


Impact of cognitive impairment on clinical outcomes in elderly patients with atrial fibrillation: ANAFIE Registry

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ABSTRACT

Background This subcohort study of All Nippon AF in the Elderly (ANAFIE) Registry based on 33 275 elderly patients (aged ≥75 years) with non-valvular atrial fibrillation (NVAF) investigated the relationship between cognitive function and 2-year clinical outcomes.

Methods A total of 2963 (mean age, 81.4 years) patients participated in this subcohort study and were classified as having normal cognition (Mini-Mental State Examination (MMSE) score ≥24/30) or cognitive impairment (score ≤23/30) at baseline. Patients with a decrease of >2 points after 24 months were classified as having cognitive decline.

Results At baseline, 586 (19.8%) patients had cognitive impairment. These patients tended to be older and had poorer general conditions than patients with normal cognition. The 2-year probability of stroke/systemic embolic events (SEEs), major bleeding and intracranial haemorrhage was numerically higher; those of cardiovascular death, all-cause death and net clinical outcome (composite of stroke/SEE, major bleeding and all-cause death) were significantly higher (all $p < 0.001$) in patients with cognitive impairment versus normal cognition. In multivariate analysis, the risks of cardiovascular death ($p = 0.021$), all-cause death ($p < 0.001$) and net clinical outcome ($p < 0.001$) were higher in patients with cognitive impairment versus those with normal cognition. After 24 months, 642 of 1915 (33.5%) patients with repeated MMSE determination had cognitive decline. Educational background <9 years, older age and concomitant cerebrovascular disorders were significant risk factors of cognitive decline at the 2-year follow-up.

Conclusions Elderly patients with NVAF with cognitive impairment have a higher mortality risk than those with normal cognition. Several significant risk factors of cognitive decline were identified at 2-year follow-up.

Trial registration number UMIN000024006 (<http://www.umin.ac.jp/>).

INTRODUCTION

Dementia involves a decline in cognitive function beyond that expected with normal ageing. An estimated 50 million people have dementia worldwide, with around 10 million

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a known association between atrial fibrillation (AF) and the risk of cognitive impairment and dementia, but the effects of anticoagulant therapy on cognitive decline in elderly patients with AF are not clear.

WHAT THIS STUDY ADDS

⇒ Elderly patients with non-valvular AF with cognitive impairment have a significantly higher risk of cardiovascular death and all-cause death, and a tendency towards a higher risk of stroke/systemic embolic events, major bleeding and intracranial haemorrhage over 2 years, than those with normal cognition.

⇒ Patients receiving anticoagulant therapy had less cognitive decline than those treated with warfarin during the 2-year observation period, with an educational background <9 years, age ≥85 years and concomitant cerebrovascular disorders identified as significant risk factors for cognitive decline.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Baseline cognitive function should be considered as a risk factor for poorer long-term outcomes in elderly patients with non-valvular AF, along with several background factors that may indicate an increased risk of cognitive decline.

⇒ High-quality anticoagulant therapy may be beneficial not only for the prevention of stroke, but in lowering the risk of cognitive decline in elderly patients with non-valvular AF.

new cases being diagnosed every year.¹ Atrial fibrillation (AF) is one of the most common arrhythmias worldwide,^{2 3} and its prevalence has been shown to increase with age.⁴⁻⁶ In a recent analysis of global trends in AF, the worldwide prevalence of AF was reported to be approximately 38 million cases and has increased by 33% over the last 20 years.⁷

Previous studies have suggested an association between AF and the risk of cognitive impairment and dementia.^{8–12} The effects of anticoagulant therapy on cognitive decline in patients with AF have been investigated, but no clear conclusions have been reached.^{9 13 14}

A previous cohort study showed that cognitive impairment in patients with AF was significantly associated with all-cause mortality (HR 2.473, 95% CI 1.062 to 5.756, $p=0.036$).¹⁵ However, the impact of cognitive impairment on the clinical outcomes of elderly patients with AF has not been fully elucidated.

Considering the increasing prevalence of AF worldwide, the All Nippon AF In the Elderly (ANAFIE) Registry was established to clarify the current status of anticoagulant therapy in elderly patients (aged ≥ 75 years) with non-valvular AF (NVAf) in Japan.¹⁶ This subcohort study aimed to investigate the relationship between cognitive function and 2-year clinical outcomes of elderly patients with NVAf from the ANAFIE Registry,¹⁶ according to their baseline cognitive function (normal cognition vs cognitive impairment), and explore the risk factors for cognitive decline in this patient population.

METHODS

Study design

Recruitment for the ANAFIE Registry, a multicentre, prospective, observational study, started in October 2016 and participants were followed up for 2 years. Details of the study design have been published previously.¹⁷

The study was registered at the UMIN Clinical Trials Registry under the identifier number UMIN000024006.

Participants

Overall, 33 275 men and women aged ≥ 75 years at the time of informed consent with a diagnosis of NVAf were included in the ANAFIE Registry.¹⁶ This included patients aged ≥ 75 years, with confirmed NVAf, who provided informed consent, and could attend study follow-up visits.

The only specific criterion for enrolment in this subcohort study of ANAFIE Registry participants was provision of written consent to be involved in this subcohort study and to undergo the Mini-Mental State Examination (MMSE) at enrolment. The exclusion criteria have been described previously.¹⁶ At baseline, 2963 patients agreed to participate in this subcohort study and had neuropsychological assessments. Patients included in this study were receiving stroke prevention treatment (anticoagulant therapy) in accordance with the most recent guidelines at the start of the ANAFIE Registry.¹⁸

According to the results of the MMSE scores at baseline (consent provision), normal cognition was defined as an MMSE score $\geq 24/30$, and cognitive impairment was defined as an MMSE score $\leq 23/30$; these cut-off values were based on those used in previous studies.^{15 19} The validity of the MMSE for screening of cognitive impairment has been previously reported.²⁰

Outcomes

The outcomes of interest in the present study were stroke/systemic embolic events (SEEs), major bleeding according to the definition of International Society on Thrombosis and Haemostasis, intracranial haemorrhage (ICH), cardiovascular death (CVD), all-cause death, net clinical outcome (a composite of stroke/SEE, major bleeding and all-cause death) and cognitive decline. To assess cognitive decline, the MMSE was repeated after 24 months. Patients with an MMSE score decrease of >2 points were classified as having ‘cognitive decline’²¹; the remaining patients were classified as ‘stable’.

Statistical methods

The sample size for this subcohort study was set based on the following. Previous studies have shown a difference in MMSE score of 1–2 between patients with and without AF.^{22 23} Assuming that the difference in MMSE score between with and without anticoagulant therapy would be the same as that between patients with and without AF, the patient ratio with and without anticoagulant therapy was expected to be 1:1. In a comparative study of aspirin-free versus aspirin-treated patients, the change in MMSE score at 5 years was -1 in the aspirin-free group and unchanged in the aspirin-treated group.²⁴ We assumed that at 24 months, the MMSE score difference would be -0.5 without anticoagulant therapy and 0.0 (SD 2.5) with anticoagulant therapy. As the ratio of the presence or absence of anticoagulant therapy was expected to be 7:3, the above difference would be detected in 937 patients (656 patients with anticoagulant therapy and 281 patients without anticoagulant therapy). Considering factor-based analysis, the sample size was set at 3000 cases. Baseline characteristics are described using summary statistics, with mean \pm SD for continuous variables and n (%) for categorical variables. Between-group comparisons were made using a two-sample t -test for continuous variables and a χ^2 test for categorical variables. The 2-year probability of event occurrence of stroke/SEE, major bleeding, ICH, CVD, all-cause death and net clinical outcome was estimated using the Kaplan-Meier method and the corresponding p values were calculated using the log-rank test. Incidence rates per 100 person-years with 95% CIs were also estimated. HRs and corresponding 95% CIs were estimated using the Cox proportional hazards model adjusted by potential confounding factors among the normal cognition and cognitive impairment groups. Cognitive decline was analysed using logistic regression analysis. A p value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS V.9.4 or higher (SAS Institute).

RESULTS

Patients

Among the 2963 patients (mean age, 81.4 years; men, 55.9%) enrolled in this subcohort study, 2377 (80.2%) were grouped into the normal cognition group and 586

(19.8%) into the cognitive impairment group at baseline. The baseline characteristics of patients are summarised in [table 1](#) and changes in MMSE scores in online supplemental table 1. Compared with patients with normal cognition, those with cognitive impairment were significantly older; were more likely to be female; had lower body mass index and creatinine clearance; had higher risk scores for stroke and bleeding; had higher comorbidity rates of hypertension, chronic kidney disease, heart failure, cerebrovascular disease and dementia diagnosed by their physician; and had more falls within 1 year. Most patients in both groups (more than 92%) were receiving anticoagulant therapy.

Outcomes

Kaplan-Meier curves for clinical outcome events are shown in [figure 1](#). Compared with the normal cognition group, in the cognitive impairment group, the 2-year probability of stroke/SEE (4.11% vs 3.25%), major bleeding (2.60% vs 1.49%) and ICH (2.12% vs 1.37%) was numerically higher, although the difference was not statistically significant; and those for CVD (4.54% vs 1.57%, $p<0.001$), all-cause death (17.16% vs 4.73%, $p<0.001$) and net clinical outcome (21.08% vs 7.88%, $p<0.001$) were significantly higher. The incidence rates per 100 person-years are listed in [table 2](#); these findings were generally consistent with those of the Kaplan-Meier curve analysis.

In multivariate analysis, cognitive impairment was significantly associated with CVD, all-cause death and net clinical outcome ([figure 2](#)). Factors associated with CVD and all-cause death are shown in online supplemental tables 2 and 3. In multivariate analysis, no driver's licence, male sex, presence of cerebrovascular disorders and renal impairment were associated with CVD and all-cause death, and not self-managing personal finances was associated with all-cause death.

Among the 1915 of 2963 (64.6%) patients in whom MMSE scores were also evaluated at the end of the 24-month observation period, 642 (33.5%) patients were classified as having cognitive decline, with a mean change in MMSE score from baseline of -4.9 ± 4.0 . The remaining 1273 (66.5%) were classified as stable, with a mean change in MMSE score from baseline of 0.9 ± 2.0 . An educational background <9 years, not self-managing personal finances, older age (≥ 85 years), warfarin use versus non-oral anticoagulant (OAC) use and having cerebrovascular disorders were associated with cognitive decline by multivariate analysis ([table 3](#)).

DISCUSSION

There has been a lack of knowledge on the impact of cognitive impairment on the clinical outcomes of elderly patients with AF. The present study has clarified the association between cognitive function and various clinical outcomes and risk factors for cognitive decline in a large number of elderly patients with AF. The major findings of the present subcohort study of elderly patients with NVAF

were as follows: first, almost 20% of patients had cognitive impairment and, compared with those with normal cognition, these patients were older; more likely to be female; and had lower body mass index and creatinine clearance, higher rates of comorbidities and risk scores for stroke and bleeding, and more falls within 1 year. Second, most patients (both groups) were receiving anticoagulant therapy—primarily, direct oral anticoagulants (DOACs; 70%). Third, the 2-year cumulative incidence rates of CVD, all-cause death and net clinical outcome were significantly higher in the cognitive impairment than in the normal cognition group; although the difference was not statistically significant, the 2-year cumulative incidence rate of stroke/SEE, major bleeding and ICH tended to be higher in the cognitive impairment than in the normal cognition group. Fourth, multivariate analysis showed that the risk of CVD and net clinical outcome was approximately two times higher, and the risk of all-cause death was almost three times higher in patients with cognitive impairment than in those with normal cognition (the net clinical outcome was mainly driven by all-cause death). Fifth, cognitive decline was observed in approximately 33% of cases. Multivariate analysis showed that an educational background <9 years, not self-managing personal finances, older age (≥ 85 years) and presence of cerebrovascular disorders were associated with cognitive decline over 2 years; a greater proportion of patients receiving warfarin had cognitive decline compared with non-OAC users.

Although the incidence rates of stroke/SEE, major bleeding and ICH were numerically higher in patients with cognitive impairment than in those with normal cognition, the difference was not statistically significant. Because the patients with cognitive impairment had higher risk of stroke at baseline, we had not anticipated these results. This may be explained, in part, by the relatively smaller sample size in this subcohort study, and the lower incidence rates compared with previous studies in patients with AF.^{25 26} More than 90% of patients with NVAF (both groups) had been treated with anticoagulant therapy. The majority of patients were on DOACs, and the time in the therapeutic range (TTR) was as high as 75% in those on warfarin. These findings indicate that high-quality anticoagulant therapy provided beneficial effects for preventing stroke/SEE, major bleeding and ICH in patients with normal cognition and also those with cognitive impairment.

By contrast, cognitive impairment significantly influenced the incidence of CVD and all-cause death in elderly patients with NVAF in our study. These findings are consistent with the results from a previous single-centre study conducted in Italy that reported a significant association between cognitive impairment and all-cause death in patients with AF¹⁵ and a study conducted in the USA that reported a significantly increased mortality risk in patients with AF with dementia.¹² Cognitive impairment was independently associated with death in patients with AF even after adjustment for demographic factors and

Table 1 Patient characteristics

	Normal cognition (MMSE \geq 24) n=2377	Cognitive impairment (MMSE \leq 23) n=586	Total n=2963	P value*
Men	1374 (57.8)	283 (48.3)	1657 (55.9)	<0.001
Age, years	80.7 \pm 4.5	83.9 \pm 5.2	81.4 \pm 4.8	<0.001
MMSE score	27.9 \pm 2.0	18.9 \pm 4.6	26.1 \pm 4.5	–
BMI, kg/m ²	23.5 \pm 3.5	22.7 \pm 3.5	23.4 \pm 3.5	<0.001
SBP, mm Hg	129.6 \pm 16.3	126.5 \pm 18.1	129.0 \pm 16.7	<0.001
DBP, mm Hg	72.1 \pm 11.2	70.3 \pm 13.1	71.7 \pm 11.6	0.001
Creatinine clearance, mL/min	50.8 \pm 16.7	41.5 \pm 16.8	49.1 \pm 17.1	<0.001
CHADS ₂ score	2.8 \pm 1.1	3.2 \pm 1.2	2.8 \pm 1.2	<0.001
CHA ₂ DS ₂ -VASc score	4.3 \pm 1.3	4.8 \pm 1.4	4.4 \pm 1.3	<0.001
HAS-BLED score	1.8 \pm 0.8	2.0 \pm 0.9	1.8 \pm 0.8	<0.001
History of major bleeding	83 (3.5)	29 (4.9)	112 (3.8)	0.098
AF type				<0.001
Paroxysmal	990 (41.6)	188 (32.1)	1178 (39.8)	
Persistent	778 (32.7)	219 (37.4)	997 (33.6)	
Permanent	609 (25.6)	179 (30.5)	788 (26.6)	
Non-pharmacological AF therapy	347 (14.6)	51 (8.7)	398 (13.4)	<0.001
Catheter ablation	211 (8.9)	12 (2.0)	223 (7.5)	<0.001
Electrical defibrillation	34 (1.4)	8 (1.4)	42 (1.4)	0.905
ICD	10 (0.4)	2 (0.3)	12 (0.4)	0.786
Pacemaker	123 (5.2)	32 (5.5)	155 (5.2)	0.781
Others	10 (0.4)	0 (0.0)	10 (0.3)	0.116
Comorbidities				
Hypertension	1789 (75.3)	465 (79.4)	2254 (76.1)	0.038
Diabetes mellitus	585 (24.6)	144 (24.6)	729 (24.6)	0.985
Chronic kidney disease	436 (18.3)	137 (23.4)	573 (19.3)	0.006
Dyslipidaemia	1025 (43.1)	224 (38.2)	1249 (42.2)	0.032
Myocardial infarction	110 (4.6)	31 (5.3)	141 (4.8)	0.500
Heart failure	700 (29.4)	262 (44.7)	962 (32.5)	<0.001
Cerebrovascular disease	546 (23.0)	208 (35.5)	754 (25.4)	<0.001
Gastrointestinal disease	664 (27.9)	153 (26.1)	817 (27.6)	0.376
Active cancer	225 (9.5)	49 (8.4)	274 (9.2)	0.409
Dementia†	99 (4.2)	194 (33.1)	293 (9.9)	<0.001
Fall within 1 year	199 (8.4)	95 (16.2)	294 (9.9)	<0.001
Anticoagulant therapy	2191 (92.2)	544 (92.8)	2735 (92.3)	0.593
Warfarin	536 (22.5)	149 (25.4)	685 (23.1)	0.159
TTR	76.9 \pm 28.7	74.9 \pm 29.6	76.5 \pm 28.9	0.520
PT-INR	2.0 \pm 0.4	2.0 \pm 0.5	2.0 \pm 0.4	0.457
DOAC	1655 (69.6)	395 (67.4)	2050 (69.2)	0.159
Dabigatran	162 (6.8)	27 (4.6)	189 (6.4)	0.045
Rivaroxaban	493 (20.7)	131 (22.4)	624 (21.1)	0.432
Apixaban	634 (26.7)	137 (23.4)	771 (26.0)	0.082
Edoxaban	366 (15.4)	100 (17.1)	466 (15.7)	0.352

Data are n (%) or mean \pm SD.

*Normal cognition versus cognitive impairment group.

†The diagnosis of dementia was made by the attending physician. Therefore, some patients with dementia had high MMSE scores, and some patients had low MMSE scores, but were not diagnosed as having dementia by their physicians.

AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; ICD, implantable cardioverter-defibrillator; MMSE, Mini-Mental State Examination; PT-INR, international normalised ratio of prothrombin time; SBP, systolic blood pressure; TTR, time in the therapeutic range (PT-INR 1.6–2.6).

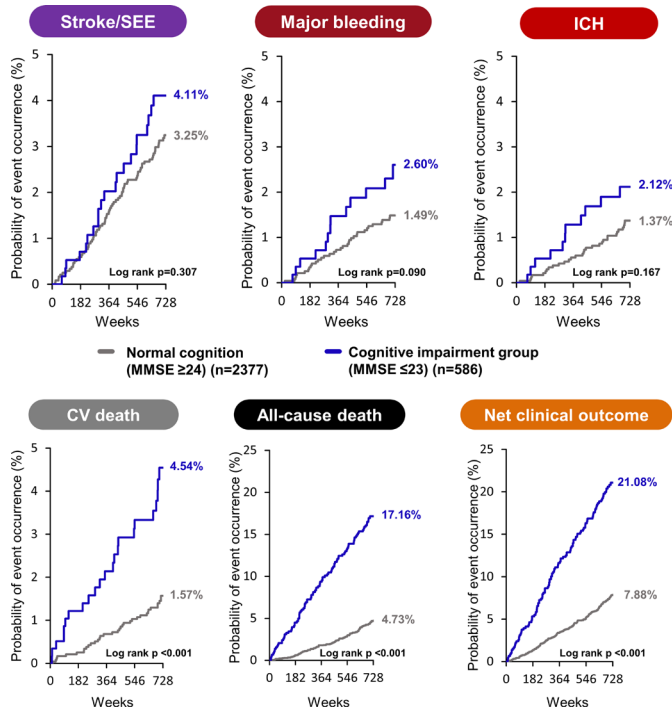


Figure 1 Kaplan-Meier curves for stroke/SEE, major bleeding, ICH, cardiovascular death, all-cause death and net clinical outcome according to MMSE. ICH, intracranial haemorrhage; MMSE, Mini-Mental State Examination; SEE, systemic embolic event.

comorbidities in those reports, although comorbidity and disability have been reported to increase mortality after a dementia diagnosis.^{27 28} In our study, multivariate analysis identified not having a driver’s licence, male sex,

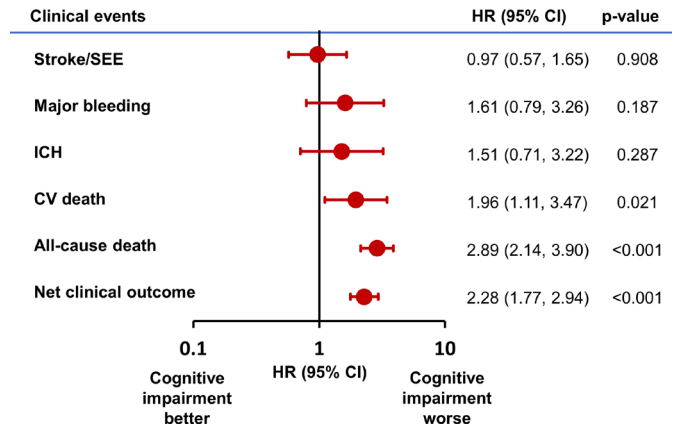


Figure 2 Impact of cognitive impairment on clinical outcomes adjusted by multivariate analysis. CV, cardiovascular; ICH, intracranial haemorrhage; SEE, systemic embolic event.

cerebrovascular disorders and renal impairment as risk factors for CVD and all-cause death. Not having a driver’s licence could be associated with less physical or social activity in elderly subjects. These findings highlight the importance of managing the risk of both cardiovascular events and comorbidities in elderly patients with AF. An increased number of medications, including antipsychotics, has also been associated with a higher mortality rate in elderly patients with cognitive impairment.^{29 30}

By multivariate analysis, shorter educational background, not self-managing personal finances, older age and presence of cerebrovascular disorder were significantly associated with cognitive decline during 2-year

Event	Group	Number	Event	Incidence per 100 patient-years (95% CI)
Stroke/systemic embolic event	Overall	2963	95	1.73 (1.39 to 2.08)
	Normal cognition	2377	74	1.65 (1.27 to 2.03)
	Cognitive impairment	586	21	2.11 (1.21 to 3.01)
Major bleeding	Overall	2963	47	0.85 (0.61 to 1.10)
	Normal cognition	2377	34	0.75 (0.50 to 1.01)
	Cognitive impairment	586	13	1.30 (0.59 to 2.01)
Intracranial haemorrhage	Overall	2963	42	0.76 (0.53 to 0.99)
	Normal cognition	2377	31	0.69 (0.44 to 0.93)
	Cognitive impairment	586	11	1.10 (0.45 to 1.75)
Cardiovascular death	Overall	2963	58	1.05 (0.78 to 1.32)
	Normal cognition	2377	35	0.77 (0.52 to 1.03)
	Cognitive impairment	586	23	2.27 (1.35 to 3.20)
All-cause death	Overall	2963	204	3.68 (3.17 to 4.18)
	Normal cognition	2377	108	2.38 (1.93 to 2.83)
	Cognitive impairment	586	96	9.49 (7.60 to 11.39)
Net clinical outcome	Overall	2963	299	5.48 (4.86 to 6.10)
	Normal cognition	2377	181	4.05 (3.46 to 4.64)
	Cognitive impairment	586	118	11.91 (9.76 to 14.06)

Table 3 Risk factors for cognitive decline

Item	Cognitive decline N=642	Stable N=1273	Univariate		Multivariate*	
			OR (95% CI)	P value	OR (95% CI)	P value
Educational background	<9 years	434 (34.1)	1.41 (1.16 to 1.71)	<0.001	1.42 (1.12 to 1.82)	0.004
	≥9 years†	821 (64.5)	–	–	–	–
Monetary management (bank accounts and pensions)	Self-managed†	924 (72.6)	–	–	–	–
	Managed by a family member/ others	239 (37.2)	1.67 (1.36 to 2.04)	<0.001	1.45 (1.10 to 1.90)	0.008
Age	<85 years†	1036 (81.4)	–	–	–	–
	≥85 years	194 (30.2)	1.89 (1.52 to 2.36)	<0.001	1.44 (1.08 to 1.93)	0.013
BMI (kg/m ²)	<18.5	46 (7.2)	1.48 (0.99 to 2.22)	0.056	1.52 (0.93 to 2.47)	0.094
	≥18.5–<25.0†	365 (56.9)	–	–	–	–
Hypertension	SBP <130 mm Hg†	370 (29.1)	0.83 (0.66 to 1.04)	0.107	0.87 (0.66 to 1.14)	0.306
	SBP ≥130–<140 mm Hg	269 (41.9)	–	–	–	–
Cerebrovascular disorders	SBP ≥140 mm Hg	306 (24.0)	1.23 (0.97 to 1.55)	0.086	1.26 (0.96 to 1.67)	0.099
	Yes	191 (29.8)	1.12 (0.88 to 1.43)	0.366	1.13 (0.85 to 1.51)	0.401
Oral anticoagulants	None†	279 (21.9)	1.51 (1.22 to 1.87)	<0.001	1.41 (1.08 to 1.83)	0.011
	Warfarin†	994 (78.1)	–	–	–	–
MMSE score at baseline	No use	269 (21.1)	–	–	–	–
	DOACs	104 (8.2)	0.67 (0.44 to 1.00)	0.051	0.59 (0.36 to 0.96)	0.034
MMSE score at baseline	≥24†	900 (70.7)	0.80 (0.64 to 1.00)	0.054	0.77 (0.59 to 1.01)	0.057
	≤23	1085 (85.2)	–	–	–	–
	116 (18.1)	188 (14.8)	1.27 (0.99 to 1.64)	0.063	0.80 (0.58 to 1.12)	0.192

Values are n (%), unless otherwise indicated.

*Educational background, volunteer activities, employment, participation in neighbourhood associations and resident associations, participation in learning activities such as open lectures for citizens, driving status, mobile telephone use, frequency of calls (fixed-line and mobile phones), computer use, internet use, going out, main means of going out, shopping, monetary management (bank accounts/pensions), travel and business trips to other prefectures, exercise habits, use of long-term care services, sex, age, BMI, anticoagulants, hypertension, diabetes mellitus, heart disease: heart failure, left ventricular systolic dysfunction, cerebrovascular disorders, creatinine clearance and MMSE score at baseline were included as adjustment factors in the model.

†Reference.

BMI, body mass index; DOACs, direct oral anticoagulants; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.

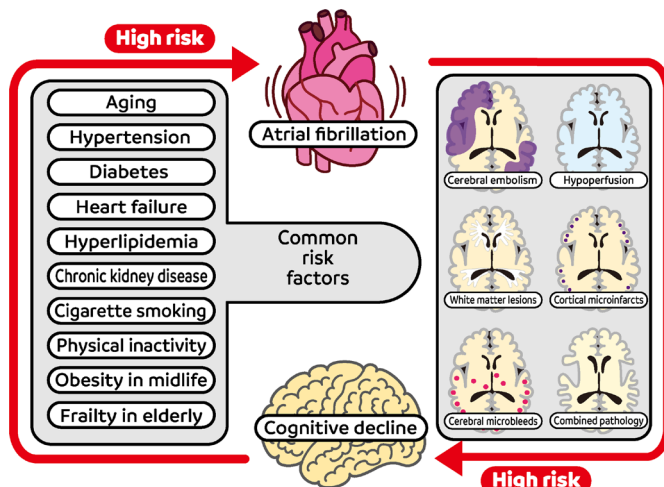


Figure 3 Common risk factors for atrial fibrillation and cognitive decline.

follow-up. Not self-managing personal finances was regarded as a part of executive dysfunction. Similar to the present study, education level and age were found to be risk factors of poor cognitive function in a previous study in which other risk factors such as anticoagulation, smoking history, NT-proB-type natriuretic peptide and haemoglobin were also identified in Chinese patients with AF with milder cognitive impairment (MMSE <26/30).³¹

An association between AF and the risk of cognitive decline and dementia has been reported previously.^{8–12} Patients with AF are currently regarded as having a high risk of cognitive decline because the direct relationship between AF and cognitive decline is associated with cardiogenic cerebral embolism, cerebral hypoperfusion, subcortical white matter lesions, cerebral microbleeds and subclinical cerebral infarcts.^{32–36} As there are also common risk factors in AF and cognitive decline (ie, ageing, hypertension, diabetes, heart failure, hyperlipidaemia, chronic kidney disease, cigarette smoking, physical inactivity, obesity in midlife and frailty in late life), patients with cognitive decline have a high risk of AF (figure 3).

In the present study, 65% of the study population was re-examined for cognitive function at the 2-year follow-up. Among the patients retested, 33.5% showed cognitive decline; this low percentage may be attributable to deaths and lack of testing. Baseline cognitive status did not significantly influence the progression of cognitive function during the 2-year follow-up period. However, in our study, patients with NVAF with cognitive impairment were older and had more profound vascular risk factors, including higher CHADS₂ and CHA₂DS₂-VASc scores, than those with normal cognition.

This could be partly explained by the relatively small sample size in this subanalysis and the high-quality anti-coagulant therapy, including the use of DOACs in both patient groups. In a previous large-scale cohort study in which 9%–11% of subjects were treated with warfarin and 19.1%–21.8% were on acetylsalicylic acid, CHA₂DS₂-VASc

scores were closely associated with dementia incidence among patients with AF.³⁷ The quality of anticoagulant therapy with warfarin as reflected by the TTR was also strongly associated with cognitive decline in elderly patients with AF,^{38 39} and cognitive dysfunction was related to less effective anticoagulation and more vascular events in elderly patients with AF.⁴⁰ The analysis in the present study found that the DOAC and non-OAC groups had less cognitive decline during the observation period compared with the warfarin-treated group; however, there was no direct comparison between the DOAC and non-OAC groups. Furthermore, a recent meta-analysis claimed that the use of DOACs might lower the tendency for the risk of cognitive impairment in comparison with warfarin or acetylsalicylic acid.⁴¹ Thus, high-quality anti-coagulant therapy, possibly with DOACs, may be recommended not only for the prevention of stroke, but also to lower the risk of cognitive decline in elderly patients with AF.

Limitations

This study has some limitations, including those inherent to the observational study design. The finding of a high prevalence of cognitive impairment in elderly patients with NVAF in this study is aligned with the findings of prior studies in patients with AF who have reported a relationship between cognitive impairment and multimorbidity and death. However, the incidence of major bleeding in the main ANAFIE Registry was lower than expected, which may have affected the results of this subanalysis.¹⁶ The cause of dementia and cognitive impairment was not determined, and there may have been selection bias as patients in the registry may have been reviewed by several physicians with a primary interest in cognitive dysfunction. Further, it is possible that the selection of a small subset of patients to undergo cognitive testing may have introduced a healthy participant bias. The impact of OAC use on the prognosis of patients was not sufficiently examined because most patients used OACs. Additionally, neuropsychological assessments at baseline were limited to MMSE, and the changes in cognitive function over time were not sufficiently investigated considering the relatively short 2-year observation period. The natural variation in the performance of the MMSE may have reduced the sensitivity of this test to detect true cognitive deterioration. Multivariate analysis was performed with the obtained factors that were expected to be associated with each event according to current guidelines. Nonetheless, some confounders that could not be fully adjusted may have affected the present results. Finally, our findings are limited to Japanese patients eligible for outpatient management and cannot be generalised to other ethnic populations.

CONCLUSION

Elderly patients with NVAF with cognitive impairment have higher risks of CVD and all-cause death than those

with normal cognition. Fewer years of education, older age and presence of cerebrovascular disorders were found to be significant risk factors of cognitive decline at the 2-year follow-up.

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