAC ones.

In the AF START-Register patients, the bleeding risk was similar in both groups, even if the mortality rate due to bleeding events was higher among patients on VKAs. This finding is different from data reported in the registrative studies comparing DOACs with VKAs,[7] and in the GARFIELD-AF study.[24] Centers participating in AF START-Register are anticoagulation clinics and followed patients on VKAs with careful management, which is associated with a lower bleeding risk with respect to routine management of anticoagulation.[25]

In our cohort, patients on DOACs received a reduced dose in 43.1% of the cases. A high prevalence of a reduced dose prescription was previously reported,[26,27] even though in these stud-

Table 1. Characteristics of patients accordingly to the type of anticoagulant treatment.

	All patients	Patients on VKAs	Patients on DOACs	P value
Patients, N (%)	11078	5135 (46.4)	5943 (53.6)	
Females, N (%)	5071 (45.7)	2310 (45.0)	2752 (46.3)	0.2
Men, N (%)	6029 (54.3)	2825 (55.0)	3191 (53.7)	0.2
Median age (range) [IQR], years	77 (18-99) [71-83]	76 (18-98) [70-82]	79 (20-99) [72-84]	<0.001
Age >75 years, N (%)	6896 (62.2)	2390 (57.1)	3966 (66.7)	<0.001
Total follow-up, years	22238	12118	10120	
Median follow-up (range) [IQR], years	1.5 (0.1-9.7) [1.0-2.6]	1.9 (0.1-9.7) [0.9-3.5]	1.3 (0.1-8.9) [1.0-2.0]	<0.001
Paroxysmal AF, N (%)	2340 (39.6)	1682 (32.8)	2340 (39.6)	<0.001
Hypertension, N (%)	8889 (80.2)	4002 (77.9)	4887 (82.2)	<0.001
Diabetes mellitus, N (%)	2275 (20.5)	1048 (20.4)	1226 (20.6)	0.8
Heart failure, N (%)	2115 (19.1)	1046 (20.4)	1069 (18.0)	0.001
Coronary artery disease, N (%)	1869 (16.9)	1019 (19.9)	848 (14.3)	<0.001
Peripheral occlusive arterial disease, N (%)	648 (5.8)	332 (6.5)	316 (5.3)	0.004
COPD, N (%)	1355 (12.2)	623 (12.1)	732 (12.3)	0.03
Active cancer, N (%)	308 (2.8)	140 (2.7)	168 (2.8)	0.5
Dementia, N (%)	341 (3.1)	113 (2.2)	228 (3.8)	<0.001
Anemia, N (%)	300 (2.7)	145 (2.8)	155 (2.6)	0.5
Platelet count <100.000/μL, N (%)	102 (0.9)	59 (1.1)	43 (0.7)	0.02
Bed rest, N (%)	94 (0.8)	28 (0.5)	66 (1.1)	<0.001
Frequent falls, N (%)	221 (2.0)	109 (2.1)	112 (1.9)	0.7
Previous bleeding, N (%)	412 (3.7)	122 (2.4)	290 (4.9)	<0.001
Previous stroke, N (%)	1688 (15.2)	725 (14.1)	963 (16.2)	0.004
Renal function (5907/5943)				
eGFR <30 mL/min	560 (5.1)	369 (7.2)	191 (3.2)	<0.001
30-60 mL/min	4721 (42.6)	2092 (41.0)	2629 (44.2)	<0.001
>60 mL/min	5669 (51.2)	2618 (51.3)	3051 (51.3)	0.7
Antiplatelet drugs, N (%)	1306 (11.8)	707 (13.8)	599 (10.1)	<0.001
Psychotropic drugs, N (%)	936 (8.4)	384 (7.5)	552 (9.3)	0.003
Mean CHA2DS2VASc score (SD)	3.7 (1.5)	3.6 (1.6)	3.7 (1.5)	0.03
CHA2DS2VASc ≤2, N (%)	2374 (21.4)	1255 (24.4)	1119 (18.8)	<0.001
Mean HAS-BLED score (SD)	2.1 (0.8)	2.0 (0.9)	2.1 (0.8)	0.4
HAS-BLED ≥3, N (%)	2840 (25.6)	1335 (26.0)	1505 (25.3)	0.4
Anticoagulant Treatment, N (%)				
Naive		5135 (100.0)	4022 (67.7)	
Warfarin		5053 (98.4)	-	
Apixaban		-	1880 (31.6)	
Dabigatran		-	1397 (23.5)	
Edoxaban		-	1101 (18.5)	
Rivaroxaban			1565 (26.3)	
DOAC reduced dose, N (%)			2562 (43.1)	

N, number; VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants; AF, atrial fibrillation; IQR, interquartile range; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

Table 2. Adverse events recorded during follow-up.

	All patients, N (rate×100 pt-yrs)	Patients on VKAs, N (rate×100 pt-yrs)	Patients on DOACs, N (rate×100 pt-yrs)
All bleedings	542 (2.44)	291 (2.40)	251 (2.48)
Major bleedings	240 (1.08)	119 (0.99)	121 (1.19)
ICH	76 (0.34)	45 (0.37)	31 (0.32)
GI bleed	63 (0.28)	26 (0.21)	37 (0.37)
Anemia requiring blood transfusion >2 RCU	85 (0.38)	39 (0.32)	46 (0.45)
Intra articular	7 (0.03)	2 (0.02)	5 (0.05)
Retroperitoneal	5 (0.02)	1 (0.01)	4 (0.04)
Hematuria	3 (0.01)	2 (0.02)	1 (0.01)
Metrorrhagia	1 (0.00)	1 (0.01)	-
Fatal bleedings	25 (0.11)	19 (0.16)	6 (0.06)
CRNMB	301 (1.34)	171 (1.41)	130 (1.28)
Median time to bleedings (range), years	0.8 (0.1-7.0)	1.2 (0.1-6.7)	0.9 (0.1-5.8)
Thrombotic events	84 (0.37)	36 (0.30)	48 (0.47)
Stroke	52 (0.23)	21 (0.17)	31 (0.30)
TIA	21 (0.09)	12 (0.10)	9 (0.09)
Arterial embolism	5 (0.02)	1 (0.01)	4 (0.04)
Intracardiac thrombosis	5 (0.02)	1 (0.01)	4 (0.04)
Fatal stroke	10 (0.04)	8 (0.07)	2 (0.02)
Median time to stroke (range), years	1.4 (0.1-7.0)	1.3 (0.1-6.5)	1.2 (0.1-5.4)
Death	781 (3.50)	550 (4.54)	231 (2.28)

N, number; VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants; pt-yrs, patient-years; CRNMB, clinically relevant non-major bleeding; GI, gastrointestinal bleeding; ICH, intracranial bleeding; TIA, transient ischemic attack; RCU, red cell units.

ies a percentage ranging from 16% and 22% was reported. The use of reduced doses of DOACs is more frequent in routine clinical practice than in clinical trials.[28,29] Moreover, when reduced doses were prescribed, frequent underdosing has been reported, with an increased risk of thrombotic complications due to inadequate anticoagulation.[28,30] The elevated median age of our cohort may have contributed to the elevated prescription of a reduced dose, as it is known that older age is associated with anticoagulant underdosing.[27]

Strengths and limitations of the study

Strengths of our study include the prospective design, the large cohort with a long duration of follow-up, and the participation of highly experienced centers.

This study has also several limitations. Firstly, caution should be required when interpreting comparisons between two classes of drugs, due to the observational design for the risks of bias reported for these studies.[23] Secondly, the causes of death described in the electronic case report forms were reported as deaths related to bleeding events, or to cerebral ischemic events. All the other causes of death were defined as not related to anticoagulant treatment, including cancer, infectious diseases, vascular events (not cerebral), heart failure, renal failure, respiratory insufficiency, or sudden death. However, 10.2% of deaths were not reported in the case report forms; therefore, we cannot exclude an underestimation of adverse events. Finally, there was no central adjudication of outcome events in this study.

Conclusions

During the last 10 years, in Italy, the management of AF patients has changed because of the large diffusion of DOACs, in line with international guidelines.[31] DOAC patients are frequently treated with low-dose DOACs. The AF START-Register included a large cohort of elderly patients recruited all over the Country and confirmed the low bleeding risk for VKA patients followed by Italian anticoagulation clinics; however, these patients have a higher mortality rate, that is double as compared to DOAC patients. This finding is partially explained by the higher prevalence of arterial diseases and reduced renal function reported in these patients.

References

1. Wolf PA, Abbott RD and Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the framingham study. Stroke 1991;22:983-8.
2. Hart RG, Pearce LA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146: 857-67.
3. Jorgensen HS, Nakayama H, Reith J, et al. Acute stroke with atrial fibrillation. The Copenhagen stroke study. Stroke 1996;27:1765-9.
4. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of

atrial fibrillation on the risk of death: the framingham heart study. Circulation 1998;98:946-52.
5. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the european society of cardiology (ESC). Eur Heart J 2010;31:2369-429.
6. Ogilvie IM, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010;123:638-45.e4.
7. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
8. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: global anticoagulant registry in the FIELD (GARFIELD). Am Heart J 2012;163:13-19.e1.
9. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001;285:2370-5.
10. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC guidelines on atrial fibrillation: primary results of the prevention of thromboemolic events—European registry in atrial fibrillation (prefer in AF). Europace 2014;16:6-14.
11. Banerjee A, Fauchier L, Vourc'h P, et al. Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the Loire valley atrial fibrillation project. J Am Coll Cardiol 2013;61:2079-87.
12. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J 2011;162:606-12.e1.
13. Poli D, Antonucci E, Pengo V, et al. Comparison of HAS-BLED and HAS-BED versus CHADS(2) and CHA(2)DS (2)VASC stroke and bleeding scores in patients with atrial fibrillation. Am J Cardiol 2017;119:1012-6.
14. Denas G, Zoppellaro G, Padayattil Jose S, et al. Warfarin prescription in patients with nonvalvular atrial fibrillation and one non-gender-related risk factor (CHA(2) DS(2) VASC 1 or 2): a treatment dilemma. Cardiovasc Ther 2018;36.
15. Antonucci E, Poli D, Tosetto A, et al. The Italian START-Register on anticoagulation with focus on atrial fibrillation. PloS One 2015;10:e0124719.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
17. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
18. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. Chest 2010;138:1093-100.
19. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
20. Kaatz S, Ahmad D, Spyropoulos AC, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-26.
21. Apenteng PN, Gao H, Hobbs FR, et al. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ Open 2018;8:e018905.
22. Ten Cate V, Ten Cate H, Verheugt FW. The global anticoagulant registry in the FIELD-atrial fibrillation (GARFIELD-AF) : exploring the changes in anticoagulant practice in patients with non-valvular atrial fibrillation in the Netherlands. Neth Heart J 2016;24:574-80.
23. Farjat AE, Virdone S, Thomas LE, et al. The importance of the design of observational studies in comparative effectiveness research: lessons from the GARFIELD-AF and ORBIT-AF registries. Am Heart J 2022;243:110-21.
24. Bassand JP, Virdone S, Badoz M, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. Blood Adv 2021;5:1081-91.
25. Entezari-Maleki T, Dousti S, Hamishehkar H et al. A systematic review on comparing 2 common models for management of warfarin therapy; pharmacist-led service versus usual medical care. J Clin Pharmacol 2016;56:24-38.
26. Steinberg BA, Shrader P, Pieper K, et al. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (the outcomes registry for better informed treatment of atrial fibrillation II). J Am Heart Assoc 2018;7:e007633.
27. Arbel R, Sergienko R, Hammerman A, et al. Effectiveness and safety of off-label dose-reduced direct oral anticoagulants in atrial fibrillation. Am J Med 2019;132:847-55.e3.
28. Santos J, Antonio N, Rocha M, Fortuna A. Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: a systematic review. Br J Clin Pharmacol 2020;86:533-47.
29. Gibson CM, Smith CB, Davis S, Scalese MJ. Assessment of apixaban prescribing patterns for nonvalvular atrial fibrillation in hospitalized patients. Ann Pharmacother 2018;52:54-9.
30. Bo M, Corsini A, Brunetti E, et al. Off-label use of reduced dose direct oral factor Xa inhibitors in subjects with atrial fibrillation: a review of clinical evidence. Eur Heart J Cardiovasc Pharmacother 2021;7:334-45.
31. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016;74:1359-469.

Online supplementary material:

List of participating centers and investigators who contributed to the START2 AF Registry.