

A history of falls and clinical outcomes in older adult patients with non-valvular atrial fibrillation from the ANAFIE Registry

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COI Disclosure

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This research was supported by Daiichi Sankyo Co, Ltd. The sponsor contributed to the study design, data analysis planning, data interpretation, and the decision to submit the manuscript for publication. However, the sponsor was not directly involved in data management, direct data access, or statistical analysis.

Background

- Frailty is widely acknowledged as a risk factor for both bleeding and mortality, and it is also strongly associated with an increased risk of thromboembolism.

BMC Med. 2020;18:401.

- In the All Nippon AF In the Elderly (ANAFIE) Registry:

- **Frailty**, as defined by the KIHON Checklist, was associated with increased risks of thromboembolism, major bleeding, and mortality; however, these associations did not remain significant for thromboembolism or major bleeding after multivariable adjustments.

Arch Gerontol Geriatr. 2022;101:104661.

- Conversely, **a history of falls** within the past year was significantly associated with increased risks of thromboembolism, major bleeding, and mortality, even after multivariable adjustments.

Eur Heart J Qual Care Clin Outcomes. 2022;8:202-213.

These findings suggest that a history of falls may exert a stronger influence on anticoagulation therapy aimed at stroke prevention in AF patients compared to other frailty-related factors.

Background

- To date, evidence regarding NVAf patients with a history of falls is scarce. Although widely spread evidence concerning safety of warfarin in patients with falls has already been described, information regarding DOACs compared to warfarin in anticoagulated patients with falls is still lacking.

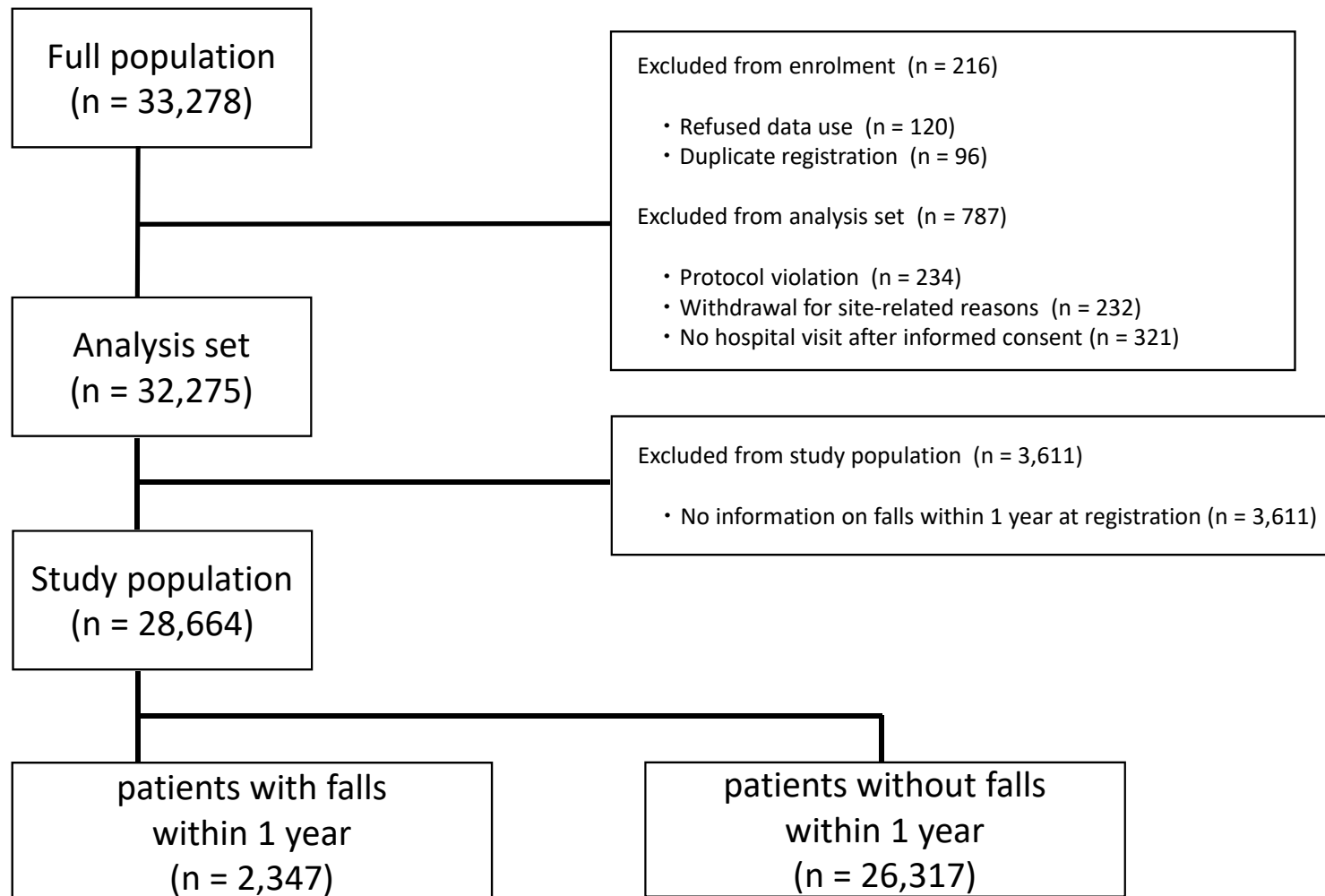
Arch Intern Med. 1999;159:677-85.

- We raised three critical questions;
 - First, **how are the outcomes** of patients with a history of falls within the past year compare to those without such a history?
 - Second, **is DOAC therapy more appropriate than warfarin** for prevention of subsequent falls/fractures?
 - Third, what is the **impact of new falls or fractures on patient outcomes** during follow-up?

Purpose

- This study conducts a subanalysis of the ANAFIE registry, focusing on the clinical implications of fall history in elderly patients with NVAF.

Patient Disposition



Patient Characteristics 1/2

	Total N = 28664	With falls N = 2347	Without falls N = 26317	P-value #
Male	16410 (57%)	1149 (49%)	15261 (58%)	<0.001
Age (year)	81 ± 5	83 ± 5	81 ± 5	<0.001
Age ≥ 85 (years)	7485 (26%)	907 (39%)	6578 (25%)	<0.001
Height (cm)	157 ± 9	155 ± 10	157 ± 9	<0.001
Body weight (kg)	58 ± 11	55 ± 11	58 ± 11	<0.001
Body mass index (kg/m ²)	23.3 ± 3.6	22.9 ± 3.8	23.4 ± 3.5	<0.001
SBP (mmHg)	127 ± 17	126 ± 18	128 ± 17	<0.001
DBP (mmHg)	71 ± 12	69 ± 12	71 ± 12	<0.001
Creatinine clearance (mL/min)	49 ± 18	43 ± 18	49 ± 17	<0.001
CHADS ₂ score	2.8 ± 1.2	3.1 ± 1.3	2.8 ± 1.2	<0.001
CHA ₂ DS ₂ VASc score	4.4 ± 1.4	4.9 ± 1.4	4.4 ± 1.4	<0.001
HAS-BLED score	1.9 ± 0.9	2.0 ± 0.9	1.8 ± 0.9	<0.001
History of major bleeding	1262 (0%)	162 (7%)	1100 (4%)	<0.001

Baseline characteristics were compared between patients with a history of falls and those without. Differences were tested using the chi-square test for categorical variables and the unpaired t-test for continuous variables..

Patient Characteristics 2/2

	Total N = 28664	With falls N = 2347	Without falls N = 26317	P-value #
AF type				
Paroxysmal	11981 (42%)	955 (41%)	11026 (42%)	0.255
Persistent	4708 (16%)	350 (15%)	4358 (17%)	0.033
Long-standing persistent/permanent	11975 (42%)	1042 (44%)	10933 (42%)	0.008
History of non-pharmacological AF therapy	4907 (17%)	404 (17%)	4503 (17%)	0.899
Catheter ablation	2549 (9%)	145 (6%)	2404 (9%)	<0.001
Electrical defibrillation	616 (2%)	66 (3%)	550 (2%)	0.041
ICD	133 (0%)	9 (0%)	124 (0%)	0.549
Pacemaker	2052 (7%)	240 (10%)	1812 (7%)	<0.001
Others	90 (0%)	11 (0%)	79 (0%)	0.245
Comorbidities				
Hypertension	21534 (75%)	1772 (76%)	19762 (75%)	0.661
Diabetes mellitus	7616 (27%)	685 (29%)	6931 (26%)	0.004
Chronic kidney disease	6010 (21%)	611 (26%)	5399 (21%)	<0.001
Myocardial infarction	1617 (6%)	149 (6%)	1468 (6%)	0.141
Heart failure	10564 (37%)	1032 (44%)	9532 (36%)	<0.001
History of cerebrovascular disease	6455 (23%)	786 (33%)	5669 (22%)	<0.001
Gastrointestinal disease	8292 (29%)	775 (33%)	7517 (29%)	<0.001
Active cancer	3041 (11%)	277 (12%)	2764 (11%)	0.061
Dementia	2245 (8%)	374 (16%)	1871 (7%)	<0.001
Anticoagulant therapy	26496 (94%)	2180 (95%)	24316 (94%)	0.032
Warfarin	7324 (26%)	660 (28%)	6664 (25%)	0.004
DOAC	19160 (67%)	1518 (65%)	17642 (67%)	0.022
Dabigatran	2098 (7%)	117 (5%)	1981 (8%)	<0.001
Rivaroxaban	5750 (20%)	404 (17%)	5346 (20%)	<0.001
Apixaban	7094 (24%)	636 (27%)	6458 (25%)	0.007
Edoxaban	4218 (15%)	359 (15%)	3857 (15%)	0.342
Others	12 (0%)	2 (0%)	10 (0%)	

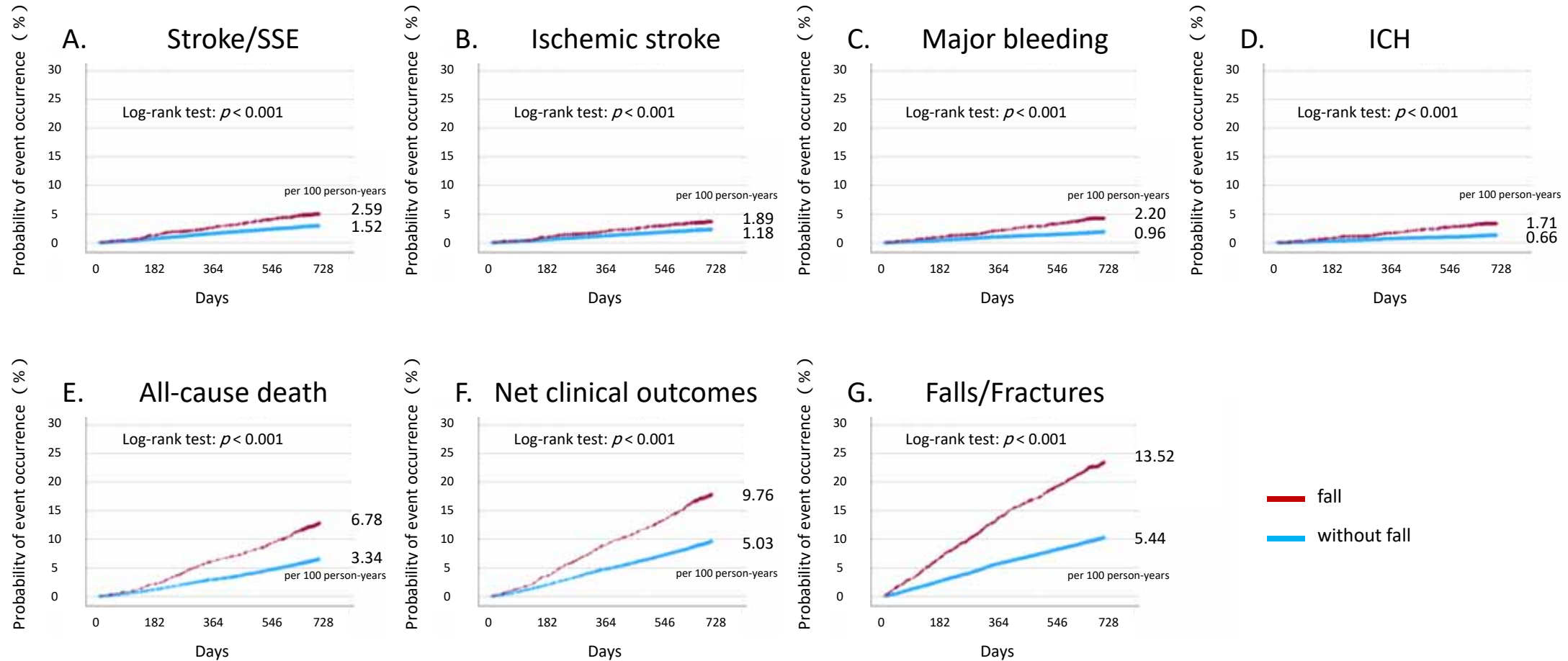
1. A history of falls and patient outcomes
2. OAC types and incidence of new falls/fractures
3. Impact of new falls/fractures on patient outcomes

1. A history of falls and patient outcomes

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Kaplan-Meier curves for clinical outcomes



Impact of previous falls within 1 year on adverse clinical outcomes (Univariate and multivariate Cox regression analyses)

	Univariate model			Multivariate model #		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Stroke/SEE	1.71	1.40-2.09	<0.001	1.36	1.07-1.73	0.012
Ischemic stroke	1.60	1.27-2.03	<0.001	1.37	1.05-1.80	0.022
Major bleeding	2.29	1.83-2.87	<0.001	1.89	1.46-2.46	<0.001
Intracranial hemorrhage	2.58	2.00-3.34	<0.001	2.18	1.61-2.95	<0.001
GI bleeding	1.35	1.10-1.66	0.004	1.20	0.95-1.51	0.126
Heart failure hospitalization	1.78	1.57-2.02	<0.001	1.39	1.20-1.60	<0.001
Cardiovascular death	2.20	1.76-2.76	<0.001	1.68	1.31-2.15	<0.001
All-cause death	2.04	1.80-2.31	<0.001	1.48	1.29-1.71	<0.001
Falls/Fractures	2.48	2.26-2.73	<0.001	2.07	1.86-2.32	<0.001
Net clinical outcomes ^a	1.95	1.75-2.16	<0.001	1.48	1.31-1.67	<0.001

In the multivariate model, fall within 1 year, age (year), male, body mass index, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, chronic kidney disease, severe hepatic disease, myocardial infarction, heart failure, reduced left ventricular ejection fraction, cerebrovascular disease, respiratory disease, digestive diseases, active cancer, dementia, type of AF, history of major bleeding, history of catheter ablation, creatine clearance, and use of antiarrhythmic medications, antiplatelet agents, proton pump inhibitors, P-glycoprotein inhibitors and the use of anticoagulant therapy were forcedly introduced..

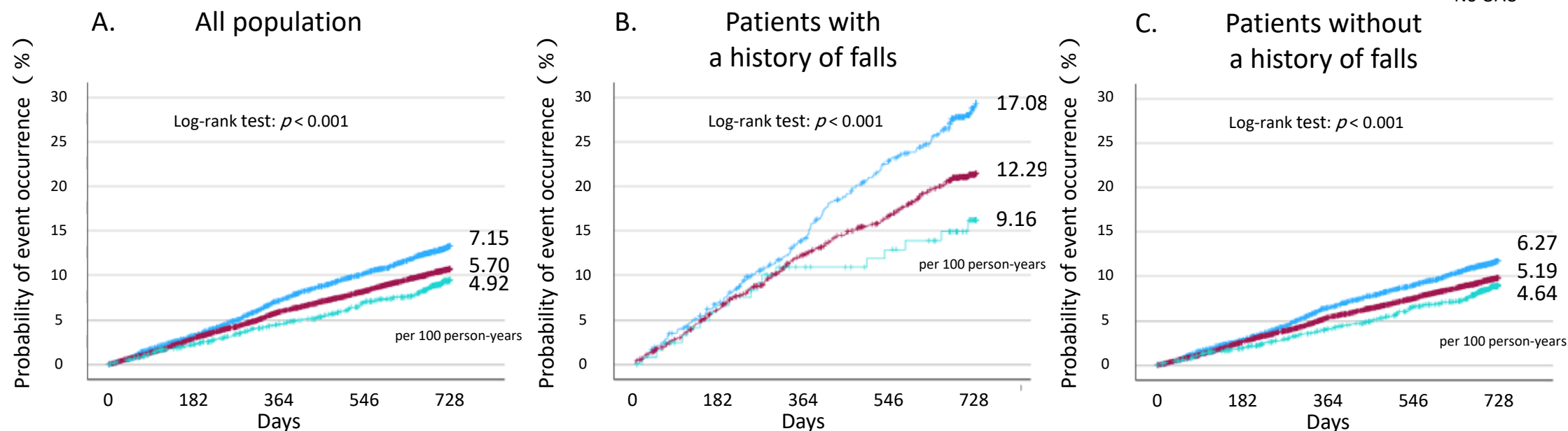
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OAC types and incidence of new falls/fractures

Warfarin
DOACs
No OAC

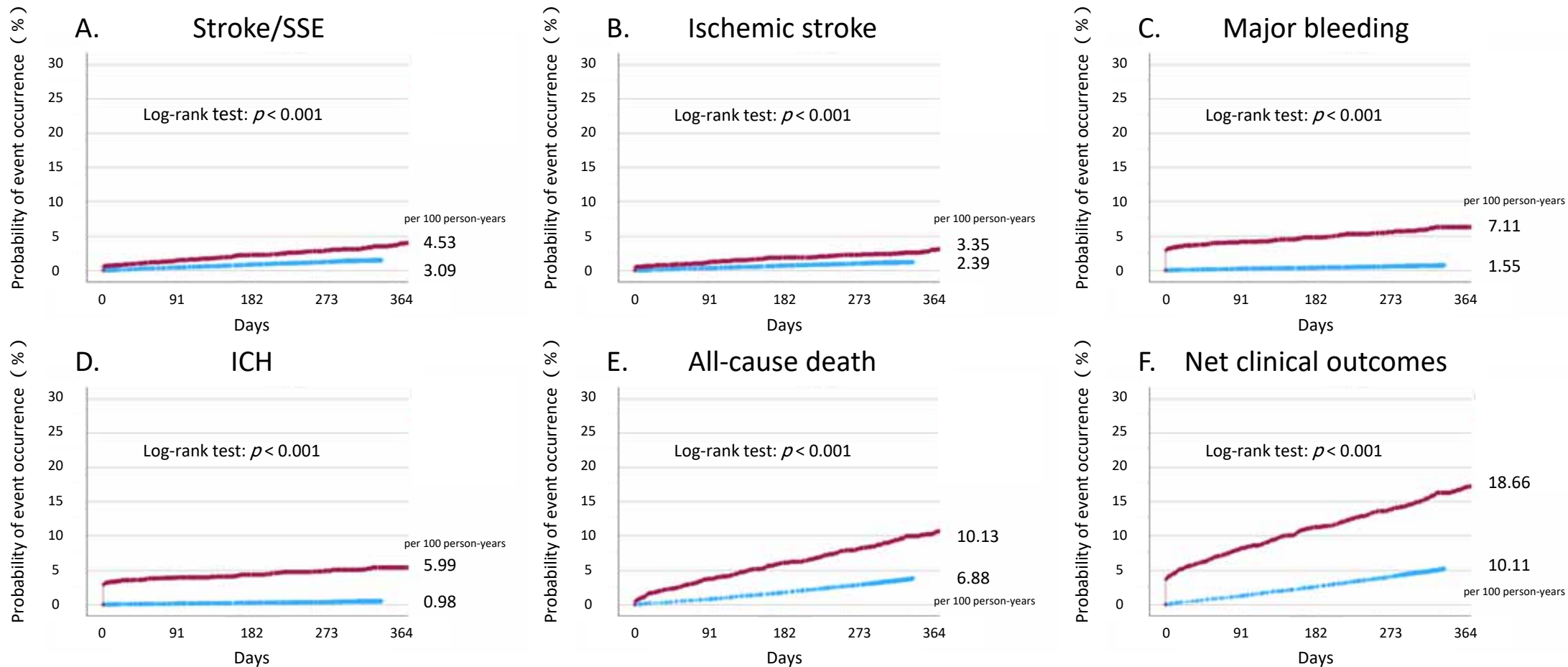


	DOACs vs. warfarin				No OAC vs. warfarin			
	Crude HR (95% CI)	p-value	Adjusted HR # (95% CI)	p-value	Crude HR (95% CI)	p-value	Adjusted HR # (95% CI)	p-value
All population	0.80 (0.74–0.86)	<0.001	0.82 (0.75–0.90)	<0.001	0.69 (0.58–0.82)	<0.001	0.64 (0.52–0.78)	<0.001
Patients with a history of falls within 1 year	0.72 (0.60–0.87)	<0.001	0.70 (0.57–0.87)	0.001	0.54 (0.33–0.87)	0.012	0.44 (0.25–0.77)	0.004
Patients without a history of falls within 1 year	0.83 (0.76–0.90)	<0.001	0.87 (0.78–0.96)	0.007	0.74 (0.62–0.89)	0.001	0.72 (0.57–0.89)	0.003

In the multivariate models, same variables of model in slide 12, except for fall within 1 year, and the use of anticoagulant therapy were forcedly introduced..

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Kaplan-Meier curves for clinical outcomes after falls/fractures among patients with and without falls/fractures during follow-up



- Clinical outcomes in patients without falls/fractures during follow-up are presented as a reference, with the observation period set to begin at 342 days, the average time to the occurrence of falls/fractures events.

— fall
— without fall

Summary

1. A history of falls and patient outcomes

- The two-year incidence rates of all clinical outcomes were significantly higher in patients with fall history compared to those without falls.
- Multivariate analysis revealed that patients with falls had approximately twice the risk of major bleeding and ICH, as well as more than twice the risk of falls/fractures, while they had approximately one-and-half the risk of stroke/SEE, ischemic stroke, all-cause death, and net clinical outcomes, compared to those without falls.

2. OAC types and incidence of new falls/fractures

- DOACs and no OAC use were associated with significantly lower risks of falls/fractures compared to warfarin, irrespective of baseline fall history.

3. Impact of new falls/fractures on patient outcomes

- All of adverse events increased following falls/fractures event during the observation period, and major bleeding (particularly ICH) substantially increased.

Discussion 1

Falls/fractures and patient outcomes

- In our population, a history of falls is a general prognostic factor for adverse outcomes in NVAF patients, with increased risks of all-cause death, major bleeding, and ICH, which was consistent with previous researches.
- Falls are strongly associated with intracranial hemorrhage, as they can cause head trauma due to head impact.
- The direct causality between falls and stroke/SEE appears implausible. In our population, the incidence of stroke/SEE increased immediately following falls/fractures events.
- A study in the United States reported that the resumption rate of anticoagulants was 41% in cases of traumatic brain injury, highlighting that anticoagulant therapy was not resumed in nearly half of these cases. Therefore, discontinuation of OACs after falls/fractures may explain the association between falls and stroke/SEE.

Discussion 2

Influence of DOACs and no OAC on falls/fractures compared to warfarin

- Recently, meta-analysis showed that DOACs users have a lower risk of fractures than the warfarin users. Warfarin inhibit the carboxylation of vitamin K-dependent bone mineralization proteins, including osteocalcin, matrix Gla protein, and periostin, thereby increasing the risk of fractures.

PLoS One. 2015;10:e0133847.

Front Cardiovasc Med. 2022;9:896952.

- Observational studies found that better physical performance is associated with higher plasma concentrations of Vitamin K exhibited higher lower extremity physical performance. Although causal relationship was not confirmed by intervention studies, inhibit of Vitamin K may adversely affect muscle mass and function, which may lead to falls.

J Gerontol A Biol Sci Med Sci. 2016;71:1348-55.

Discussion 2

Influence of DOACs and no OAC on falls/fractures compared to warfarin

- In our population, the most frequently observed event in all clinical events was falls/fractures, and major bleeding (particularly ICH) and stroke/SEE occurred or substantially increased following falls/fractures. It is crucial to prevent such falls/fractures in older adult patients with NVAf. In this regard, DOACs may be more preferable than warfarin, as they do not increase the incidence of falls/fractures.

Conclusions

- A history of falls within one year was identified as an independent risk factor for clinical outcomes. DOACs were associated with significantly lower risks of falls/fractures compared to warfarin, irrespective of baseline fall history.