

Safety of switching from a VKA to a NOAC in frail older patients with atrial fibrillation

Results of the FRAIL-AF randomised controlled trial



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27 August 2023

Declaration of interest

- I have nothing to declare

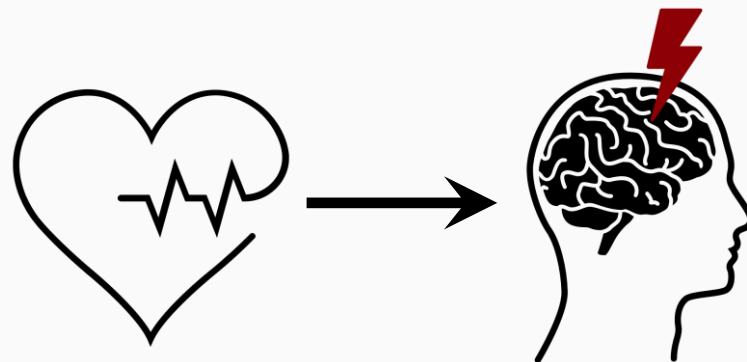
Background



Prevalence frailty in the community: **12%**

Prevalence AF in frail older people: **18%**

Incidence stroke in frail AF patients: **12.3%**
versus non-frail AF patients: **3.9%**



Current evidence

- **2020 ESC guidelines**

- New AF patients → NOAC
- On VKA with low TTR → NOAC
 ↘ efforts to improve TTR

Class ^a	Level ^b
I	A
I	B
IIa	B

- **2023 EHRA expert consensus document
on the management of arrhythmias in frailty syndrome**

The advantages of NOACs relative to VKAs are likely consistent in frail and non-frail AF patients



Research question

**Does switching from a VKA to a NOAC
compared to continuing a VKA
reduce bleeding in frail older patients with AF?**

Patient population, intervention and outcomes

PATIENTS

- Outpatient setting, GFI ≥ 3 , ≥ 75 years
- VKA for non-valvular AF
- eGFR ≥ 30 ml/min/1.73m²

OUTCOMES

- **Primary:**
 - Major or clinically relevant non-major bleeding
- **Secondary:**
 - Thromboembolic events
 - All-cause mortality

INTERVENTION	CONTROL
VKA  ↓ NOAC 	VKA 

Definition of the primary outcome

Major bleeding:

- Any bleeding in a **critical area** or organ (e.g. intracranial)
- A **fatal** bleeding
- Bleeding leading to a **transfusion** of 2 or more units of whole blood or red cells
- Bleeding leading to a **fall in haemoglobin level** of 1.25mmol/L or more

Clinically relevant non-major bleeding:

any bleeding not being major, but including at least one of the following items:

- Prompting a **face-to-face consultation**
- Leading to **hospitalisation or increased level of care**
- Requiring a **medical intervention** by healthcare professionals

Study design

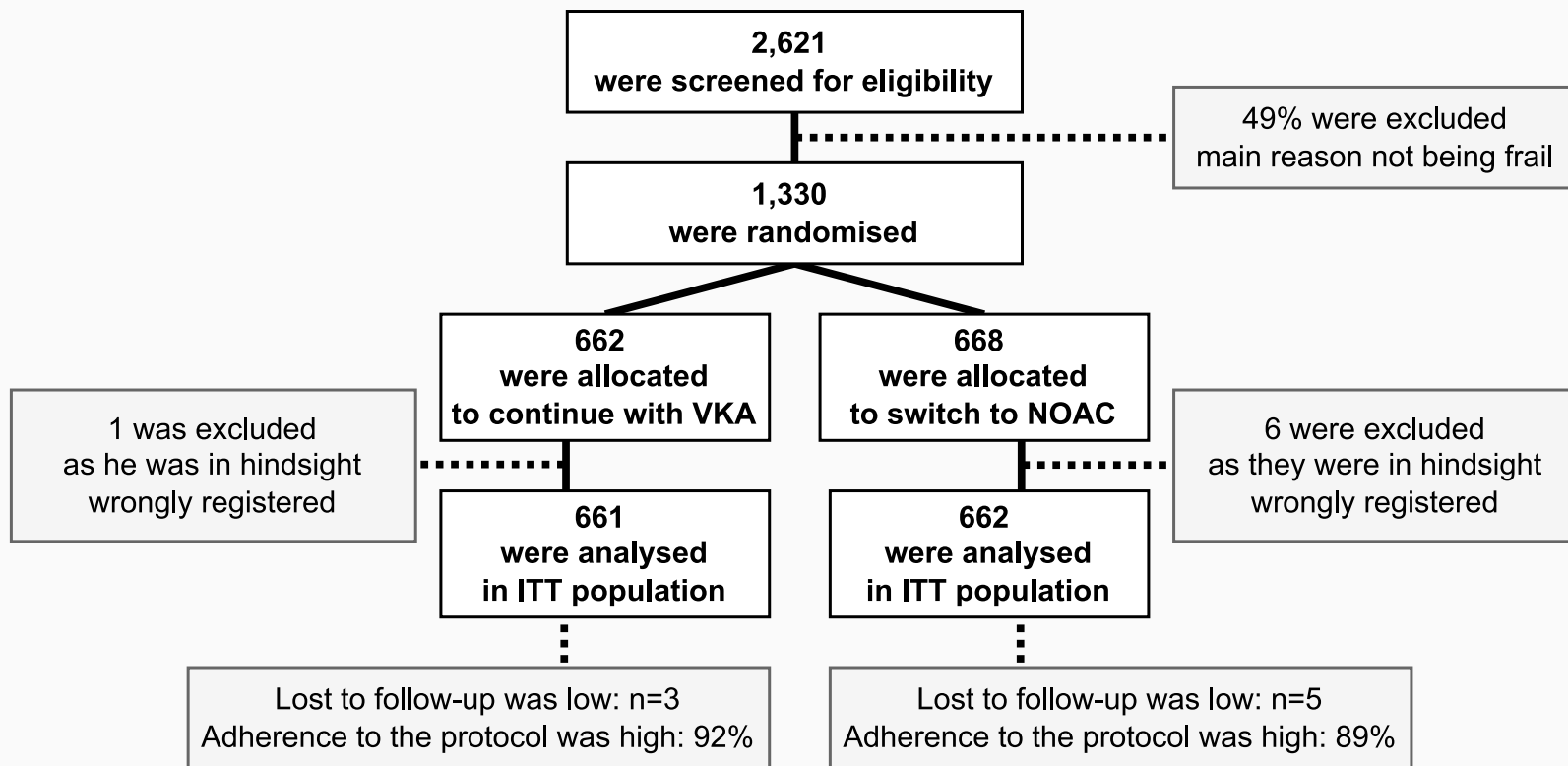
- Investigator-initiated randomised, pragmatic, multicentre, open-label, superiority trial
- 1 year follow-up
- Funding from:
 - Dutch government
 - unrestricted educational grants from all 4 NOAC-companies



Statistical analysis

- **Superiority trial**
- **Sample size: 1,250 patients per treatment arm**
- **Interim analysis after ≥ 160 primary outcome events**
 - DSMB could advice to halt/modify the trial (if P-value < 0.002)
- **Cox regression analysis on an intention-to-treat basis**

Flowchart of included study participants



Baseline characteristics

Characteristic	Continue with VKA (n=661)	Switch to NOAC (n=662)
Age in years*	83 (5)	83 (5)
Female sex†	239 (36)	274 (41)
Groningen Frailty Indicator score‡	4 (3-6)	4 (3-6)
CHA ₂ DS ₂ -VASc score‡	4 (3-5)	4 (3-5)
Heart failure†	150 (23)	129 (20)
Hypertension†	336 (51)	365 (55)
Diabetes mellitus†	140 (21)	140 (21)
eGFR in mL/min/1.73m ² *	63 (16)	63 (16)



Intervention arm

NOAC type	Number (%)
Dabigatran	57 (8.6)
Rivaroxaban	332 (50.2)
Apixaban	115 (17.4)
Edoxaban	109 (16.5)
Missing information on the prescribed NOAC	3 (0.5)
Continued with VKA-therapy	22 (3.3)
Withdrew consent	24 (3.6)

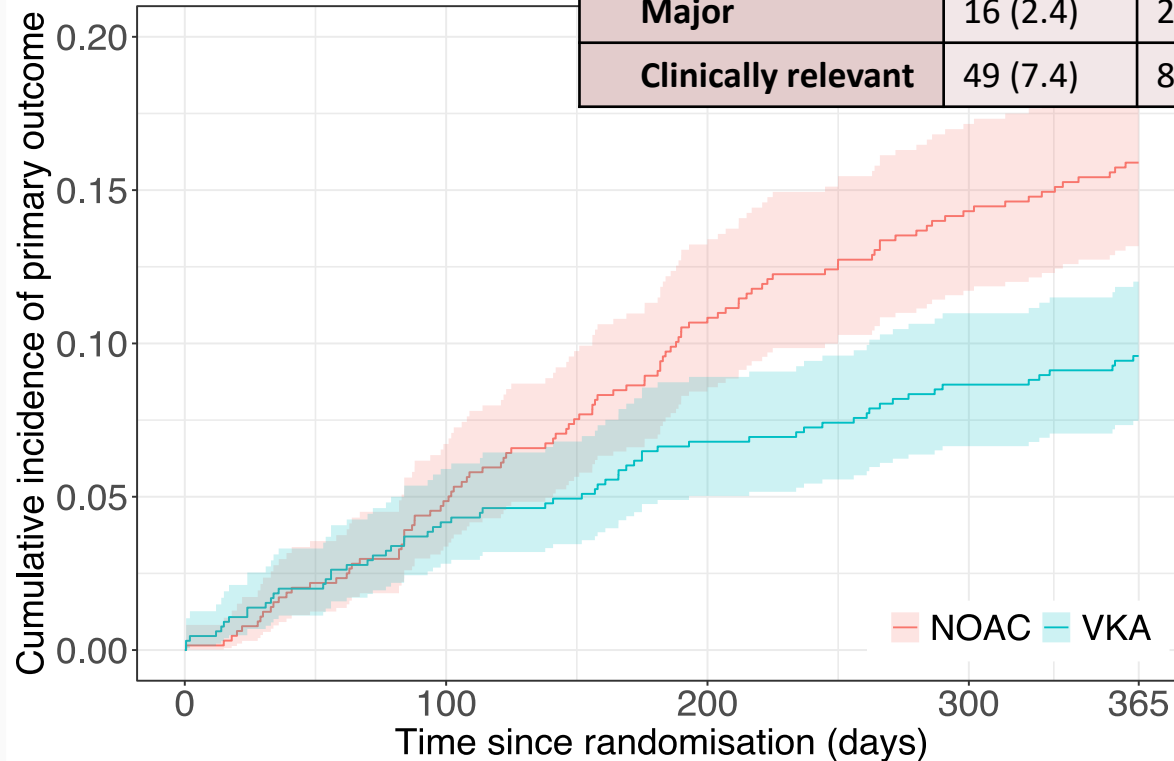


NOAC dose	Number (%)
Off-label dose reduction	44 (6.6)



Primary outcome

	VKA-arm no. (%)	NOAC-arm no. (%)	Hazard ratio (95% CI)	P-value
Bleeding	62 (9.4)	101 (15.3)	1.69 (1.23-2.32)	0.00112
Major	16 (2.4)	24 (3.6)	1.52 (0.81-2.87)	
Clinically relevant	49 (7.4)	84 (12.7)	1.77 (1.24-2.52)	

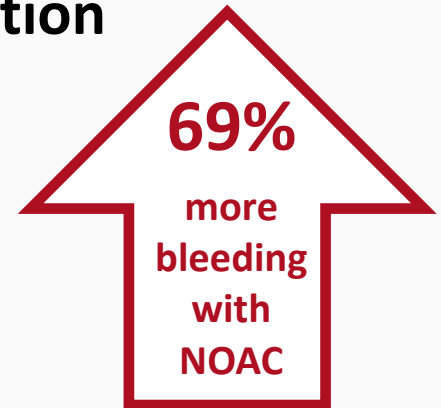


Secondary outcomes

	VKA-arm no. (%)	NOAC-arm no. (%)	Hazard ratio (95% CI)
Thromboembolic events	13 (2.0)	16 (2.4)	1.26 (0.60-2.61)
All-cause mortality	46 (7.0)	44 (6.7)	0.96 (0.64-1.45)

Conclusions

- **FRAIL-AF is a unique study as it is the first randomised NOAC trial that exclusively included frail older patients**
- **Switching from a VKA to a NOAC should not be considered without a clear indication in frail older patients with AF**



Results of the FRAIL-AF randomised controlled trial

- The first randomised NOAC trial that exclusively included frail older patients
- Switching from a VKA to a NOAC should not be considered without a clear indication in frail older patients with AF

69%

more
bleeding
with
NOAC

Circulation

CIRCULATION. 2023; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.123.066485

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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[HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.123.066485](https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.066485)



RESULTS FRAIL-AF

Contact:

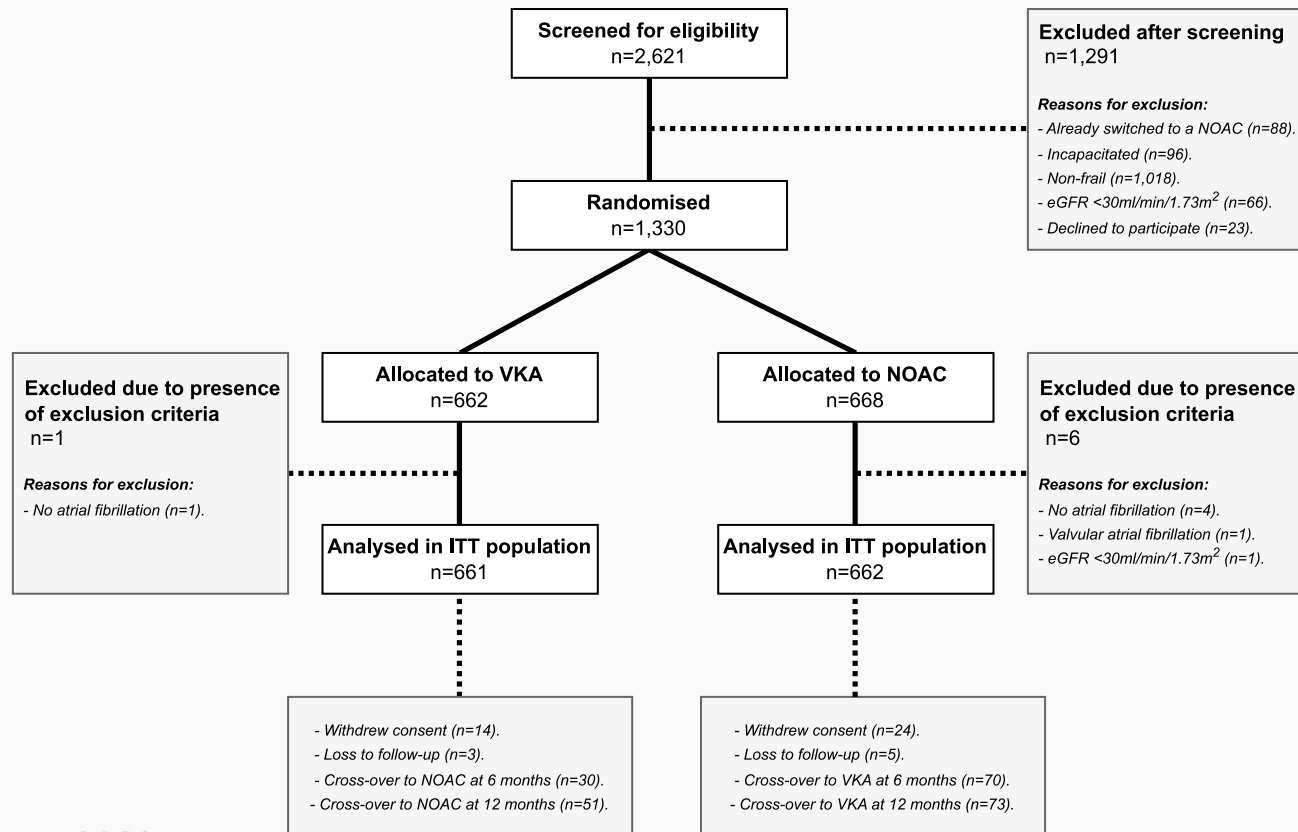
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Additional information

Groningen Frailty Indicator

Mobility	Can the patient perform the following tasks without assistance from another person (walking aids such as a can or a wheelchair are allowed):	YES	NO	SOMETIMES
	Grocery shopping	1	0	
	Walk outside house (around house or to a neighbor)	1	0	
	Getting (un)dressed	1	0	
	Visiting restroom	1	0	
Vision and hearing	Does the patient encounter problems in daily life because of impaired vision?	1	0	
	Does the patient encounter problems in daily life because of impaired hearing?	1	0	
Nutrition	Has the patient unintentionally lost a lot of weight in the past 6 months (6kg in 6 months or 3kg in 3 months)?	1	0	
Comorbidity	Does the patient use 4 or more different types of medication?	1	0	
Cognition and psychosocial	Does the patient have any complaints on his/her memory diagnosed with dementia)?	1	0	1
	Does the patient ever experience emptiness around him?	1	0	1
	Does the patient ever miss the presence of other people around him? Or do you miss anyone you love?	1	0	1
	Does the patient ever feel left alone?	1	0	1
	Has the patient been feeling down or depressed lately?	1	0	1
	Has the patient felt nervous or anxious lately?	1	0	1
Physical fitness		0-6	7-10	
	How would the patient rate his/her own physical fitness?	1	0	

Flowchart of included study participants



Baseline characteristics

Characteristic	Continue with VKA (n=661)	Switch to NOAC (n=662)
Age in years – mean (SD)	82.8 (5.1)	83.0 (5.1)
Female sex – no. (%)	239 (36.2)	274 (41.4)
Duration of atrial fibrillation in years – mean (SD)	13.0 (9.9)	12.0 (9.2)
Groningen Frailty Indicator score – median (IQR)	4 (3-6)	4 (3-6)
Groningen Frailty Indicator 3 – no. (%)	171 (25.9)	170 (25.7)
Groningen Frailty Indicator ≥4 – no. (%)	490 (74.0)	492 (74.3)
CHA ₂ DS ₂ -VASc score – median (IQR)	4 (3-5)	4 (3-5)
Heart failure – no. (%)	150 (22.7)	129 (19.5)
Hypertension – no. (%)	336 (50.8)	365 (55.1)
Diabetes mellitus – no. (%)	140 (21.2)	140 (21.1)
History of major bleeding – no. (%)	88 (13.3)	105 (15.9)
History of thromboembolic event – no. (%)	117 (17.7)	139 (21.0)
Active cancer – no. (%)	35 (5.3)	44 (6.6)
Body Mass Index – mean (SD)	27.4 (11.7)	27.4 (6.0)
eGFR in mL/min/1.73m ² – mean (SD)	62.7 (15.6)	62.5 (15.8)
Off-label reduced NOAC dose – no. (%)	-	44 (6.6)
Concurrent platelet inhibitor use – no. (%)	13 (2.0)	16 (2.4)

First major or clinically relevant non-major bleeding location per treatment arm

Bleeding location	Major bleedings (n=32)		Clinically relevant non-major bleedings (n=131)	
	Switch to NOAC (n=19)	Continue with VKA (n=13)	Switch to NOAC (n=82)	Continue with VKA (n=49)
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)

Secondary outcomes

	VKA-arm no. (%)	NOAC-arm no. (%)	Hazard ratio (95% CI)
Thromboembolic events	13 (2.0)	16 (2.4)	1.26 (0.60-2.61)
Primary outcome and thromboembolic events	73 (11.0)	115 (17.4)	1.65 (1.23-2.21)
Ischemic and hemorrhagic stroke	11 (1.7)	14 (2.1)	1.30 (0.59-2.87)
All-cause mortality	46 (7.0)	44 (6.7)	0.96 (0.64-1.45)

Subgroup analyses

