JGG 2025;73:33-40
doi: 10.36150/2499-6564-N796

Progression of cognitive decline in older adult patients with dementia: the role of atrial fibrillation and oral anticoagulant therapy

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Background and aim. The pathophysiology of dementia remains incompletely understood, and there are conflicting findings regarding the contribution of atrial fibrillation (AF) to cognitive decline. Additionally, oral anticoagulants may influence the progression of dementia. This study aims to explore whether AF is associated with the progression of cognitive decline and functional deterioration in older adults with dementia. Additionally, it seeks to evaluate the potential impact of anticoagulant therapy on cognitive and functional decline.

Methods. This observational retrospective study involved 179 older adults with dementia under the care of the University of Padua from 2015 to 2020. Each participant underwent a two-year observation period, during which cognitive function was assessed using the Mini-Mental State Examination (MMSE), and functional abilities were measured with the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales.

Results. AF patients made up 29.6% of the sample. According to ANOVA test for repeated measures, no significant differences in MMSE scores were observed over time between the AF and nAF groups or across the three time points based on anticoagulant therapy type. However, individuals with nAF showed a more pronounced decline in IADL and ADL scores over time. Linear mixed model analysis revealed that Alzheimer's dementia (-1.98, 95% CI: -3.16, -0.79; p = 0.001) and age (-0.09, 95% CI: -0.18, -0.00; p = 0.044) were significantly associated with MMSE decline. Significant predictors of IADL decline included male sex (-1.20, 95% CI: -1.77, -0.64, p < 0.001), MMSE (0.15, 95% CI: 0.06, 0.25, p = 0.002), and age (-0.08, 95% CI: -0.13, -0.04, p < 0.001), with a notable interaction between nAF and time (-0.48, 95% CI: -0.86, -0.12, p = 0.010). For ADL, MMSE (0.15, 95% CI: 0.09, 0.22, p < 0.001), and age (-0.03, 95% CI: -0.07, -0.003, p < 0.001) were the main predictors.

Conclusions. AF was not identified as a factor associated with cognitive decline when accounting for other variables. Instead, age and the presence of Alzheimer's disease emerged as key factors linked to functional and cognitive deterioration.

Key words: older adults, cognitive decline, functional abilities, non valvular atrial fibrillation, anticoagulant therapy

Received: August 13, 2024
Accepted: April 30, 2025
Published online: June 25, 2025

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How to cite this article: Tasso G, Mizzon E, Ceolin C, et al. Progression of cognitive decline in older adult patients with dementia: the role of atrial fibrillation and oral anticoagulant therapy. Journal of Gerontology and Geriatrics 2025;73:33-40. https://doi.org/10.36150/2499-6564-N796

Abbreviations

AF: atrial fibrillation
nFA: no Atrial Fibrillation
DOAC: Direct Oral Anticoagulant
MMSE: Mini Mental State Examination
ADL: Activities of daily Living
IADL: Instrumental Activities of daily Living
CDCD: Center for Cognitive Decline and Dementia

INTRODUCTION

Recent studies suggest that in industrialized countries, about 8% of people over 65 suffer from dementia, with peak incidence rates between 10-17% in those over the age of 80 [1,2]. Given the progressive aging of the general population, these numbers are expected to increase [3]. According to the Italian Longitudinal Study on Aging (ILSA), dementia affects 5.3% of Italian men and 7.2% of women over the age of 65, with nearly half of these individuals suffering from at least three chronic diseases [3].

There is growing evidence that atrial fibrillation (AF) may contribute to the development of cognitive decline and dementia (including both Alzheimer's and vascular types) in older adults, regardless of the presence of clinical stroke or the timing of AF onset [4-8]. The role of anticoagulants in the progression of cognitive decline remains a topic of debate. For example, Diener and colleagues reported that it has not yet been demonstrated whether anticoagulation, despite its well-established efficacy in reducing clinical strokes, also prevents cognitive decline and dementia in patients with AF [9]. Additionally, other studies have found no significant differences in cognitive performance between anticoagulant therapies (such as dicoumarol and direct oral anticoagulants [DOACs]) or among different DOACs [7,8,10-13]. Consequently, the impact of anticoagulant therapy on dementia remains unclear. Furthermore, despite growing interest in the pathophysiological mechanisms linking AF to cognitive decline, few studies have investigated its effect on the actual progression of dementia.

One crucial aspect to establish is the role of AF in functional decline among individuals with dementia. For instance, AF has been linked to a heightened risk of silent cerebral infarcts, which can impair cognitive function across multiple domains, even in the absence of overt stroke [14]. This subtle cognitive impairment may manifest as difficulties with complex daily tasks. Although the association between AF and increased cognitive decline implies a corresponding deterioration in functional abilities, the potential link between AF and performance in daily activities – particularly among older adults – warrants further investigation.

Given these premises, the aim of our study was to assess whether the progression of cognitive decline and the deterioration in functional abilities among older adults with dementia is associated with the presence of AF.

MATERIALS AND METHODS

Study population

This retrospective cohort study was conducted on 179 patients followed at the Center for Cognitive Decline and Dementia (CDCD) in Padua. Patients were enrolled between 2015 and 2020 in our outpatient clinics (T0) and were then followed for two years (T24) to assess cognitive trajectory, with data collection every 12 months (T12). The inclusion criteria for selected patients were: age > 65 years; a Mini-Mental State Examination (MMSE) score < 27/30 at the initial evaluation; a diagnosis of Alzheimer's disease, vascular dementia, or mixed-type dementia (documented by imaging), with or without the presence of behavioral disturbances; Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores greater than zero; and the presence of no valvular-AF being treated with oral anticoagulants.

Data collection

Trained physicians gathered the following information from each participant:

Patient characteristics

Sociodemographic data (age, sex, living status, years of education), risk behaviors (smoking and alcohol consumption), medical history (including diagnosis of cognitive impairment, atrial fibrillation, and other coexisting chronic diseases and comorbidities), and drug treatments.

Cognitive and functional evaluation

Cognitive performance was assessed with the Mini Mental State Examination (MMSE) [15], and functional autonomy was measured with the ADL [16], and IADL [17] scales.

Statistical analysis

Taking Ding's 2018 study [18] as a reference, in which the difference in slopes between participants with AF and those without was 0.28, we used the *edland.linear.power* function in R [19] to estimate the required sample size. Assuming a difference of less than 0.28 between the slopes (indicating the annual rate of cognitive decline assessed by the MMSE) for cognitive performance

in subjects with controlled AF versus those without AF, and using a one-sided test with measurements repeated every 6 months for at least 2 years, with a random slope, alpha = 0.05, and beta = 0.20, the estimated sample size was 63 subjects per group, resulting in a total of 126 participants. Assuming a dropout rate of 20%, we determined that at least 152 subjects needed to be enrolled in the study.

The characteristics of the sample are expressed as means ± standard deviation for continuous quantitative variables with a normal distribution and as medians (interquartile range) for variables with a non-normal distribution. Categorical variables are presented as numbers and percentages. The normality of continuous quantitative variables was assessed using the Shapiro-Wilk test. Comparisons of participant characteristics based on the presence or absence of AF were conducted using the Student's t-test for continuous variables and the Chi-square test for categorical variables, depending on the variable type. The functional variable was derived from ADL and IADL scores, which were considered both as continuous variables and with a cut-off of 2 to distinguish between individuals with preserved functional autonomy and those who were functionally dependent, as previously reported [20], resulting in a dichotomous variable. All MMSE scores were adjusted for age and educational level. The ANOVA for repeated measures was used to assess eventual differences in cognitive decline in people treated with different anticoagulant therapy. To assess the variables associated with changes over time in MMSE, ADL, and IADL scores, linear mixed models (LMM) were used. The models included time as an independent variable, along with the interaction between AF and time, and between AF and MMSE. The model structure incorporated fixed effects for the variables of interest and a random effect for the subject to account for intra-individual correlation. Results were expressed as coefficients with 95% confidence intervals (95% CI). Statistical significance was set at $p < 0.05$. All analyses were conducted using IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp).

RESULTS

The socio-demographic characteristics and clinical-anamnestic data at baseline are presented in Table I. Patients with AF constituted 29.6% of the sample (52.8% of whom were female). They were found to be more functionally compromised compared to individuals without AF, particularly regarding IADL profiles. Among the AF patients, 50.9% were on warfarin and 49.1% on a DOAC, and also the use of memantine was more frequent (11.3 *vs* 1.7%, p = 0.01). No significant differences were observed between the two groups regarding living status, educational level, or main comorbidities.

The repeated-measures ANOVA revealed a significant effect of time on MMSE scores ($F_{2,74} = 12.491$, $p < 0.001$, $\eta^2 = 0.252$), indicating a significant change in cognitive function over the follow-up period. However, no significant interaction was found between time and the type of anticoagulant therapy ($F_{2,74} = 0.164$, $p = 0.849$, $\eta^2 = 0.004$), suggesting that the observed cognitive decline does not differ between patients treated with vitamin K antagonists or DOACs (Fig. 1 and Supplementary Fig. 1).

However, individuals with nAF experienced a more pronounced decline in functional autonomy over time, as evidenced by the IADL and ADL scores (Fig. 2). Specifically, in the nAF group, the proportion of individuals with IADL scores below 2 increased from 10.3% at baseline to 35% at T24 ($p < 0.001$), while in the AF group, it rose from 54.4 to 67.8%. A similar trend was observed for ADL scores, with the percentage of individuals scoring below 2 increasing from 5.1 to 22.5% in the nAF group and from 10.3 to 35% in the AF group ($p < 0.001$ for both).

The results of the linear mixed model analysis for MMSE scores presented in Table II indicated that both the presence of Alzheimer's dementia and age were significantly associated with a decline in MMSE. Specifically, Alzheimer's dementia was linked to an estimated reduction of -1.98 (95% CI: -3.16, -0.79; p = 0.001), while age was associated with a smaller, yet significant, decline of -0.09 (95% CI: -0.18, -0.00; p = 0.044). Conversely, the use of acetylcholinesterase inhibitors was significantly correlated with an improvement in MMSE scores, with a beta coefficient of 2.50 (95% CI: 0.23, 4.77; p = 0.031). The interaction between AF and time was not significant (p = 0.676), suggesting that the decline over time is comparable between individuals with and without AF. For IADL score, significant predictors of decline include male sex (-1.20, IC95% -1.77; -0.64, $p < 0.001$), MMSE (0.15, IC95% 0.06; 0.25, p = 0.002), and age (-0.08, IC95% -0.13;-0.04, $p < 0.001$), with a notable interaction between nAF and time (-0.48, IC95% -0.86; -0.12, p = 0.010), highlighting a steeper decline in individuals with nAF (Tab. III). In contrast, for ADL, significant predictors include nAF (1.96, IC95% 0.18; 3.75, p = 0.031), MMSE (0.15, IC95% 0.09; 0.22, $p < 0.001$), and age (-0.03, IC95% -0.07; -0.003, $p < 0.001$). No significance was observed for nAF and time interaction (Tab. III).

DISCUSSION AND CONCLUSIONS

Several studies over the last decade have found that AF is associated with a higher risk of all forms of dementia,

Table I. Characteristics of the sample at baseline according to the presence or absence of atrial fibrillation.

Variables	All	nAF	AF	p value
	(n = 179)	(n = 126)	(n = 53)	
Age (years)	80 ± 5	80 ± 6	81 ± 5	0.22
Sex – female	117 (65.4%)	89 (70.6%)	28 (52.8%)	**0.02**
Living status				0.14
Alone	39 (23.2%)	23 (19.0%)	16 (34.0%)	
Cohabiting	102 (60.7%)	76 (62.8%)	26 (55.3%)	
Relatives	24 (14.3%)	19 (15.7%)	5 (10.6%)	
Education (years)	6.47 ± 3.25	6.40 ± 3.21	6.64 ± 3.36	0.67
MMSE	20.80 ± 3.24	20.80 ± 3.29	20.76 ± 3.14	0.90
Smoking				0.19
Current	34 (19.1%)	20 (16%)	14 (26.4%)	
Previous	12 (6.7%)	10 (8%)	2 (3.8%)	
Functional status				
ADL	5.32 ± 1.02	5.31 ± 1.01	5.36 ± 1.04	0.77
IADL	3.81 ± 2	4.03 ± 2.04	3.28 ± 1.81	**0.03**
No.people with ADL > 2	175 (97.8%)	124 (98.4%)	51 (96.2%)	0.58
No.people with IADL > 2	126 (70.4%)	95 (75.4%)	31 (58.5%)	**0.03**
Comorbidities				
Hypertension	108 (60.7%)	73 (58.4%)	35 (66%)	0.40
Diabetes	35 (19.7%)	24 (19.2%)	11 (20.8%)	0.83
Ischemic heart disease	17 (9.6%)	12 (9.6%)	5 (9.4%)	0.91
Peripherical vascular disease	26 (14.6%)	15 (12%)	11 (20.8%)	0.16
Depression	33 (18.5%)	25 (20%)	8 (15.1%)	0.53
Neurodegenerative disease	14 (7.9%)	13 (10.4%)	1 (1.9%)	0.07
Dysthyroidism	26 (14.5%)	20 (15.8%)	6 (11.3%)	0.51
Neoplasm	45 (25.3%)	28 (22.4%)	17 (32.1%)	0.19
Type of dementia				0.75
AD	57 (31.8%)	42 (33.3%)	15 (31.8%)	
VD	48 (26.8%)	34 (27%)	14 (26.4%)	
MD	74 (41.3%)	50 (39.7%)	24 (45.3%)	
Dementia drugs				
Acetylcholinesterase inhibitors	29 (17%)	24 (20.3%)	5 (9.4%)	0.05
Memantine	8 (4.7%)	2 (1.7%)	6 (11.3%)	***0.01***

Results are expressed as means ± SD, or counts (%), as appropriate.

AF: atrial fibrillation; nAF: non-atrial fibrillation; AD: Alzheimer's disease; VD: vascular dementia; MD: mixed dementia.

particularly Alzheimer's disease, regardless of the presence of acute cardiovascular disease [5,21,22]. However, it remains unclear whether cardiac pathology subsequently influences the progression of cognitive decline into dementia.

In our study, we did not observe any differences in cognitive performance over time between patients with and without AF. This finding contrasts with expectations, as silent strokes that may occur before the diagnosis of AF or the initiation of anticoagulant therapy could potentially damage cerebral parenchyma, leading to structural brain changes and progressive cognitive decline [17,23,24]. Evidence suggests that, in older adults, AF is associated with reduced cardiac output, which can diminish cerebral blood flow, particularly to the temporal lobes [25]. No significant differences in cognitive outcomes among patients with AF based on the type of anticoagulant treatment were found, with respect to both MMSE scores and the progression of cognitive decline over the first two years of follow-up. This finding aligns with other studies in the medical literature, in which DOACs are no less effective than dicumarolic drugs in reducing the incidence of cognitive decline, despite potential minor pharmacological interactions and side effects [13].

Moving to the variables associated with MMSE changes over time, AF had no significant impact on the progression of cognitive decline. In contrast, aging and Alzheimer's disease, emerged as the factors primarily

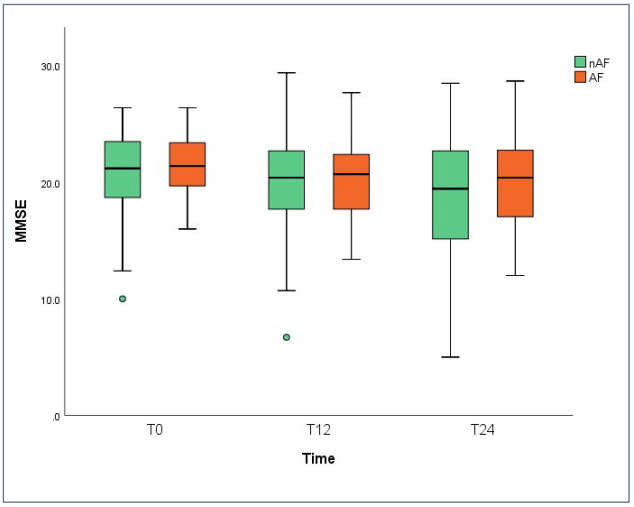


Figure 1. Changes in MMSE scores over time in AF and nAF groups.
AF: atrial fibrillation; nAF: non-atrial fibrillation; MMSE: Mini Mental State Examination.

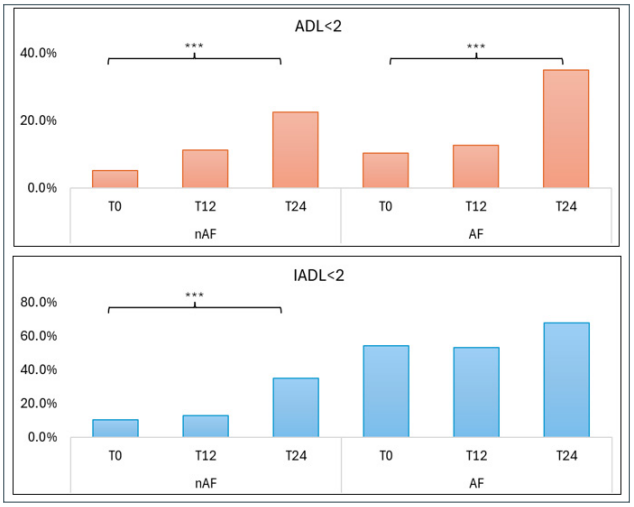
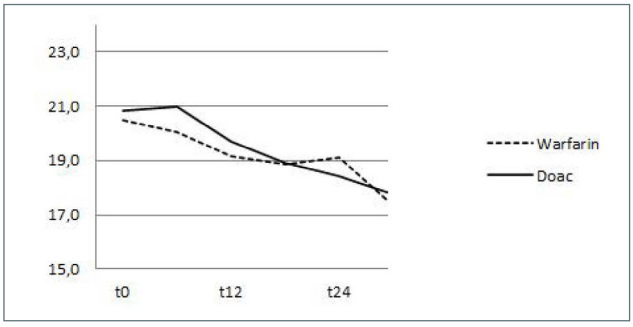


Figure 2. Changes in functional autonomy among individuals with and without atrial fibrillation over time.
AF: atrial fibrillation; nAF: non-atrial fibrillation; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.

associated with cognitive decline. This may be due to the increasing vulnerability of small cerebral vessels to occlusion with age, leading to strokes or micro-hemorrhages, which are especially common in Alzheimer's disease. As documented in the medical literature, these vascular events significantly accelerate cognitive deterioration [26,27]. Moreover, numerous studies have shown that Alzheimer's disease is characterized by a more rapid decline in cognitive functions, such as memory loss (amnesia) and difficulty with motor tasks (apraxia), often accompanied by behavioral disturbances. This progression is typically faster than in other forms of dementia examined in our study [28]. One intriguing finding was the association between cognitive deterioration and Alzheimer's disease, while no such link was observed with other forms of dementia. This could be attributed to several factors. First, the MMSE is specifically designed to assess domains such as memory, language, and orientation. Since Alzheimer's disease typically impairs memory and language early in its progression, the MMSE is likely more sensitive to detecting these deficits [29]. This may explain why it captures cognitive decline more effectively in Alzheimer's dementia compared to vascular or mixed dementia [30]. In contrast, vascular and mixed dementias often present with more variable cognitive profiles, depending on the extent and location of vascular damage, making it harder for a general screening tool like the MMSE to detect consistent changes. Furthermore, cognitive decline in Alzheimer's disease is usually progressive and continuous, whereas in vascular and mixed dementias, it tends to remain stable for extended periods with sudden episodes of rapid



Supplementary Figure 1. Estimated means of adjusted MMSE scores in patients with atrial fibrillation over the observation period.
DOAC: direct oral anticoagulants.

deterioration. As a result, our two-year follow-up period may not have been sufficient to capture the more variable progression seen in vascular or mixed dementia [31]. Currently, literature regarding the impact of AF on functional abilities is limited [32,33]. Few studies have investigated the relationship between AF and specific performance tests, such as grip strength and walking speed, without focusing on frailty [34-36]. To the best of our knowledge, this study is among the few that explore the relationship between AF and ADL and IADL. Analyzing the variables potentially associated with changes in functional autonomy, it emerged that both the MMSE score and age play a significant role in determining the variation in IADL and ADL. In particular, higher MMSE scores were associated with better functional autonomy, confirming the well-established correlation

Table II. Results of linear mixed model analysis for MMSE scores.

Parameter	B coefficient	p value	CI 95%
Sex M	0.80	0.200	[-0.43, 2.03]
Living alone	-2.32	0.517	[-9.38, 4.74]
nAF	-0.06	0.946	[-1.74, 1.62]
Alzheimer dementia	-1.98	**0.001**	[-3.16, -0.79]
Acetylcholinesterase inhibitors	2.50	**0.031**	[0.23, 4.77]
Age	-0.09	**0.044**	[-0.18, -0.00]
Time	-1.15	**0.000**	[-1.69, -0.61]
Education (years)	0.12	0.153	[-0.05, 0.29]
AF*time	0.14	0.676	[-0.52, 0.81]

M: male; nAF: non-atrial fibrillation; AF: atrial fibrillation.

Table III. Results of linear mixed model analysis for IADL and ADL scores.

	IADL			ADL		
Parameter	**Beta coefficient**	**p value**	**CI95%**	**Beta coefficient**	**p value**	**CI95%**
Sex M	**-1.20**	**< 0.001**	[-1.77, -0.64]	0.02	0.911	[-0.40, 0.45]
Living alone	**2.16**	**0.024**	[0.29, 4.04]	1.22	0.090	[-0.19, 2.64]
nAF	2.23	0.092	[-0.37, 4.83]	**1.96**	**0.031**	[0.18, 3.75]
Alzheimer dementia	0.02	0.926	[-0.55, 0.61]	0.33	0.140	[-0.11, 0.77]
MMSE	**0.15**	**0.002**	[0.06, 0.25]	**0.15**	**< 0.001**	[0.09, 0.22]
Acetylcholinesterase inhibitors	-0.14	0.811	[-1.29, 1.01]	0.13	0.758	[-0.73, 1.005]
Age	**-0.08**	**< 0.001**	[-0.13, -0.04]	**-0.03**	**0.030**	[-0.07, -0.003]
Time	**-0.50**	**< 0.001**	[-0.68, -0.28]	**-0.48**	**< 0.001**	[-0.68, -0.28]
nAF * tempo	**-0.48**	**0.010**	[-0.86, -0.12]	0.01	0.956	[-0.23, 0.24]
nAF * MMSE	-0.05	0.37	[-0.16, 0.01]	-0.04	0.47	[-0.22, 0.01]

ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; M: male; nAF: non-atrial fibrillation; AF: atrial fibrillation.

between cognitive decline and loss of autonomy. Indeed, a decline in cognitive function often leads to a decline in functional abilities, with IADL typically being the first to show changes, as they reflect instrumental daily living skills, followed by ADL. Regarding the association with AF, patients with nAF exhibited higher ADL scores compared to those with AF, with no significant effect of time. Conversely, although patients with nAF tended to achieve better IADL scores than those with AF, the interaction between nAF and time was significant, suggesting that individuals with nAF experience a more pronounced decline in IADL over time.

This seemingly paradoxical result may be explained by the possibility that patients without AF may have other comorbidities affecting functional autonomy, or that patients with AF may have "stabilized" at a certain performance level, already compromised by the disease (as reflected in their lower ADL and IADL scores), making their decline less sensitive to the effects of time. Finally, the gender differences observed in IADL scores may be related to the fact that, in older generations, men are generally less accustomed to performing instrumental daily activities, such as cooking, grocery shopping, or managing finances, compared to women, particularly in past generations.

The primary limitations of this study include the small sample size and the imbalance in group sizes, with the AF group being notably smaller than the non-AF group (53 *vs* 126 patients). Additionally, the subgroups receiving different anticoagulant therapies within the AF group are even smaller, which may limit the statistical power and generalizability of the findings. Moreover, one important limitation of the study is the lack of data on adherence to anticoagulant therapy regimens, including the use of DOACs or dicumarol. Information on the time in therapeutic range is also missing, which would have been highly relevant for understanding treatment effectiveness. Additionally, we do not have data on how many patients discontinued anticoagulant therapy during the study, nor do we have records of ischemic or cerebral hemorrhagic events that may have occurred during follow-up. Conversely, the strengths of our study include the long follow-up period. Additionally, the stability of the sample size throughout the study, with no

loss to follow-up, represents another strength, ensuring consistency in data collection and reducing potential biases related to attrition. Finally, the balanced distribution of patients with and without AF, as well as the nearly equal number of patients treated with DOACs and dicoumarols, further enhances the robustness of our findings.

In conclusion, AF itself was not identified as an independent risk factor for cognitive decline once other variables were accounted for. Age and the presence of Alzheimer's disease emerged as the primary factors associated with cognitive decline in this old population, while male sex, age, and MMSE scores were the key variables linked to changes in functional autonomy over time. Larger studies will be needed to confirm these findings and to explore the potential impact of anticoagulant therapy, with particular attention to the different types of direct oral anticoagulants available.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

GT, EM, AC: conceptualisation; GT, EM, CC, AC: methodology; CC, AC: formal analysis and investigation; GT: writing - original draft preparation; CC, AC: writing - review and editing; MDR, MD, AB, BMZ, CC, GS, AC: supervision.

Ethical consideration

The study was conducted in full compliance with the ISHLT ethics guidelines, and the protocol was approved by the local ethics committee (Comitato Etico per la Provincia di Padova, approval number 5234/AO/21). Written informed consent was obtained from all participants prior to their inclusion in the study.

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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