ANTICOAGULATION FOR STROKE PREVENTION IN ATRIAL FIBRILLATION:

MULTIMORBIDITY, POLYPHARMACY AND FRAILTY

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Disclosures

I have received speaker’s fees from Medtronic, St Jude and Boston Scientific

Background

Prevalence of atrial fibrillation (AF) *rises with age*

~ 10% > 80 years of age[1]

~ 4.4% of the world's population will be > 80 years by 2050[2]

Stroke risk *rises with age*[1]

Elderly patients with AF and co-morbidities, frailty and polypharmacy are at high risk of stroke AND bleeding - > challenges with anticoagulation

1. Wolf et al. Stroke, 1991
2. Rietbrock et al. Am Heart J, 2008

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REFERENCES

Definitions

Definition of Frailty

“Clinical syndrome - characterized by high biological vulnerability, decreased physiological reserve, reduced capacity to resist stressors, due to multiple impairments in interrelated systems”

Prevalence of frailty in AF patients: 5-75%

Prevalence of AF in frail patients: 48-75%

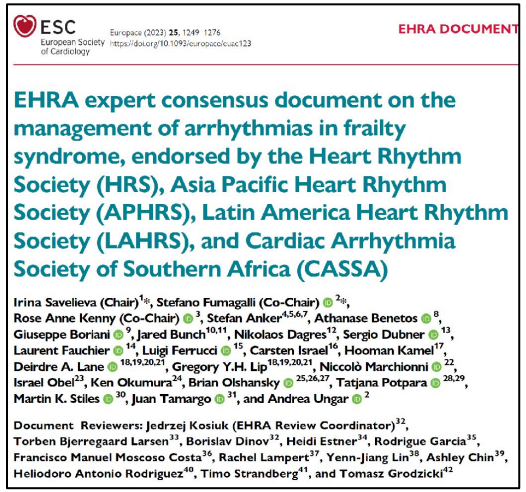


Table 2 Diagnostic criteria used for the diagnosis of frailty (Fried criteria)

Measure	Definition
Weight loss	Lost 4.5 kg or more unintentionally over the last year
Exhaustion	Self-report of either 'felt that everything I did was an effort' and/or 'could not get going' in the last week
Low physical activity	Self-report, equivalent to <90 kCal in women and <128 kCal in men
Slow walking	4 m at usual pace: speed <0.76 m/s for height <159 cm in women and <173 cm in men or speed <0.80 m/s for height >159 cm in women and >173 cm in men
Weakness	Grip strength Women: <17 kg for BMI <23 kg/m^2; <17.3 kg for BMI 23.1–26 kg/m^2; <18 kg for BMI 26.1–29 kg/m^2; and <21 kg for BMI >29 kg/m^2 Men: <29 kg for BMI <24 kg/m^2; <30 kg for BMI 24.1–26 kg/m^2; <30 kg for BMI 26.1–28 kg/m^2; <32 kg for BMI >28 kg/m^2

Please note diagnostic thresholds for different criteria were modified for different population and different studies. At least 2/5 positive criteria defines pre-frailty and >3/5 criteria defines frailty.
BMI, body mass index.

DEFINITION OF FRAILTY:
FRIED MODEL

Table 14 The 'Canadian Study of Health and Aging' (CHSA) Clinical Frailty Scale

From http://www.csha.ca and Ref.[404]

(1) Very fit – People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.

(2) Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

(3) Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

(4) Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being 'slowed up', and/or being tired during the day.

(5) Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

(6) Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

(7) Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

(8) Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

(9) Terminally ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

FUNCTIONAL DEFINITION OF FRAILTY

Frailty

Associated with:

1. Co-morbidities

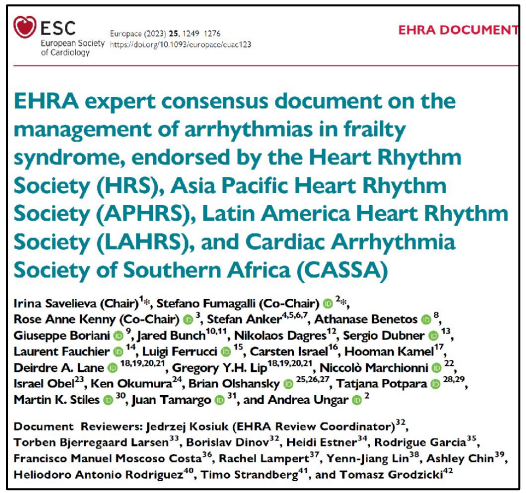
   ~33% of frail subjects have 3-4 chronic diseases

2. Polypharmacy

   ~ 7 drugs in frail patients > 75 years

3. Falls

   ~2.5x increased risk of falls



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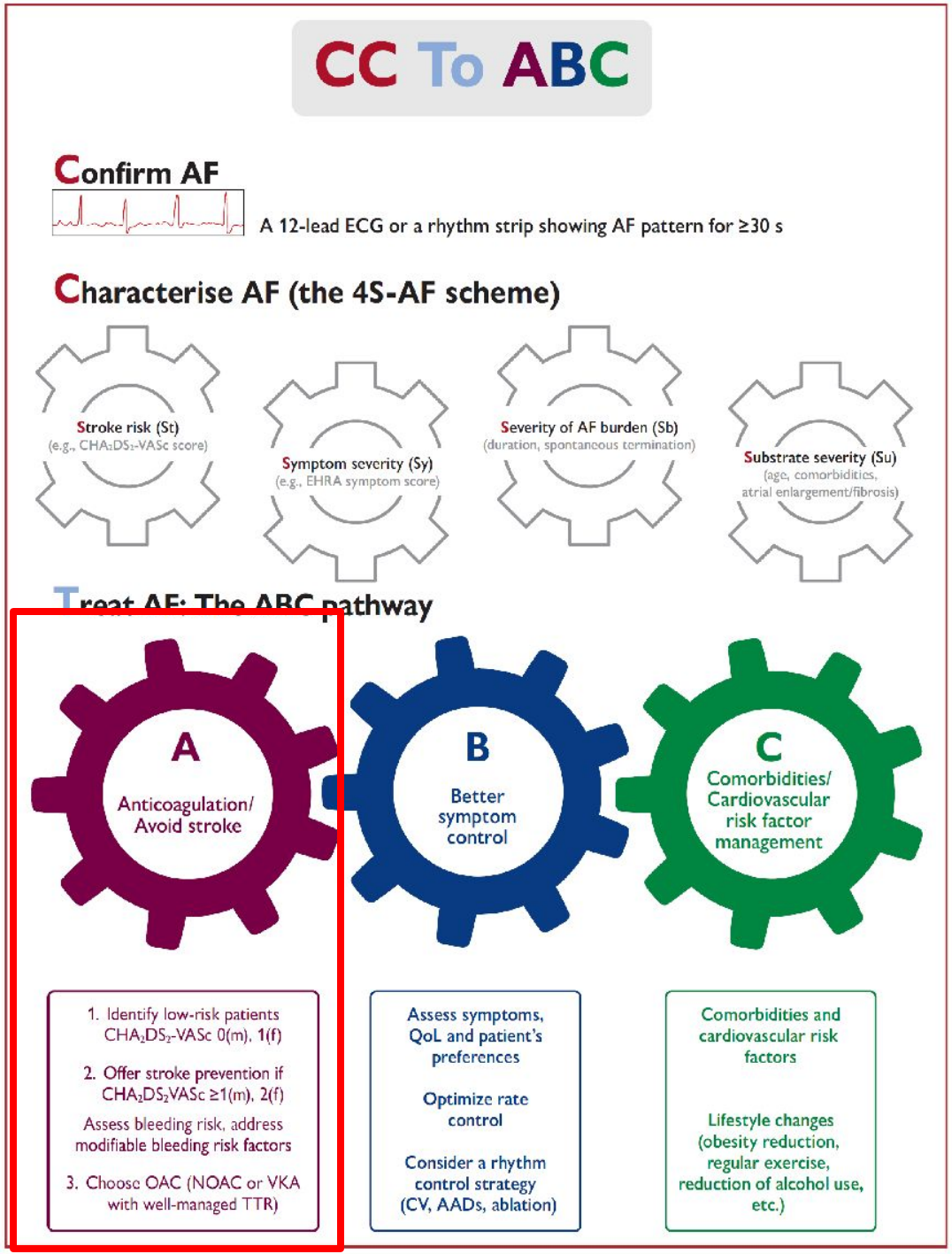
Consensus statement

- Until further data are available, frail AF patients should receive anticoagulation as otherwise indicated for non-frail patients.

MANAGEMENT OF ATRIAL FIBRILLATION

CC to ABC pathway also applies to frail patients but can be more challenging to achieve



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Risk factors for stroke		Score	Risk factors for major bleeding		Score
C	Congestive heart failure	1	H	Hypertension (uncontrolled) SBP >160 mm Hg	1
H	Hypertension (BP >140/90 mm Hg)	1	A	Abnormal renal liver function	1
A_2	Age ≥75 y	2	S	Stroke	1
D	Diabetes	1	B	Bleeding tendency	1
S_2	Stroke/TIA	2	L	Labile INR	1
V	Vascular disease	1	E	Age >65 y	1
A	Age 65-74 y	1	D	Drugs (concomitant aspirin or NSAIDs) or alcohol	1
Sc	Sex (female)	1			

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (*n*=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

CONSIDER NOAC (preferable)/WARFARIN when STROKE RISK IS >=1-2% per year:

>=1 for men
>=2 for women

Consensus statements

Stroke risk and bleeding risk should be calculated; those at the highest risk of bleeding often derive the greatest overall benefit from anticoagulation

Clinicians should not use bleeding scores to withhold OAC but instead focus on the addressing modifiable bleeding risk factors

Consideration must be given to patient's preferences and personal values

Benefits outweigh risks in most frail patients unless severe frailty or a history of recurrence of major bleeding

Consensus statements

NOACs preferred over VKAs; frail patients may have a greater absolute benefit

Aspirin is not a suitable alternative to anticoagulation in frail patients – not effective, similar risk of bleeding compared to NOACs/VKAs

NOAC choice, dosing, drug-interactions are important

Follow-up is important, including stroke and bleeding re-assessment

Table 2. Efficacy and safety of NOACs compared with warfarin in patients with AF aged 75 y or older

Trial acronym	Comparisons	Number of patients ≥75 y	Stroke/SEE HR (95% CI)	Major bleeding HR (95% CI)	Intracranial bleeding HR (95% CI)
RE-LY	DE 150 mg bid vs warfarin	7258	0.67 (0.49-0.90)	1.18 (0.98-1.42)	0.42 (0.25-0.70)
	DE 110 mg bid* vs warfarin		0.88 (0.66-1.17)	1.01 (0.83-1.23)	0.37 (0.21-0.64)
ROCKET-AF	Rivaroxaban daily vs warfarin	6229	0.80 (0.63-1.02)	1.11 (0.92-1.34)	0.80 (0.50-1.28)
ARISTOTLE	Apixaban bid vs warfarin	5678	0.71 (0.53-0.95)	0.64 (0.52-0.79)	0.34 (0.20-0.57)
ENGAGE-AF	Edoxaban 60 mg daily vs warfarin	8474	0.83 (0.66-1.04)	0.83 (0.70-0.99)	0.40 (0.26 -0.62)
	Edoxaban 30 mg† daily vs warfarin*		1.12 (0.91-1.37)	0.47 (0.38 -0.58)	0.31 (0.19-0.49)

Age >=75 years (31-43% of patients in the NOAC trials)

* **Frail patients were under-represented in these trials**

Reduced rates of stroke and intracranial bleeding with NOACs compared VKAs

Reduction of major bleeding with Apixaban and Edoxaban

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Table 11 Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			30 mg o.d.
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: • Age ≥80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: • Age ≥80 years, • Body weight ≤60 kg, or • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of the following: • CrCl 30 - 50 mL/min, • Body weight ≤60 kg, • Concomitant use of dronedarone, ciclosporine, erythromycin, or ketoconazole

<u>Factors that require dose reduction:</u>

Age > 80 years (Dabigatran, Apixaban)
Body weight < 60kg (Apixaban, Edoxaban)
CrCl< 50 (Rivaroxaban, Edoxaban, Apixaban)
Polypharmacy

Table 4. Choice of NOACs for stroke prevention in AF according to patient characteristics or preference

Patient characteristics	Considerations	Drug choices
Older patients	Consider anticoagulants with the lowest risk of major bleeding and the most convenience	NOACs preferred over VKAs Apixaban, dabigatran 110 mg, and edoxaban are associated with lower rates of major bleeding than warfarin
High risk of bleeding	Consider anticoagulants with lowest risk of major bleeding	Apixaban, dabigatran 110 mg, or edoxaban.
Previous GI bleeding	Consider anticoagulants with lowest risk of GI bleeding	Apixaban or edoxaban
Severe renal impairment	Consider anticoagulants with the least renal clearance	Apixaban > rivaroxaban > edoxaban
Dyspepsia or GERD	Consider agent less likely to cause GI side effects	Apixaban, rivaroxaban, or edoxaban
Feeding via nasogastric or PEG tube	Consider anticoagulants with pharmacokinetic data suggesting bioequivalence between oral and enteral administration*	Apixaban or rivaroxaban
Nonadherence to twice-daily regimens or request to minimize pill burden	Consider anticoagulant with once-daily dosing regimen	Rivaroxaban or edoxaban

Falls

Frailty predisposes to falls and risk of subdural bleeds

Falls per se should not be used an exclusion criteria for OAC

“Numbers needed to fall” - 295 falls needed with Warfarin to outweigh risks of subdural bleed[1]

Treatment effects of Apixaban (ARISTOTLE) and Edoxaban (ENGAGE TIMI 48) were seen irrespective of low risk or high risk of falling with a larger benefit with NOAC compared to Warfarin 2,3

1. Man-Son-Hing, Archives of Internal Medicine, 1999
2. Rao, Am J Med 2018
3. Steffel, J Am Col Cardiol 2016

Table 14 Examples of falls risk assessment

(A) High risk of falls[a]

Presence of one or more of

- prior history of falls
- lower extremity weakness
- poor balance
- cognitive impairment
- orthostatic hypotension
- use of psychotropic drugs
- severe arthritis
- dizziness

(B) Probability of falls assessment[b]

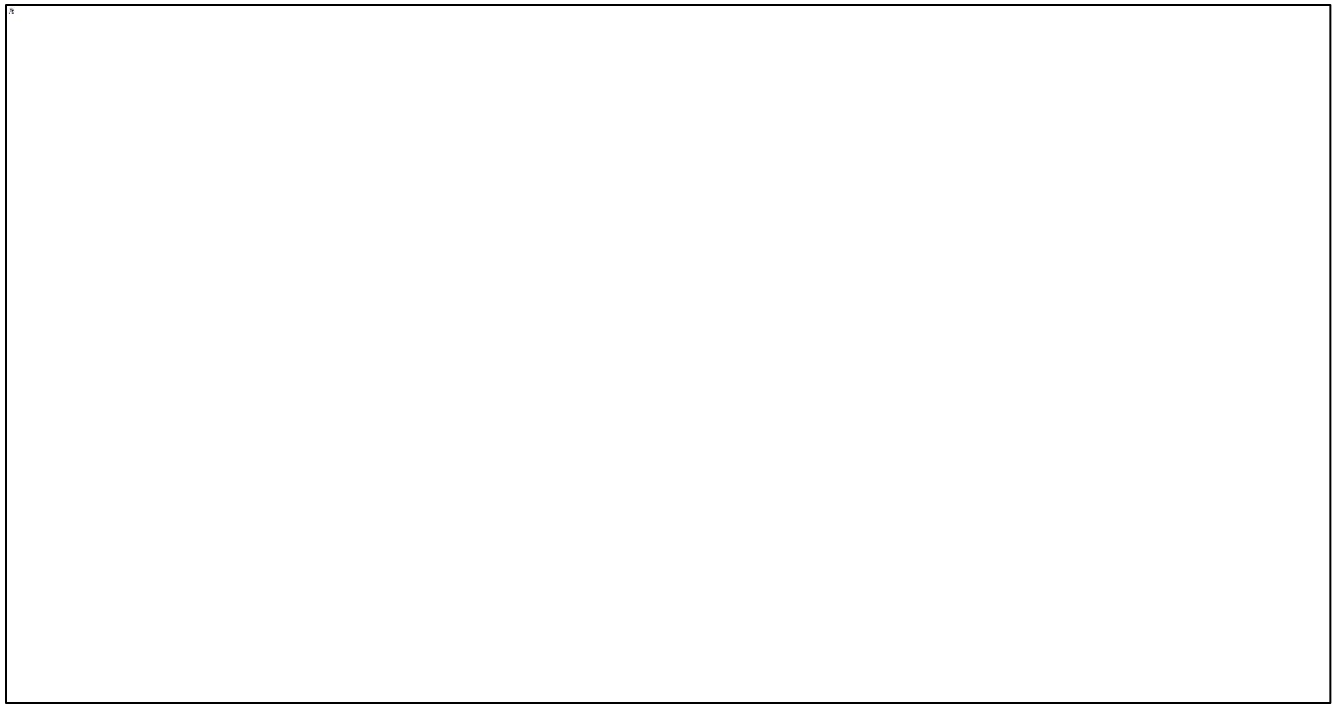
1 point for each 'yes'

Previous falls	Yes/no
Medications	
>4	Yes/no
Psychotropics	Yes/no
Low visual acuity	Yes/no
Diminished sensation	Yes/no
Near tandem stand 10 s	Yes/no
Alternate step test 10 s	Yes/no
Sit to stand 12 s	Yes/no

Score	0–1	2–3	4–5	6+
Probability of fall per year	7%	13%	27%	49%

Multidisciplinary team approach, including formal geriatric assessment recommended.

Measures should be taken to reduce risk of falls – including referral to a geriatric clinic if available



Drug-drug interactions should be evaluated at baseline and follow-up

Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40%[521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[524]	No effect[523]	No effect[525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40%[526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77%[523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR)[523] (no dose reduction required by label)	+40%[527] (probably not relevant)[528]
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction[529]	No data yet	No effect[523]	No effect[530]
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65%[SmPC] (give loading dose 2h after dabigatran)[d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max}[531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	– 66% AUC; – 67% Cmax (SmPC)	– 54% AUC; – 42% Cmax (SmPC)	– 35% AUC, (but with compensatory increase of active metabolites)[532]	– 50% AUC; – 22% Cmax (SmPC)

Table 7 **Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels**

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29%[542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC[543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPc)			

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

Results of the FRAIL-AF randomised controlled trial

Linda P.T. Joosten (MD, PhD candidate), **Geert-Jan Geersing** (MD, PhD, principal investigator)

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on behalf of the FRAIL-AF study team

27 August 2023

Patient population, intervention and outcomes

PATIENTS

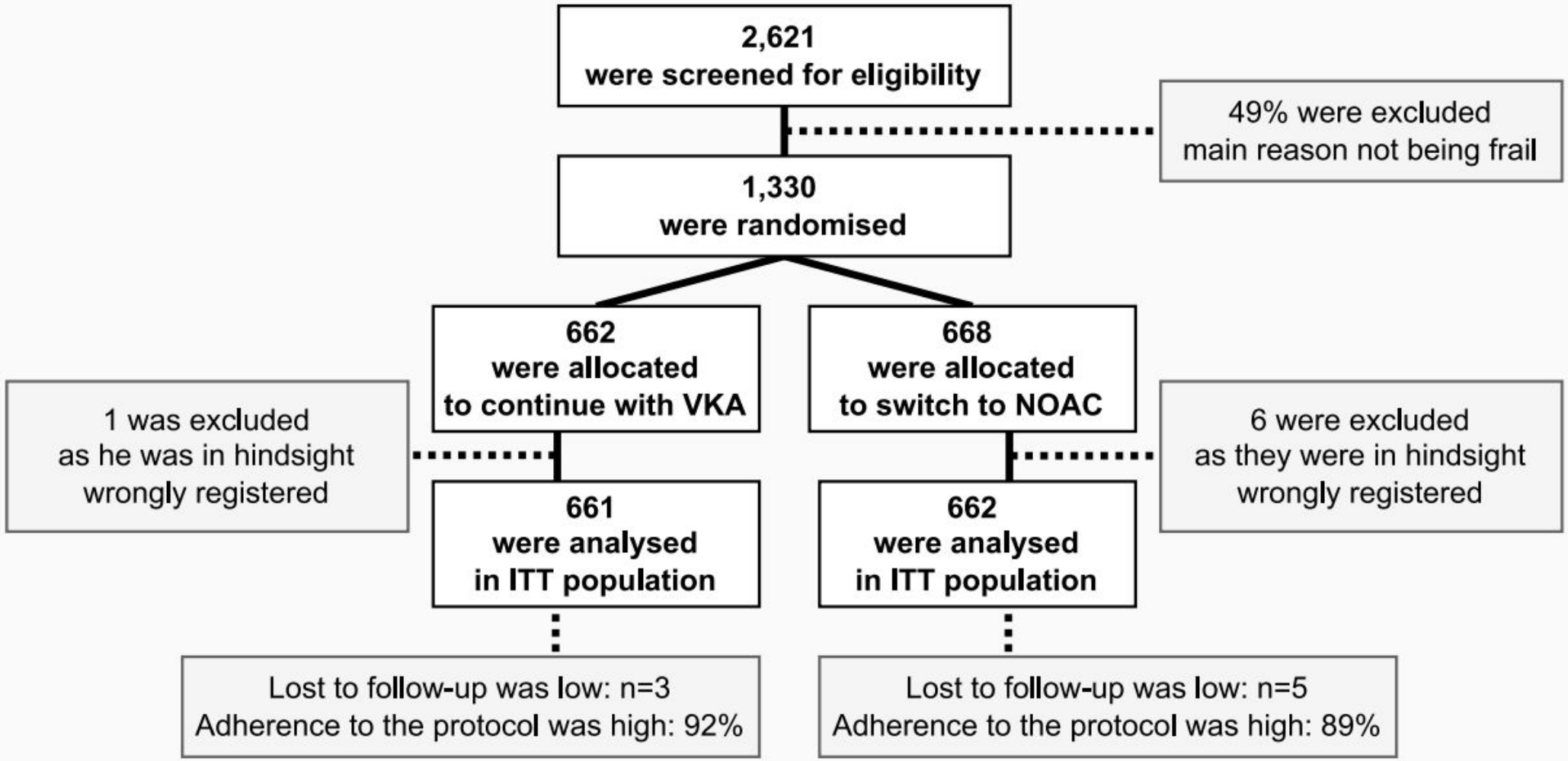
- Outpatient setting, GFI ≥3, ≥75 years
- VKA for non-valvular AF
- eGFR ≥30ml/min/1.73m^2

INTERVENTION	CONTROL
VKA  ⇩ NOAC 	VKA 

OUTCOMES

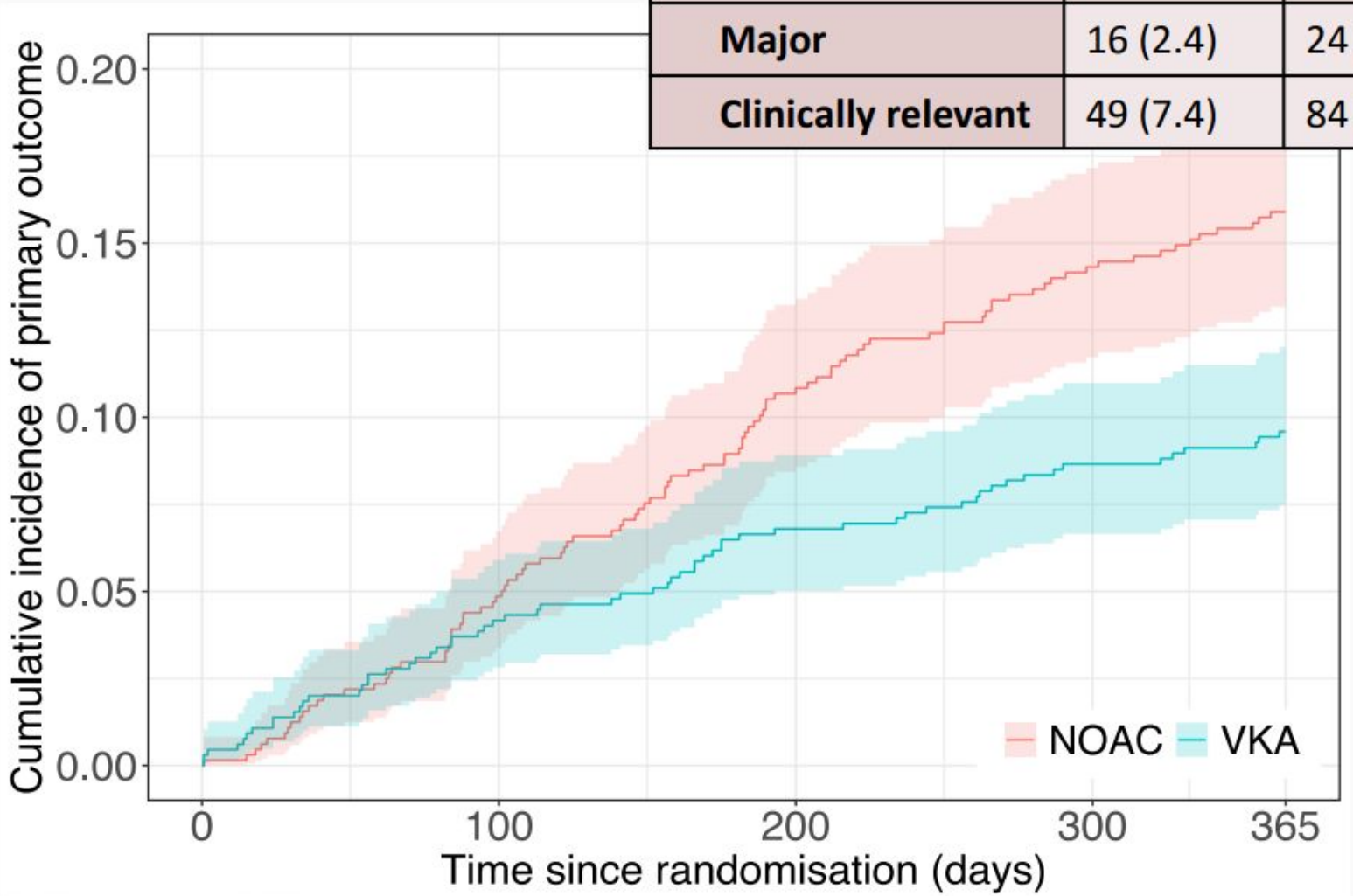
- **Primary**:
  - Major or clinically relevant non-major bleeding
- **Secondary**:
  - Thromboembolic events
  - All-cause mortality

Flowchart of included study participants



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**