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ORIGINAL ARTICLE

Antithrombotic treatment switching in elderly patients with atrial fibrillation and the risk of thromboembolism, bleeding, and cardiac death

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Abstract

Background: Risks of antithrombotic switching is not investigated in elderly atrial fibrillation patients.

Objectives: To investigate the effectiveness and safety of antithrombotic treatment and switching of antithrombotic treatment in elderly patients (aged 75 years or older) with atrial fibrillation (AF).

Methods: We conducted a cohort study of 2943 patients with AF (Carrebean-elderly), hospitalized during 2010–2017. Cox models were used to estimate the association of antithrombotic treatment (warfarin, direct oral anticoagulants [DOAC] and non–guideline-recommended therapy [NG], i.e., aspirin and low-molecular-weight heparin) at discharge and antithrombotic treatment switching during follow-up with the risk of a composite and single end points of thromboembolism, bleeding, and cardiac death. Crude and adjusted risk estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All-cause death was evaluated, with competing risk regression and estimates expressed as subhazard ratios and 95% CIs.

Results: We observed an increased risk for the composite end point associated with NG as compared to warfarin at discharge (HR, 1.18; 95% CI, 1.01–1.38) with congruent competing risk regression results, while no significant risk difference was seen for DOACs compared to warfarin (HR, 1.12; 95% CI, 0.92–1.36). Switching from NG to warfarin/DOAC and from warfarin to DOAC occurred in 30.4% and 33.1% of respective antithrombotic treatment groups at discharge and was associated with a decreased risk for the composite end point with an adjusted HR of 0.45 (95% CI, 0.32–0.63) and a HR of 0.50 (95% CI, 0.38–0.65), respectively.

Conclusions: Antithrombotic treatment switching is common in the elderly AF population. Importantly, switching to guideline-recommended treatment has a favorable impact on both effectiveness and safety.

KEYWORDS
aged, anticoagulants, atrial fibrillation, multimorbidity, treatment switching

Essentials

- Risks of antithrombotic switching are not investigated in elderly patients with atrial fibrillation (AF).
- We conducted a cohort study of 2943 hospitalized patients with AF at a Swedish university hospital.
- Switching of antithrombotic treatment is common in the elderly AF population.
- Switching to guideline-recommended antithrombotics is beneficial for effectiveness and safety.

1 | INTRODUCTION

Elderly patients with atrial fibrillation (AF) with multimorbidity experience the highest risk of thromboembolism and bleeding when on antithrombotic treatment.[1,2] While the efficacy of antithrombotic treatment has been established in all age categories,[3] the effectiveness of antithrombotic treatment in the elderly is still debated.[4]

Antithrombotic treatment in patients with AF is often lifelong, and switching between different antithrombotic drugs is a rather common phenomenon,[5] possibly of even greater magnitude in the group of elderly patients with AF, whose health condition is highly dynamic over time. Clinical trials and observational pharmacoepidemiologic studies investigating antithrombotic treatment often apply an intention-to-treat approach, where drug switching during follow-up is ignored, likely due to the complexity otherwise introduced to the statistical analysis.[6] Therefore, the risk of AF-related complications associated with antithrombotic treatment switching is sparsely explored and in great need of further investigation.[7]

We have analyzed clinical characteristics and antithrombotic treatment in a cohort of elderly, hospitalized patients with AF and atrial flutter (AFL), the Carrebean-elderly, and recognized this patient group as highly heterogenous, with a significantly higher risk profile among the patients aged 90 years or older.

In this study—the first, to the best of our knowledge—we investigated antithrombotic treatment switching and the associated risks of thromboembolism, bleeding, and cardiac death, as well as the effectiveness and safety of current guideline-recommended oral anticoagulants (OACs), in a cohort of 2943 elderly patients with AF aged 75–104 years.

2 | METHODS

2.1 | Study population

The Carrebean-elderly cohort (Atrial Fibrillation: Risks and Benefits of Anticoagulation in the Elderly [Carrebean-e]; Clinicaltrials.gov, NCT03828162) has previously been described.[8] Briefly, all consecutive elderly patients aged 75 years or older given inpatient care at the Department of Cardiology at Danderyd University Hospital, Stockholm, Sweden, for AF or AFL as main diagnosis, between November 1, 2010, and December 31, 2017 (n = 2943), were followed for incident thromboembolism, bleeding, and cardiac death until December 31, 2019. The cohort includes patients with both valvular (n = 21) and nonvalvular AF/AFL. History of previous diseases was retrieved from medical charts if self-reported at admission and/or previously stated in chart notes and/or in the presence of consistent diagnoses according to the International Classification of Diseases, Tenth Revision (ICD-10). Anthropometric measures, systolic and diastolic blood pressure, and biochemical parameters as well as echocardiographic data were recorded at discharge. Renal function was estimated by glomerular filtration rate (eGFR) in milliliters per min according to the Cockcroft-Gault (C-G) formula. Antithrombotic treatment was recorded at admission for patients with known AF/AFL. Time in therapeutic range (TTR) for warfarin was calculated by the number of therapeutic international normalized ratio (INR) values (2.0–3.0) divided by the total number of values registered, that is, the fraction of INR values in the target range, during the year before admission for all patients on warfarin at admission (Figure 1).

2.2 | Registry data sources

Antithrombotic treatment at discharge and during follow-up were obtained from the Swedish Prescribed Drug Register.[9] End point data of thromboembolic and bleeding events were obtained from the National Patient Register.[10] The Swedish Cause of Death Register was used for mortality data.[11]

2.3 | Definition of exposure and outcome

In this study, we considered antithrombotic treatment switching and antithrombotic treatment at discharge as main exposures. The first antithrombotic treatment collected from a pharmacy after discharge was defined as the antithrombotic treatment at discharge. During the follow-up period, switching to other antithrombotic regimens occurred, for which we annotated the new prescribed antithrombotic regimen as well as the first and last date of claimed prescriptions of the drug to which the patient was switched. The date of switch was defined as the first date of claimed prescription of the new drug. When investigating antithrombotic treatment switching patterns, we chose to restrict the number of switches to include to two, due to low frequency of a third switch; from first-line antithrombotic treatment to second-line (switch 1) and from second- to third-line (switch 2).

Antithrombotic treatment included warfarin and the four DOAC regimens available at the time our study was conducted—dabigatran, rivaroxaban, apixaban, and edoxaban—as well as aspirin

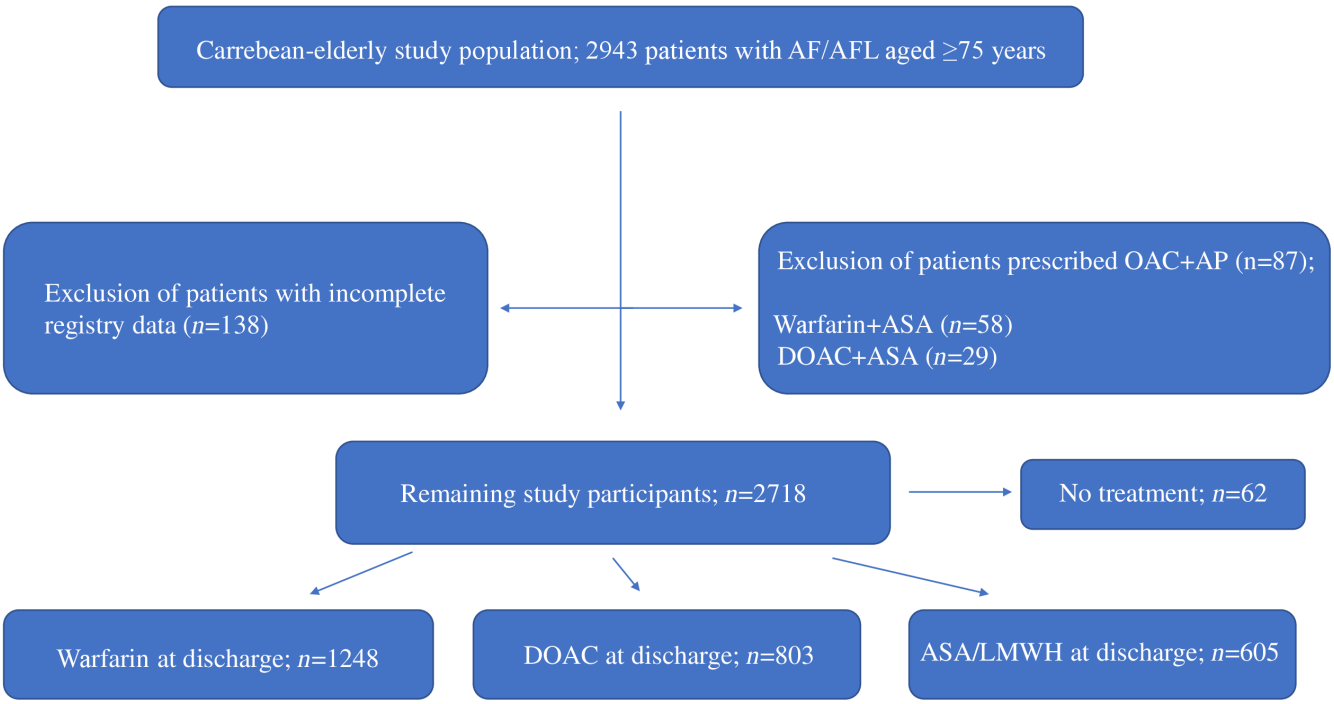

FIGURE 1 Flowchart of the study population with inclusion and exclusion criteria, as well as exposure groups of antithrombotic treatment at discharge. AF, atrial fibrillation; AFL, atrial flutter; AP, antiplatelets; ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; *n*, number; OAC, oral anticoagulant; y, years

and low-molecular-weight heparin (LMWH) regimens (dalteparin and tinzaparin). In the analyses, we categorized warfarin and DOAC as "antithrombotic treatment in AF patients according to the European Society of Cardiology guidelines" (G),[12] and treatment with aspirin and LMWH as "non-guideline therapy" (NG). Patients with incomplete registry records (n = 138), patients prescribed both an OAC and antiplatelet treatment (n = 87), and patients discharged without any antithrombotic treatment (n = 62) were excluded, resulting in 2656 patients remaining in the analyses. Patients who temporarily were bridged with LMWH after being prescribed warfarin or DOAC at discharge, were classified as nonswitchers (n = 143).

Our primary composite end point includes the first occurrence of thromboembolism (transient ischemic attack, ischemic stroke, or peripheral embolism); a bleeding event, defined as major bleeding[13] or clinically relevant nonmajor bleeding[14] according to the ISTH; or cardiac death, defined as death caused by a cardiovascular disease–related diagnosis. Secondary end points are thromboembolism, bleeding, and cardiac death as separate end points. Table S1 summarizes the included diagnosis codes of the studied end points according to ICD-10.

2.4 | Ethics

This study was approved by the Regional Ethics Review Board, Stockholm, Sweden (Dnr 2016/63-31/1, 2017/1520-32, and 2019-01850).

2.5 | Statistical analysis

Descriptive data were reported as median (interquartile range) for continuous variables and number (percentages) for categorical variables.

We calculated the proportion of patients in each antithrombotic treatment group who switched regimens before and after the first incident event. Further, the median time from first switch to first incident event (in days) and the number of patients switching from antithrombotic treatment at discharge to second-line and from second- to third-line were reported.

For each antithrombotic treatment group at discharge (warfarin/DOAC/NG), we calculated incidence rate (IR) per 1000 person-years of thromboembolism, bleeding, and cardiac death as both a composite and as separate end points. We used Cox regression models to estimate the risk of the composite end point and of thromboembolism/bleeding/cardiac death separately, expressed as hazard ratio (HR) with 95% confidence interval (CI). In this analysis, warfarin-treated patients represented the reference group. A multivariate analysis was performed after adjustments by age, sex, renal function (eGFR), previous thromboembolism, previous bleeding, and admission year.

Further, we investigated the effect of antithrombotic treatment switching on the incidence of the composite and separate end points (thromboembolism/bleeding/cardiac death). In this analysis, all study participants switching drugs after an event (n = 412) were excluded because of possible reverse causation. Four antithrombotic

treatment switching patterns were identified and compared to the corresponding nonswitching group: (i) NG users switching to G versus NG not switching; (ii) warfarin users switching to DOAC versus warfarin users not switching; (iii) DOAC users switching to warfarin versus DOAC users not switching; and (iv) G switching to NG versus G not switching. Cox regression models were used, with time estimated from baseline to end point/end of follow-up. Results are presented as crude and adjusted HR with 95% CI, using the confounding factors stated above.

Assumption of proportionality of the hazards was tested by the Schoenfeld residuals test. We used complete-case analysis in the regression models due to a few missing values of the studied variables. We evaluated the impact of all-cause death as a competing risk to the studied outcomes, with a competing risk regression analysis with both antithrombotic treatment switching and antithrombotic treatment at discharge as exposures.[15] The results, expressed as subhazard ratios (SHRs) with 95% CIs, were compared with both the crude and adjusted Cox regression models. A two-sided p value of less than 0.05 was considered statistically significant. All analyses were performed with STATA software version 14.2 (StataCorp).

3 | RESULTS

3.1 | Clinical characteristics and risk of thromboembolism, bleeding, and cardiac death according to antithrombotic treatment at discharge

Warfarin users (n = 1248) had a slightly higher prevalence of diabetes mellitus type 1 or 2, previous thromboembolism, myocardial infarction, other vascular disease, and heart failure compared to DOAC users. The warfarin group also consisted of a higher proportion of patients at high risk for both thromboembolism and bleeding than the DOAC group (n = 803) (Table 1).

Tables S2 and S3 summarize the IR and the risk for the composite and single end points, respectively, in the three antithrombotic treatment groups. While no difference was observed when comparing DOACs to warfarin, the NG group showed an increased risk for the composite end point (adjusted HR, 1.18; 95% CI, 1.01–1.38) and an increased mortality risk in comparison to warfarin users (adjusted HR, 1.31; 95% CI, 1.03–1.67).

During the follow-up period (up to 9 years), a total of 800 patients (30.1% of the study population) died of other causes than cardiac, and 700 patients (26.4%) died of a cardiac cause. A total of 523 patients had all-cause death and 404 patients cardiac death as first incident event. When considering the effect of all-cause death as a competing risk (Table S4), the group receiving NG showed an increased risk for the composite end point with an adjusted SHR of 1.21 (95% CI, 1.04–1.42), as compared to warfarin. No significant difference was observed when comparing DOACs to warfarin.

3.2 | Antithrombotic treatment switching during follow-up and relation to events

Antithrombotic treatment switching was reported in 1202 patients (45.3% of the study population). Switching of antithrombotic treatment was most common among patients prescribed warfarin at discharge; 33.1% switched to a DOAC, 32.6% switched to NG, and 34.3% stayed on warfarin. Among patients prescribed a DOAC at discharge (13.4% dabigatran and 86.6% activated factor X [FXa] inhibitors), only 3.4% switched to warfarin and 10.6% to NG, while the vast majority, 86.1%, stayed on a DOAC or switched within the DOAC group (10.7). Of the patients prescribed NG, 16.0% switched to warfarin and 14.4% to DOAC. Switches from first- to second-line and second- to third-line antithrombotic treatment are presented in Table S5A and B and in Figure 1, visualizing the flow of the two first antithrombotic treatment switches (Figure 2).

No evident association of median time between a first antithrombotic treatment switch and first incident thromboembolism or cardiac death was seen in either of the antithrombotic treatment groups. The lowest median time (days) from first antithrombotic treatment switch to thromboembolism was seen in the group switching from warfarin (470 [232–988]) and from first antithrombotic treatment switch to cardiac death in the group switching from a DOAC (437 [211–893]). The median time from first antithrombotic treatment switch to bleeding was significantly lower in the group switching from DOAC (70 [18–347]), where only 7 patients switched from a DOAC to another regimen and experienced a bleed, hence too small a group to draw any further conclusions (Table S6).

3.3 | Risk of thromboembolism, bleeding, and cardiac death in antithrombotic treatment-switching groups

3.3.1 | Switch from NG to warfarin/DOAC

When switching from NG to warfarin or DOAC (n = 159), compared to continuing treatment with NG (n = 376), both the risk of thromboembolism (adjusted HR, 0.26; 95% CI, 0.12–0.53) and cardiac death (adjusted HR, 0.53; 95% CI, 0.32–0.87) was lowered, with no significant difference in bleeding risk (adjusted HR, 0.75; 95% CI, 0.40–1.41). The risk of the composite end point was significantly decreased (adjusted HR, 0.45; 95% CI, 0.32–0.63) in switchers.

3.3.2 | Switch from warfarin to DOAC

Patients switching from warfarin to a DOAC (n = 308) had, in comparison to warfarin nonswitchers (n = 745), a decreased risk for the composite end point (adjusted HR, 0.50; 95% CI, 0.38–0.65) as well as for thromboembolism (adjusted HR, 0.28; 95% CI, 0.15–0.51) and bleeding (adjusted HR, 0.50; 95% CI, 0.32–0.79) but not for cardiac death (adjusted HR, 0.95; 95% CI, 0.64–1.42) (Table 2).

TABLE 1 Clinical characteristics, number of antithrombotic treatment switches, and frequency of thromboembolism, bleeding, and cardiac death according to antithrombotic treatment prescribed at discharge

	None	Warfarin	DOAC	NG
Clinical characteristics, n	62	1248	803	605
Age, years	88 (84–92)	81 (77–86)	81 (77–86)	85 (80–90)
Sex, female, n (%)	35 (56.5)	731 (58.6)	471 (58.7)	362 (59.8)
BMI (kg/m^2)	22.0 (20.5–23.5)	25.0 (22.5–28.1)	24.7 (22.0–27.8)	23.8 (21.0–26.7)
Underweight (<18.5)	8 (12.9)	30 (2.4)	34 (4.3)	54 (9.2)
Normal weight (18.5–24.99)	42 (67.7)	589 (47.9)	384 (48.7)	323 (54.8)
Overweight (25–29.99)	7 (11.3)	418 (34.0)	262 (33.3)	146 (24.8)
Obese (>30)	2 (3.2)	192 (15.6)	108 (13.7)	67 (11.4)
Prevalent cardiovascular risk factors				
Diabetes mellitus	6 (9.7)	195 (15.6)	108 (13.5)	99 (16.4)
Hypertension	33 (53.2)	843 (67.6)	557 (69.4)	370 (61.2)
Lipid-lowering treatment	9 (14.5)	330 (26.4)	183 (22.8)	114 (18.8)
Prevalent cardiovascular disease				
IS/TIA/SE	9 (14.5)	235 (18.8)	146 (18.2)	139 (23.0)
Myocardial infarction	7 (11.3)	171 (13.7)	82 (10.2)	101 (16.7)
Other vascular disease	4 (6.5)	221 (17.7)	104 (13.0)	120 (19.8)
Heart failure	23 (37.1)	417 (33.4)	216 (26.9)	240 (39.7)
Previous bleeding	14 (22.6)	159 (12.7)	116 (14.5)	142 (23.5)
Renal function				
Absolute GFR (ml/min)	34.4 (24.7–50.7)	54.1 (39.3–72.7)	56.8 (42.2–75.8)	45.9 (31.3–64.0)
≥60	9 (14.5)	496 (40.5)	354 (44.9)	172 (29.3)
45–59	8 (12.9)	299 (24.4)	187 (23.7)	132 (22.5)
30–44	18 (29.0)	289 (23.6)	170 (21.6)	149 (25.3)
15–29	24 (38.7)	124 (10.1)	75 (9.5)	117 (19.9)
<15	0 (0.0)	16 (1.3)	2 (0.3)	18 (3.1)
Cardiac function				
LVEF > 40	29 (46.8)	950 (83.5)	619 (88.2)	376 (80.2)
LVEF ≤ 40	8 (12.9)	188 (16.5)	83 (11.8)	93 (19.8)
Risk scores				
$CHA2DS_2$ VASc	4 (3–4)	4 (3–5)	4 (3–5)	4 (3–5)
2–4	49 (79.0)	878 (70.4)	596 (74.2)	398 (65.8)
≥5	13 (21.0)	370 (29.7)	207 (25.8)	207 (34.2)
HAS-BLED	2 (1–3)	2 (2–3)	2 (2–3)	2 (2–3)
<2	19 (30.7)	230 (18.4)	164 (20.4)	127 (21.0)
2	22 (35.5)	577 (46.2)	416 (51.8)	252 (41.7)
≥3	21 (33.9)	441 (35.3)	223 (27.8)	226 (37.4)
Antithrombotic treatment switching				
No. of switches	0 (0–0)	1 (0–2)	0 (0–0)	0 (0–2)
0	62 (100.0)	427 (34.2)	605 (75.3)	338 (55.9)
1	0 (0.0)	419 (33.6)	76 (9.5)	102 (16.9)
2	0 (0.0)	146 (11.7)	73 (9.1)	73 (12.1)
≥3	0 (0.0)	256 (20.5)	49 (6.1)	92 (15.2)
Frequency of events				
Thromboembolism (IS/TIA/SE)	9 (14.5)	151 (12.1)	79 (9.8)	105 (17.4)
IS	8 (12.9)	134 (10.7)	76 (9.5)	94 (15.5)

(Continues)

TABLE 1 (Continued)

	None	Warfarin	DOAC	NG
Bleeding	3 (4.8)	156 (12.5)	62 (7.7)	69 (11.4)
ICH	1 (1.6)	47 (3.8)	19 (2.4)	16 (2.6)
All-cause death	57 (91.9)	557 (44.6)	253 (31.5)	474 (78.4)
Cardiac death	22 (35.5)	260 (20.8)	127 (15.8)	212 (35.0)

Note: Missing values exist for BMI (1.9%), eGFR (2.0%), and LVEF (13.9%). Definition of BMI, eGFR, CHA_2DS_2VASc and HAS-BLED categories has previously been described.[7]

Abbreviations: DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; ICH, intracranial hemorrhage; IS, ischemic stroke; LVEF, left ventricular ejection fraction; NG, non–guidelines-recommended antithrombotic treatment; SE, systemic embolism; TIA, transient ischemic attack.

Continuous variables are given as median (interquartile range) and categorical as number (percentage).

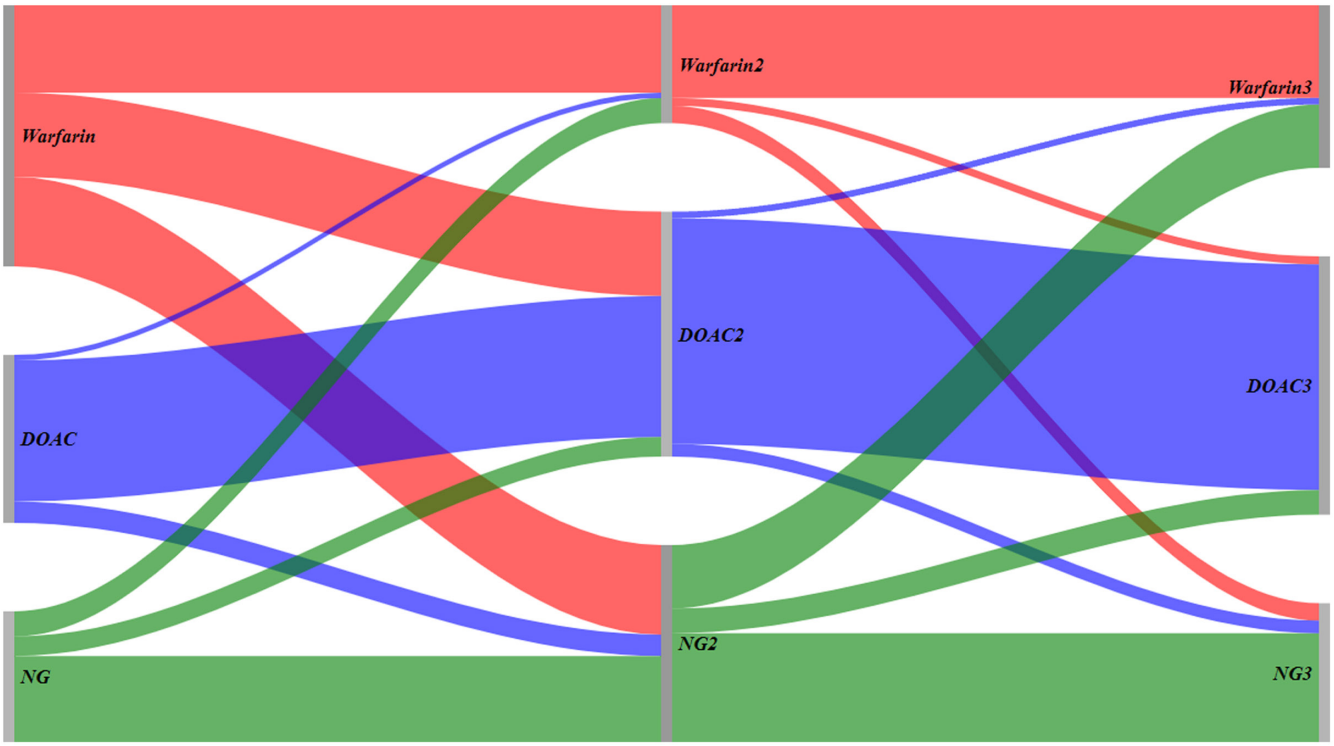

FIGURE 2 Sankey diagram illustrating switching between antithrombotic treatment groups (warfarin in red, DOAC in blue and NG in green), including switch 1 from first line to second line antithrombotic treatment and switch 2 from second line to third line antithrombotic treatment. DOAC, direct oral anticoagulants; NG, non-guideline therapy

3.3.3 | Switch from warfarin/DOAC to NG

No difference in the risk for the composite end point or for thromboembolism was observed in patients switching from warfarin or a DOAC to NG ($n = 238$), compared to warfarin and DOAC nonswitchers ($n = 1205$), with an adjusted HR of 0.89 (95% CI, 0.70–1.13) and 0.76 (95% CI, 0.49–1.16), respectively. However, switchers to NG had a lowered risk of bleeding (adjusted HR, 0.60; 95% CI, 0.37–0.99) but an increased risk of cardiac death (adjusted HR, 1.56; 95% CI, 1.10–2.21).

4 | DISCUSSION

The main findings of our study are that antithrombotic treatment switching is common and it impacts the risk of thromboembolism/bleeding/cardiac death in elderly patients with AF. Switching from NG to warfarin/DOAC was associated with 74% lower risk of thromboembolism and halved the risk of cardiac death with no increase in bleeding risk, while switching from warfarin to a DOAC decreased the risk of both thromboembolism and bleeding. At the same time, our findings confirm observational data with intention-to-treat approach of no significant difference in effectiveness and safety between DOAC and warfarin prescribed at discharge in elderly AF patients.[4]

To the best of our knowledge, this is the first study investigating the association of antithrombotic treatment switching with the risk of thromboembolism/bleeding/cardiac death in elderly patients with AF. We observed a lower risk of both thromboembolism and bleeding in patients switching from warfarin to a DOAC compared to those continuing with warfarin. The patients

TABLE 2 Risk of thromboembolism/bleeding/cardiac death in antithrombotic treatment switching groups

Antithrombotic treatment switching groups		Composite end point (n = 973)		Thromboembolism (n = 308)		Bleeding (n = 261)		Cardiac death (n = 404)	
	n	HR (95% CI)	Adjusted HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
NG	376	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
NG→warfarin/DOAC	159	0.39 (0.29–0.54)	0.45 (0.32–0.63)	0.23 (0.11–0.45)	0.26 (0.12–0.53)	0.79 (0.44–1.40)	0.75 (0.40–1.41)	0.42 (0.26–0.67)	0.53 (0.32–0.87)
Warfarin	745	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Warfarin→DOAC	308	0.46 (0.35–0.60)	0.50 (0.38–0.65)	0.29 (0.16–0.52)	0.28 (0.15–0.51)	0.44 (0.28–0.70)	0.50 (0.32–0.79)	0.78 (0.53–1.16)	0.95 (0.64–1.42)
DOAC	640	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
DOAC→warfarin	25	0.73 (0.32–1.64)	0.85 (0.37–1.95)	0.37 (0.05–2.69)	0.40 (0.05–2.93)	0.46 (0.06–3.33)	0.50 (0.07–3.65)	1.26 (0.46–3.46)	1.57 (0.55–4.43)
Warfarin/DOAC	1205	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Warfarin/DOAC→NG	238	0.90 (0.72–1.23)	0.89 (0.70–1.13)	0.86 (0.57–1.30)	0.76 (0.49–1.16)	0.60 (0.37–0.98)	0.60 (0.37–0.99)	1.33 (0.96–1.85)	1.56 (1.10–2.21)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; NG, non-guidelines recommended antithrombotic treatment; Ref, reference.

switching from warfarin to a DOAC were younger and had a slightly higher eGFR and a lower prevalence of prior thromboembolism and bleeding. Hence, they were overall a healthier group of patients in terms of prevalent cardiovascular comorbidities at the time of inclusion, which possibly contributed to the decreased risk. The current guidelines recommend switching from warfarin to a DOAC when the quality of the warfarin treatment is poor (TTR less than 70%).[16,17] However, the patient group switching from warfarin to a DOAC in this study had an even higher TTR (0.67) compared to warfarin nonswitchers (0.65). Moreover, preswitch poor quality of warfarin treatment is associated with postswitch low persistence of DOAC treatment.[18] Nevertheless, although potential unknown confounders contributed to the beneficial effects of switching from warfarin to a DOAC, our data strongly suggest that switching may be considered even in the presence of well-functioning warfarin treatment. This finding needs confirmation in a large prospective study and results from the FRAIL-AF study, an ongoing multicenter randomized clinical trial investigating the safety of switching from vitamin K antagonist (VKA) treatment to a DOAC in elderly, frail patients with AF, are therefore much awaited.[19] As for patients treated with NG, that is, acetylsalicylic acid (ASA) or LMWH, and switching to either warfarin or a DOAC, the risk of thromboembolism as well as of cardiac death was markedly lowered, with no significant difference in bleeding risk. This is consistent with the results from the AVERROES trial, where apixaban versus ASA showed a decreased risk of thromboembolism and no increase in major bleeding or intracranial hemorrhage,[20] indicating that elderly patients with AF/AFL should be treated with an OAC, as ASA does not improve the safety profile and the protection against thromboembolism is stronger. On a broader perspective, our results support the notion that appropriate treatment with an OAC has a beneficial effect regardless of age and comorbidity burden.

Our results show no significant risk difference for thromboembolism, bleeding, or cardiac death with a DOAC compared to warfarin, according to drugs prescribed at discharge. Consistently, newly published real-world data of elderly patients with AF demonstrated similar effectiveness and safety between DOACs and warfarin.[4] On the other hand, we did not observe a beneficial effect of DOACs in terms of safety, as previously demonstrated in trial data. This may depend on the fact that our study population was not randomized and probably represents a patient group with a higher burden of comorbidities, hence more prone to bleeding, than patients included in clinical trials. In subgroup analyses from the ARISTOTLE and ENGAGE AF-TIMI 48 trials of patients aged 80 years or older, an equivalent risk of thromboembolism was observed between DOACs and warfarin, yet a decreased risk of major bleeding for DOAC was reported.[21] Also, a patient-level meta-analysis of the COMBINE AF database (n = 71,683), including all patients from the four pivotal trials comparing DOACs to warfarin, showed better efficacy and safety for DOACs compared to warfarin across all ages.[3] Principally, our finding highlights the importance of a broad inclusion strategy of elderly patients in all studies, irrespective of comorbidity status and organ function.

In this study, we considered all-cause death as a competing risk factor, mainly due to its increasing incidence over time at advanced age. In the competing risk regression, we observed no change in risk estimates from the Cox models. In contrast to the post hoc analyses of the large clinical trials,[21] we did not observe a beneficial effect on the safety of DOACs when compared to warfarin, as previously stated. This may be due to the fact that the HR tends to be overestimated without proper consideration of competing risk factors[15,22] and to the high frequency of deaths in all antithrombotic treatment groups. When investigating the competing risk of all-cause death in elderly patients with AF aged 75 years or older, Shah et al.[23] showed a decreasing net clinical benefit of both warfarin and apixaban compared to no thromboprophylaxis over the years, with insufficient clinical benefit of warfarin after the age of 87 years and 92 years for apixaban. In the ELDERCARE-AF trial, investigating low-dose edoxaban compared to placebo in elderly Japanese patients with AF aged 80 years or older (n = 984) not suitable for OAC treatment at approved thromboprophylactic dosing, no net clinical benefit analysis was performed. However, the rates of all-cause death were similar in the edoxaban and the placebo groups. The reported decreased risk of thromboembolism with no increase in major bleeding indicates, nonetheless, that low-dose edoxaban may be a suitable stroke preventive alternative for elderly patients with AF with uncertain benefits of OAC treatment.[24] From a clinical perspective, an individualized management of antithrombotic treatment in elderly patients with AF with multimorbidity is preferable, with emphasis on careful consideration of the high risk of all-cause death possibly affecting the benefits of thromboembolic preventive treatment.

This study has several limitations. Due to the observational nature of the data, we cannot exclude residual confounding in the analyses. We do not have information regarding factors affecting the clinicians' choice of antithrombotic prescription. Nevertheless, to deal with confounding by indication, we adjusted for admission year, as the switching phenomenon reflects the paradigm shift in OAC treatment from warfarin to a DOAC that has taken place over the past decade and resulted in guideline changes throughout the study period. Also, our well-characterized study population gave us the possibility to adjust for clinical factors possibly contributing to both the choice of antithrombotic treatment and the outcome. Of note, however, due to lacking data of clinical factors possibly changing over time, we were not able to adjust for these potential confounders in the analyses of antithrombotic treatment switching effects. We enrolled consecutively admitted patients including both OAC-naive and already OAC-treated patients, potentially introducing bias when including patients known to tolerate OAC treatment, in the analyses. Related to the observational study design, however, this broad patient inclusion may yield results attributable to a real-world clinical AF/AFL population. Moreover, we do not possess information regarding emigration, yet few patients emigrate at an old age.[25] Also, we lack information on medication adherence. However, as we miss this information for all antithrombotic treatment groups, this may possibly result in a nondifferential misclassification of exposure. Further, this is a single-center study focusing on elderly, hospitalized patients, narrowing the generalizability of the study results. As a matter of fact, choice of antithrombotic treatment may also reflect local clinical recommendations and the socioeconomic and clinical characteristics of this patient population. Regional guidelines at the study site, in fact, recommend FXa over activated factor IIa inhibitors to elderly AF patients, whereas FXa inhibitors and particularly apixaban, constitute a large proportion of DOAC prescriptions in this study, attributing the results of DOACs foremost to apixaban. However, the catchment area of the study hospital certainly includes patients mostly of European origin but with a diverse socioeconomic background living both in and outside of a large city, and only a minority of patients with AF (12%) are exclusively managed as outpatients in primary care in the study region.[26] We chose to estimate renal function using the C-G formula, as this has been used in the pivotal DOAC clinical trials. However, cystatin C–based GFR calculation would have been more appropriate in this population of elderly patients. Similarly, we cannot exclude the fact that a proportion of our study participants had a mild or moderate degree of impairment of liver function, as we reported liver function as abnormal only in the presence of liver cirrhosis/bilirubin lgreater than 2×normal values/transaminases/alkaline phosphatase greater than 3×normal values, according to the HAS-BLED definition. Finally, patients with indications of OAC and antiplatelet treatment were not included in the analyses, as they represent a patient population at very high risk of thrombosis and bleeding.

In conclusion, in spite of the possible contribution of confounding, this study shows that antithrombotic treatment switching is associated with AF-related outcomes and reveals a novel pattern of thromboembolism/bleeding/cardiac death as compared to risk assessment with an intention-to-treat approach. This highlights the importance of considering drug switching not only for antithrombotic treatment but for most of the drugs currently used for preventive treatment of chronic diseases in elderly and frail patients.

AUTHOR CONTRIBUTIONS

HE: study design, methodology, collection, interpretation, formal analysis, and curation of data as well as writing of manuscript including review and editing and visualization of data. NO: methodology, formal analysis and review and editing of manuscript as well as supervision. KM: methodology and review and editing of manuscript as well as supervision. HW: conceptualization, methodology, resources, review and editing of manuscript, and supervision. BG: conceptualization, methodology, validation, resources, review and editing of manuscript, supervision, project administration, and funding acquisition.

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RELATIONSHIP DISCLOSURE

To the authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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