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Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial

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Abstract

Background: There is ambiguity whether frail patients with atrial fibrillation (AF) managed with vitamin K antagonists (VKAs) should be switched to a non-vitamin K oral anticoagulant (NOAC).

Methods: We conducted a pragmatic, multicenter, open-label, randomized controlled superiority trial. Older AF patients living with frailty (age ≥75 years plus a Groningen Frailty Indicator (GFI) score ≥3) were randomized to switch from INR-guided VKA treatment to a NOAC or to continued VKA treatment. Patients with a glomerular filtration rate <30 mL/min/1.73 m^2 or with valvular AF were excluded. Follow-up was 12 months. The cause-specific hazard ratio (HR) was calculated for occurrence of the primary outcome which was a major or clinically relevant non-major bleeding complication, whichever came first, accounting for death as a competing risk. Analyses followed the intention-to-treat principle. Secondary outcomes included thromboembolic events.

Results: Between January 2018 and June 2022, a total of 2,621 patients were screened for eligibility and 1,330 patients were randomized (mean age 83 years, median GFI 4). After randomization 6 patients in the switch to NOAC arm and 1 patient in the continue with VKA arm were excluded due to the presence of exclusion criteria, leaving 662 patients switched from a VKA to a NOAC and 661 patients continued VKAs in the intention-to-treat population. After 163 primary outcome events (101 in the switch arm, 62 in the continue arm), the trial was stopped for futility according to a prespecified futility analysis. The HR for our primary outcome was 1.69 (95% CI 1.23-2.32). The HR for thromboembolic events was 1.26 (95% CI 0.60 to 2.61).

Conclusions: Switching INR-guided VKA treatment to a NOAC in frail older patients with AF was associated with more bleeding complications compared to continuing VKA treatment, without an associated reduction in thromboembolic complications.

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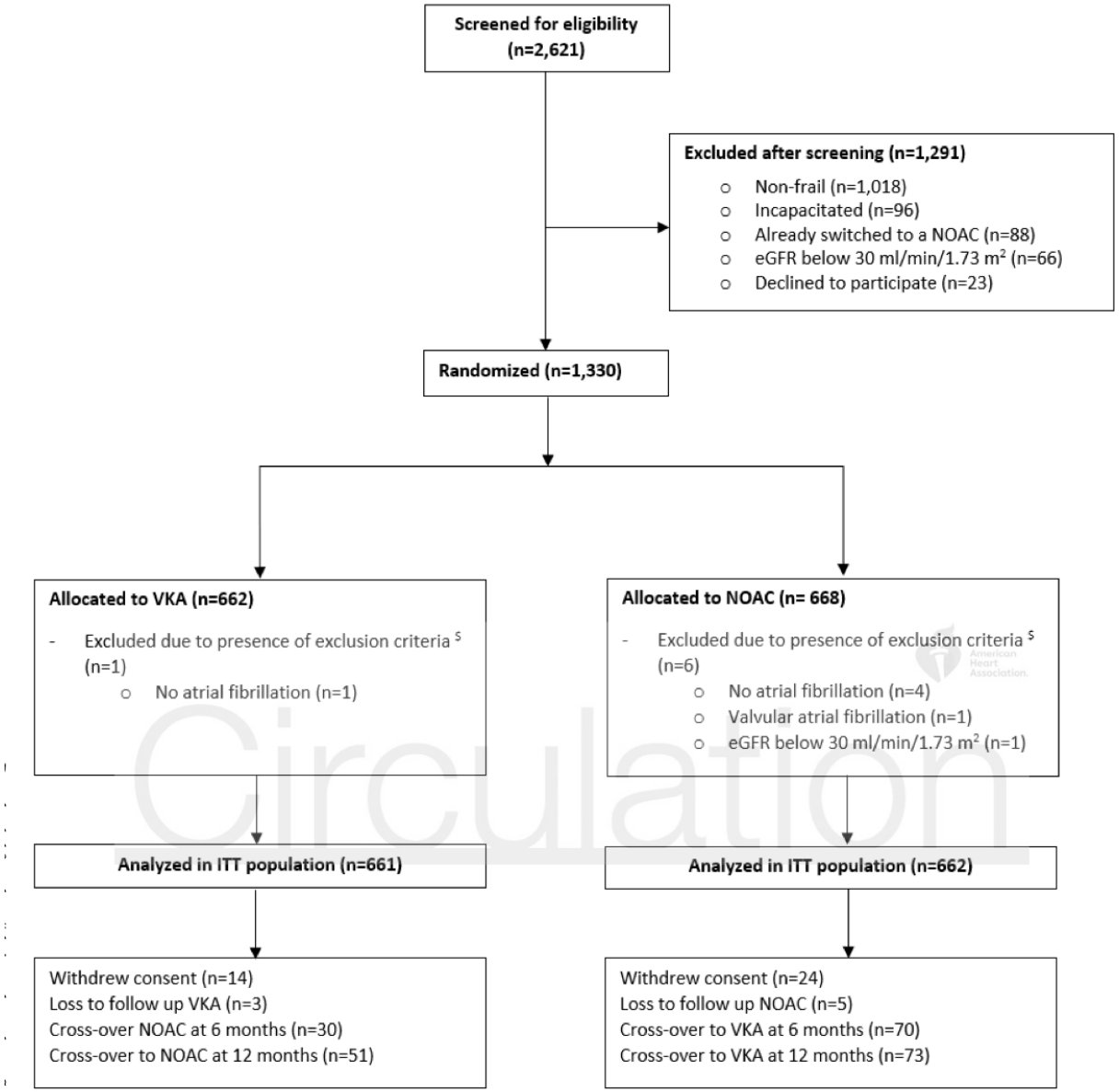

$ These patients did not receive the allocated treatment and were not analyzed in the ITT population as directly after randomization exclusion criteria were found to be present.

ITT = intention to treat; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

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Table 1. Patient Characteristics

Characteristic*	Switch to NOAC (n=662)	Continue with VKA (n=661)
Age – yr. (SD)	83.0 (5.1)	82.8 (5.1)
Female sex – no. (%)	274 (41.4%)	239 (36.2%)
Type of atrial fibrillation		
Paroxysmal atrial fibrillation – no. (%)	170 (25.7%)	201 (30.4%)
Persistent atrial fibrillation – no. (%)	63 (9.5%)	57 (8.6%)
Permanent atrial fibrillation – no. (%)	340 (52.7%)	335 (50.7%)
Unknown – no. (%)	89 (13.4%)	68 (10.3%)
Duration of atrial fibrillation – yr. (SD)	12.0 (9.2)	13.0 (9.9)
Groningen Frailty Indicator – score (IQR)	4 (3-6)	4 (3-6)
Groningen Frailty Indicator 3 (%)	170 (25.7%)	171 (25.9%)
Groningen Frailty Indicator ≥4	492 (74.3%)	490 (74.0%)
Groningen Frailty Indicator domain		
Use of ≥4 different types of medication	589 (89%)	581 (87.9)
Complaints of memory	237 (35.8%)	261 (39.5%)
Unable to walk around the house	112 (16.9%)	112 (16.9%)
Problems due to of impaired vision	297 (44.9%)	279 (42.2%)
Problems due to of impaired hearing	380 (57.4%)	353 (53.4%)
CHA_2DS_2-VASc score (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Heart failure – no. (%)	129 (19.5%)	150 (22.7%)
Hypertension – no. (%)	365 (55.1%)	336 (50.8%)
Diabetes – no. (%)	140 (21.1%)	140 (21.2%)
History of major bleeding – no. (%)	105 (15.9%)	88 (13.3%)
History of thromboembolic event – no. (%)	139 (21.0%)	117 (17.7%)
Active cancer – no. (%)	44 (6.6%)	35 (5.3%)
Liver cirrhosis – no. (%)	3 (0.5%)	5 (0.8%)
Body-mass index (SD)	27.4 (6.0)	27.4 (11.7)
eGFR mL/min/1.73 m^2 (SD)	62.5 (15.8)	62.7 (15.6)
Off-label reduced NOAC dose (%)	44 (6.6%)	-
Concurrent platelet inhibitor use – no. (%)	16 (2.4)	13 (2.0)

VKA = vitamin K antagonist; NOAC = non-vitamin K antagonist oral anticoagulant; SD = standard deviation; IQR = interquartile range; eGFR = estimated glomerular filtration rate.
*For continuous variables a mean is presented, except for the Groningen Frailty Indicator and the CHA_2DS_2-VASc score where a median is presented.

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Table 2. Primary and Secondary Outcomes

Variable	Switch to NOAC		Continue with VKA		
	No. (%)	No. of events / 100 patient-yr (95% CI)	No. (%)	No. of events / 100 patient-yr (95% CI)	Hazard Ratio (95% CI)
Primary outcome					
Major or CRNM bleeding	101 (15.3%)	17.8 (14.5-21.6)	62 (9.4%)	10.5 (8.0-13.4)	1.69 (1.23-2.32)
Secondary outcomes					
Bleeding outcomes separately					
Major bleeding	24 (3.6%)	3.9 (2.5-5.9)	16 (2.4%)	2.6 (1.5-4.2)	1.52 (0.81-2.87)
CRNM bleeding	84 (12.7%)	14.6 (11.7-18.1)	49 (7.4%)	8.2 (6.1-10.9)	1.77 (1.24-2.52)
TE events	16 (2.4%)	2.6 (1.5-4.3)	13 (2.0%)	2.1 (1.1-3.6)	1.26 (0.60-2.61)
Composite of TE events plus major or CRNM bleeding	115 (17.4%)	20.6 (17.0-24.7)	73 (11.0%)	12.4 (9.8-15.6)	1.65 (1.23-2.21)
Composite of ischemic and hemorrhagic stroke	14 (2.1%)	2.3 (1.3-3.8)	11 (1.7%)	1.8 (0.9-3.2)	1.30 (0.59-2.87)
All-cause mortality	44 (6.7%)	7.1 (5.2-9.5)	46 (7.0%)	7.4 (5.4-9.8)	0.96 (0.64-1.45)

CI = confidence interval; CRNM = clinically relevant non-major; No. = number; NOAC = non vitamin-K antagonist oral anticoagulant; TE = thromboembolic; VKA = vitamin K antagonist.

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Table 3. First Major or Clinically Relevant Non-major Bleeding* Location per Treatment Arm

Bleeding location	Switch to NOAC	Continue with VKA	Switch to NOAC	Continue with VKA
	Major bleedings		CRNM bleedings	
Skin – no. (%)			23 (3.5%)	10 (1.5%)
Oropharyngeal – no. (%)		1 (0.2%)	19 (2.9%)	16 (2.3%)
Gastrointestinal – no. (%)	9 (1.4%)	1 (0.2%)	8 (1.2%)	3 (0.5%)
Urogenital – no. (%)			20 (3.0%)	11 (1.7%)
Brain† – no. (%)	7 (1.1%)	6 (0.9%)		
Ophthalmic – no. (%)		1 (0.2%)	3 (0.5%)	2 (0.3%)
Musculoskeletal – no. (%)	1 (0.2%)		1 (0.2%)	4 (0.6%)
Lung – no. (%)		1 (0.2%)		
Other – no. (%)	2 (0.3%)	3 (0.5%)	8 (1.2%)	3 (0.5%)

CRNM = clinically relevant non-major; no. = number; NOAC = non vitamin-K antagonist oral anticoagulant; VKA = vitamin K antagonist.

* This Table includes only detailed information of the 163 primary endpoint bleeding events.

† Included intracranial bleeding, subarachnoid haemorrhage, and sub- and epidural bleeding, together haemorrhagic stroke.

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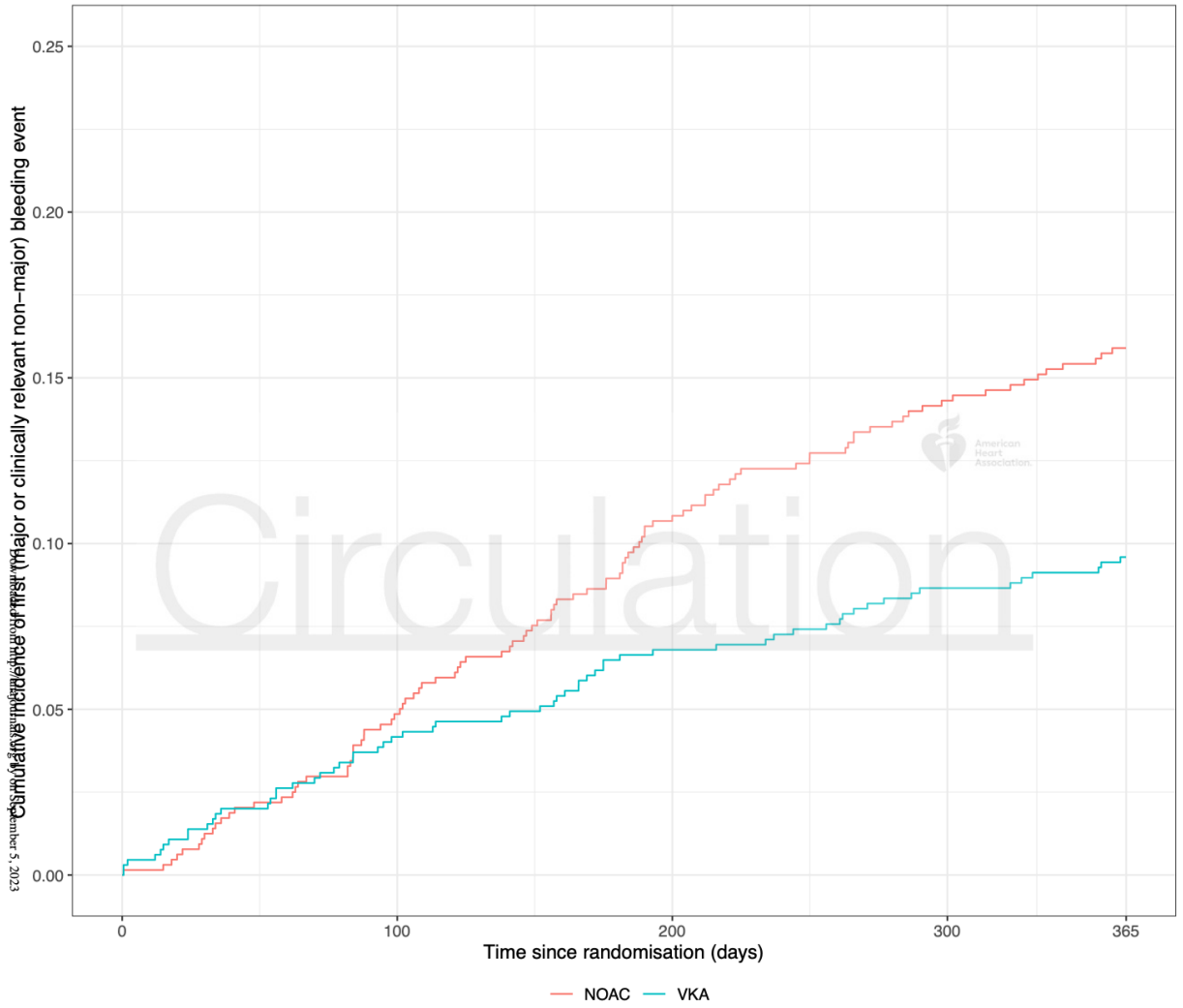

Cumulative incidence curve of first (major or clinically relevant non–major) bleeding event
Shaded areas represent 95% confidence interval

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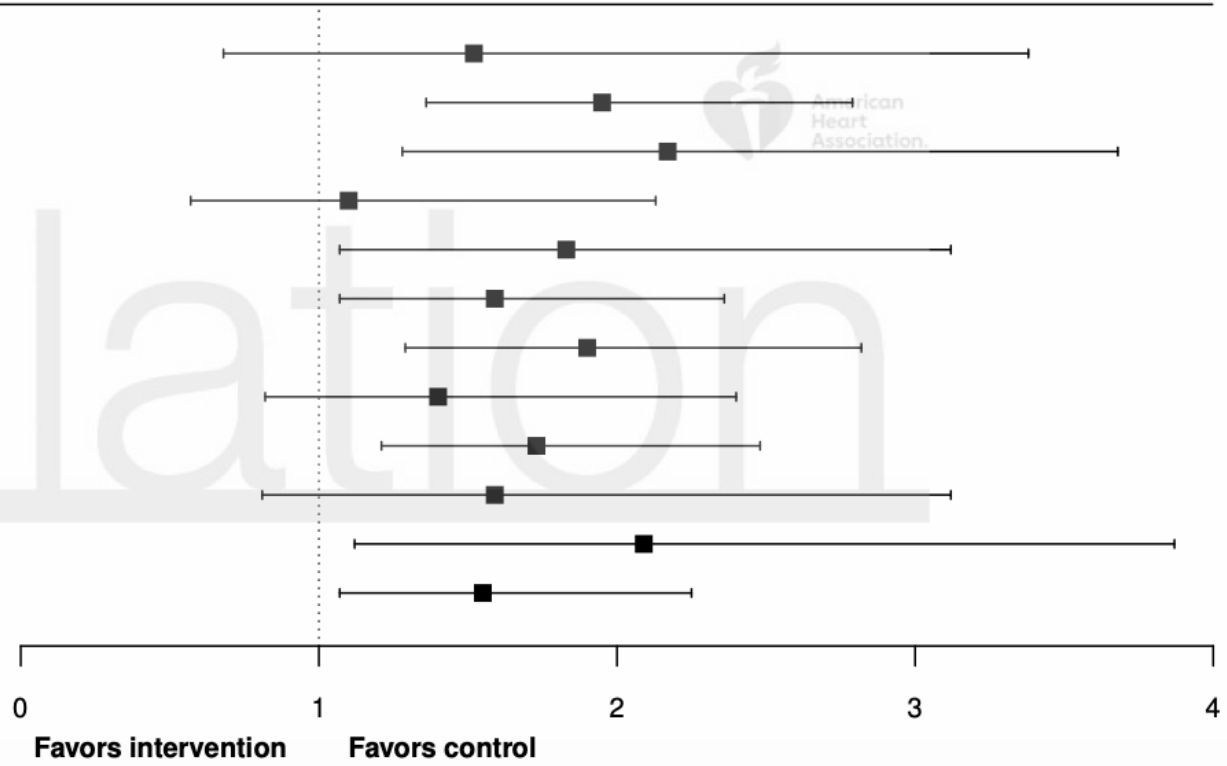
	NOAC n	IR (no. of events)	VKA n	IR (no. of events)	HR (95% CI)
Dabigatran	57	13.6 (7)	661	10.5 (62)	1.52 (0.68 – 3.38)
Rivaroxaban	332	20.8 (61)	661	10.5 (62)	1.95 (1.36 – 2.79)
Apixaban	115	19.5 (20)	661	10.5 (62)	2.17 (1.28 – 3.68)
Edoxaban	109	11.1 (11)	661	10.5 (62)	1.10 (0.57 – 2.13)
Age ...85	233	20.3 (39)	217	10.9 (21)	1.83 (1.07 – 3.12)
Age ...84	429	16.5 (62)	444	10.2 (41)	1.59 (1.07 – 2.36)
Males	388	20.4 (67)	422	10.5 (40)	1.90 (1.29 – 2.82)
Females	274	14.2 (34)	239	10.3 (22)	1.40 (0.82 – 2.40)
eGFR ...50	518	18.1 (80)	519	10.3 (48)	1.73 (1.21 – 2.48)
eGFR ...49	144	16.5 (21)	142	10.9 (14)	1.59 (0.81 – 3.12)
GFI 3	170	21.2 (31)	171	9.7 (15)	2.09 (1.12 – 3.87)
GFI ...4	492	16.6 (70)	490	10.7 (47)	1.55 (1.07 – 2.25)



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