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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on behalf of the FRAIL-AF study team

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Declaration of interest

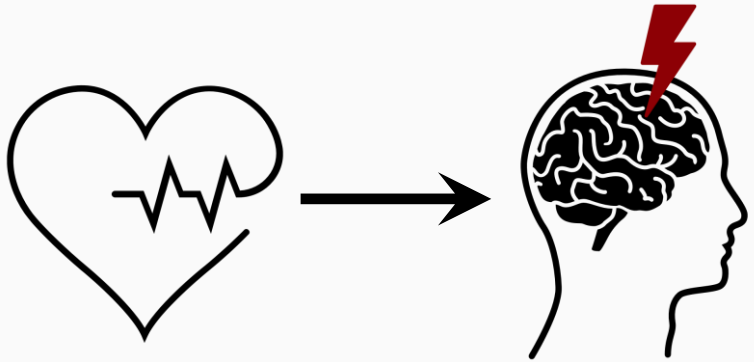
- I have nothing to declare

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%



1) Savelieva, *Europace*, 2023. 2) Proietti, *Ageing Res Rev*, 2022. 3) Wilkinson, *Age Ageing*, 2019.

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

7) Hindricks, *Eur Heart J*, 2020. 1) Savelieva, *Europace*, 2023.

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 ≥30ml/min/1.73m^2

INTERVENTION	CONTROL
VKA  ⇩ NOAC 	VKA 

OUTCOMES

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

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

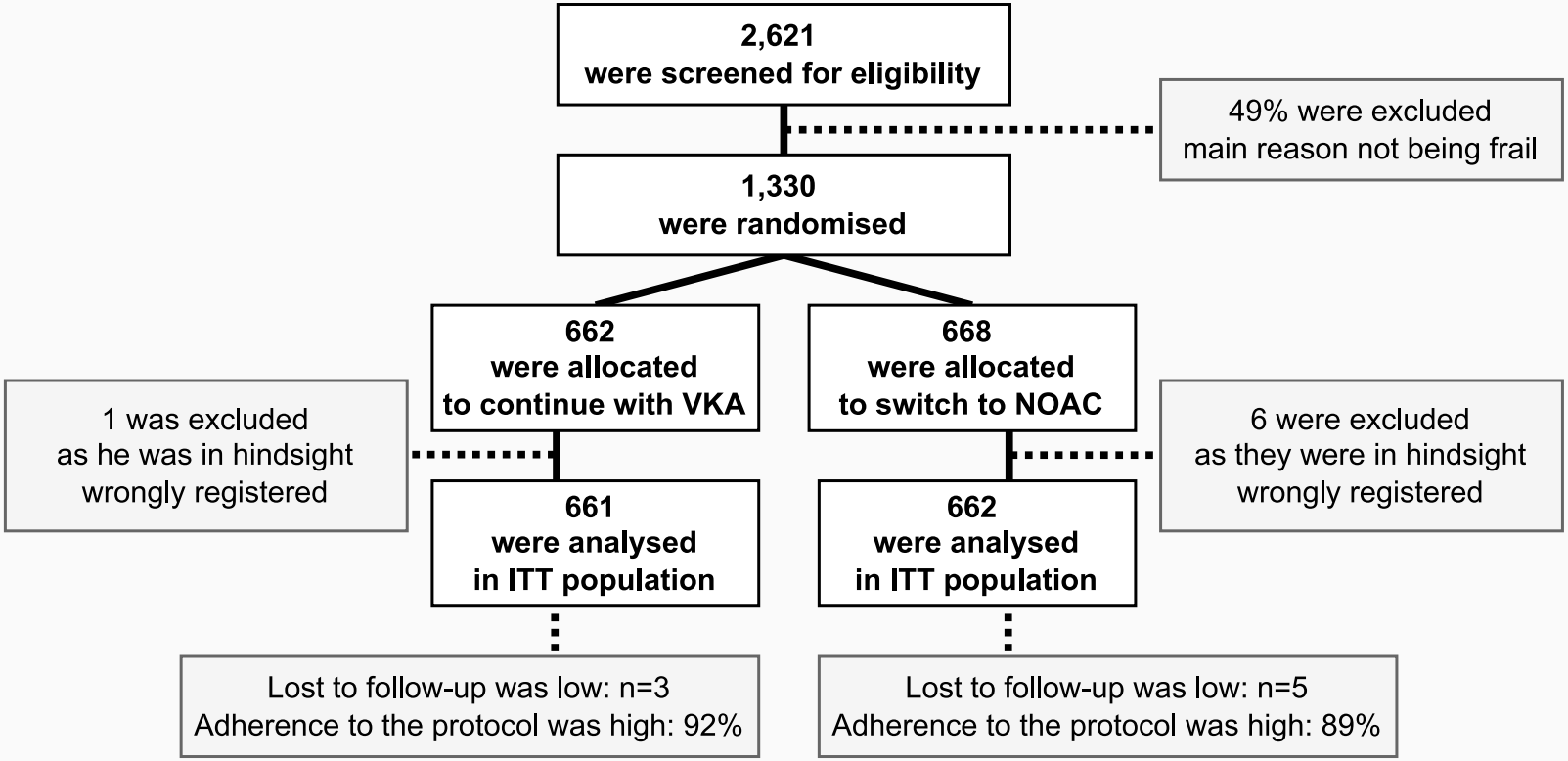
Study design

- **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_2DS_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)

* mean (SD). † number (%). ‡ median (IQR).

Intervention arm

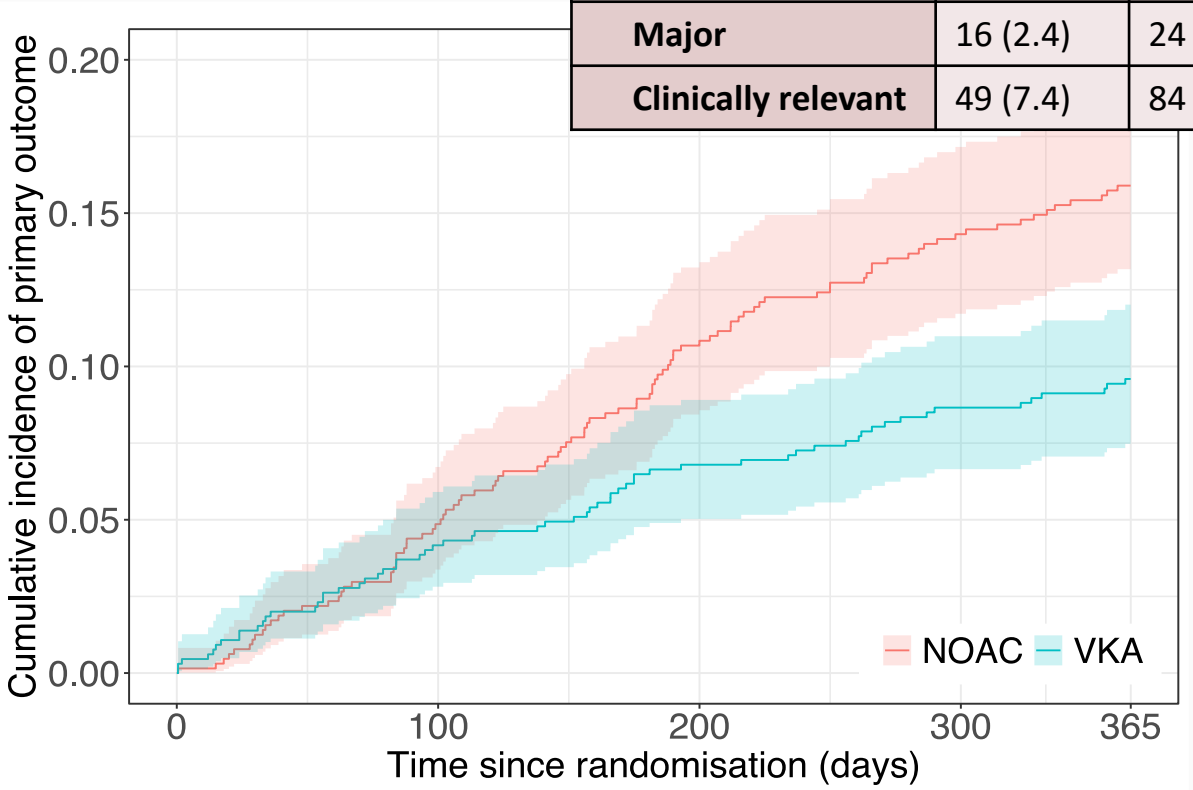
NOAC type	Number (%)
Dabigatran	57 (8.6)
Rivaroxaban	332 (50.2)
Apixaban	115 (17.4)
Edoxaban	109 (16.5)
Missing information on the prescribed NOAC	3 (0.5)
Continued with VKA-therapy	22 (3.3)
Withdrew consent	24 (3.6)

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

* mean (SD). † number (%). ‡ median (IQR).

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)	



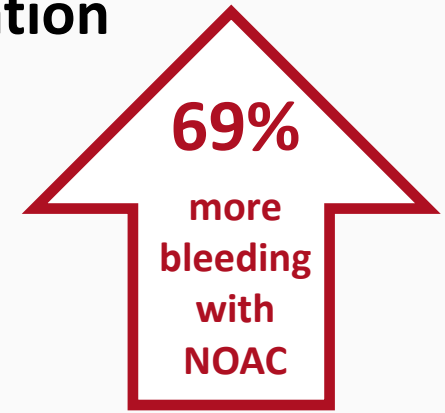
Secondary outcomes

	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 <u>not</u> be considered without a clear indication in frail older patients with AF**

69%
more bleeding with NOAC

Circulation

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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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CIRCULATION

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RESULTS FRAIL-AF

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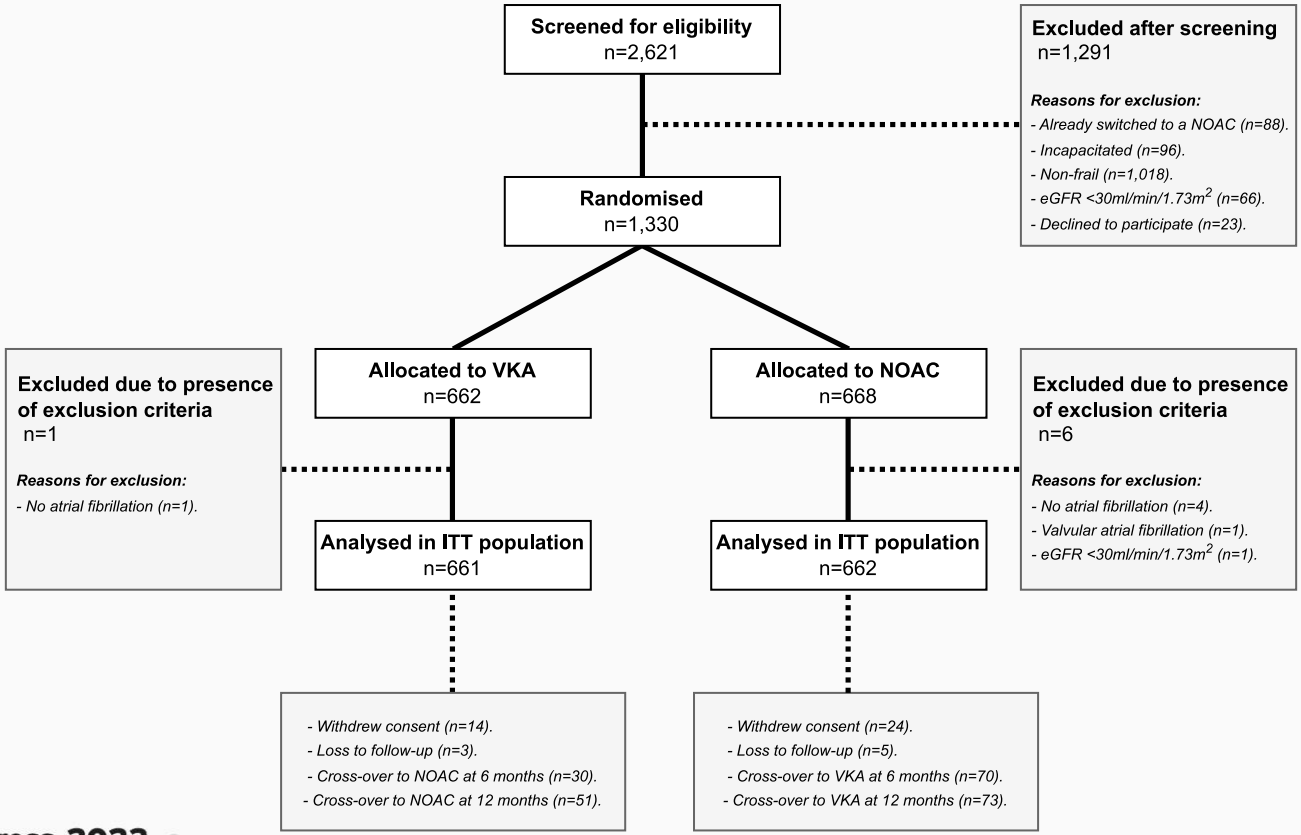
Additional information

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_2DS_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

	NOAC Incidence rate (no. of events)	VKA Incidence rate (no. of events)	HR (95% CI)
Dabigatran	13.6 (7)	10.5 (62)	1.52 (0.68 - 3.38)
Rivaroxaban	20.8 (61)	10.5 (62)	1.95 (1.36 - 2.79)
Apixaban	19.5 (20)	10.5 (62)	2.17 (1.28 - 3.68)
Edoxaban	11.1 (11)	10.5 (62)	1.10 (0.57 - 2.13)
Age ≥85	20.3 (39)	10.9 (21)	1.83 (1.07 - 3.12)
Age ≤84	16.5 (62)	10.2 (41)	1.59 (1.07 - 2.36)
Males	20.4 (67)	10.5 (40)	1.90 (1.29 - 2.82)
Females	14.2 (34)	10.3 (22)	1.40 (0.82 - 2.40)
eGFR ≥50	18.1 (80)	10.3 (48)	1.73 (1.21 - 2.48)
eGFR ≤49	16.5 (21)	10.9 (14)	1.59 (0.81 - 3.12)
GFI 3	21.2 (31)	9.7 (15)	2.09 (1.12 - 3.87)
GFI ≥4	16.6 (70)	10.7 (47)	1.55 (1.07 - 2.25)