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ORIGINAL ARTICLE

Cognitive phenotypes and factors associated with cognitive decline in a cohort of older patients with atrial fibrillation: The Strat-AF study

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Abstract

Background and purpose: The multifactorial relationship between atrial fibrillation (AF) and cognitive impairment needs to be elucidated. The aim of this study was to assess, in AF patients on oral anticoagulants (OACs), the prevalence of cognitive impairment, defined according to clinical criteria or data-driven phenotypes, the prevalence of cognitive worsening, and factors associated with cognitive outcomes.

Methods: The observational prospective Strat-AF study enrolled AF patients aged ≥ 65 years who were receiving OACs. The baseline and 18-month protocol included clinical, functional, and cognitive assessment, and brain magnetic resonance imaging. Cognitive outcomes were: empirically derived cognitive phenotypes; clinical diagnosis of cognitive impairment; and longitudinal cognitive worsening.

Results: Out of 182 patients (mean age 77.7 ± 6.7 years, 63% males), 82 (45%) received a cognitive impairment diagnosis, which was associated with lower education level and functional status, and higher level of atrophy. Cluster analysis identified three cognitive profiles: dysexecutive (17%); amnestic (25%); and normal (58%). Compared to the normal group, the dysexecutive group was older, and had higher CHA_2DS_2-VASc scores, while the amnestic group had worse cognitive and functional abilities, and medial temporal lobe atrophy (MTA). Out of 128 followed-up patients, 35 (27%) had cognitive worsening that was associated with lower education level, worse cognitive efficiency, CHA_2DS_2-VASc score, timing of OAC intake, history of stroke, diabetes, non-lacunar infarcts, white matter hyperintensities and MTA. In multivariate models, belonging to the dysexecutive or amnestic group was a main predictor of cognitive worsening.

Conclusions: In our cohort of older AF patients, CHA_2DS_2-VASc score, timing of OAC intake, and history of stroke influenced presence, type and progression of cognitive impairment. Empirically derived cognitive classification identified three groups with different clinical profiles and better predictive ability for cognitive worsening compared to conventional clinical diagnosis.

KEYWORDS
atrial fibrillation, cognition, cognitive impairment, cognitive phenotype, older patients

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its incidence and prevalence increases with age. Current evidence strongly suggests an independent association between AF and cognitive impairment, possibly related to cerebrovascular and degenerative neuropathology, even independently of stroke [1–8]. Meta-analyses showed an increased risk of cognitive impairment in AF patients compared to the general population, with hazard ratios (HRs) ranging from 1.3 to 2.3 for dementia and from 1.4 to 3.3 for mild cognitive impairment [9–13]. Looking at dementia subtypes, this association appears to be true for both vascular dementia (HR 1.7, 95% confidence interval [CI] 1.2–2.3) and Alzheimer's disease (HR 1.4, 95% CI 1.2–1.6) [13].

The risk of dementia in AF is significantly increased in patients who have experienced a stroke, but also in those without stroke history. Silent cerebral infarcts, chronic cerebral hypoperfusion, and the coexistence of cerebral small vessel disease and/or degenerative brain changes are key determinants of the association [3–6, 8]. Vascular inflammation, oxidative stress, endothelial dysfunction, and some risk factors (e.g., age, hypertension, diabetes) are associated with AF, and vascular and degenerative brain changes and might have a mediating role [1–8]. Observational studies seem to show a protective effect of oral anticoagulants (OACs) in lowering the risk of cognitive decline in AF patients.

Available evidence does not seem to suggest a different effect of the type of anticoagulant (direct OAC [DOAC] vs. vitamin K antagonist [VKA]) [1–8]. Furthermore, timing of anticoagulation initiation seems relevant as studies showed a reduced risk of cognitive decline among patients in whom treatment had been initiated early after AF diagnosis, suggesting a possible dose–response effect of unprotected time in AF [1–3].

The relationship between AF and cognitive impairment is thus likely to be multifactorial and more data are needed to fill the knowledge gap concerning the pathogenic mechanisms underlying the association beyond stroke [1–7]. Heterogeneity in neuropathology is expected to determine different patterns of cognitive deficits, therefore, we applied a data-driven exploratory approach to empirically derive groups of patients with potential distinctive cognitive phenotypes, and to evaluate their clinical utility with respect to conventional cognitive diagnostic approaches.

The present study aimed to assess in a cohort of older AF patients on OAC therapy for the primary or secondary prevention of stroke: (i) the prevalence of cognitive impairment, defined according to clinical criteria or data-driven phenotypes, and associated factors and (ii) the prevalence of cognitive worsening and associated predictors.

METHODS

The Strat-AF (Stratification of cerebral bleeding risk in AF) study is an observational prospective single-center hospital-based study that enrolled patients with diagnosis of AF, aged ≥ 65 years, on OACs for the primary or secondary prevention of thromboembolic events, and with no contraindications to magnetic resonance imaging (MRI). Consecutive eligible patients referred to the Atherothrombotic Diseases Outpatient Clinic of Careggi University Hospital were invited to participate in the study. The study was conducted in accordance with the Helsinki Declaration, the protocol was approved by the Ethics Committee of the Careggi University Hospital (Florence, Italy), and all participants gave written informed consent. Study design and methodology have been previously described in detail [14]. At baseline and at 18-month follow-up, each patient underwent an extensive clinical, cognitive, functional assessment, and brain MRI.

Data on demographic characteristics (age, sex, years of education), previous stroke, AF type (paroxysmal or permanent/persistent), OAC type (VKA or DOAC), duration of OAC (months), electrical and pharmacological cardioversion, vascular risk factors and comorbidities (hypertension, diabetes, dyslipidemia, physical activity, smoking habits, alcohol consumption, ischemic heart disease) were collected. Initiation of OAC with respect to AF diagnosis was also considered and dichotomized as starting OAC concomitant with AF diagnosis (≤1 month after diagnosis) versus starting OAC after AF diagnosis (≥2 months after diagnosis). Thromboembolic and major bleeding risk profiles were estimated by means of the CHA_2DS_2-VASc and HAS-BLED scores, respectively [15–17].

Cognitive and functional protocol

The Strat-AF neuropsychological battery included the Montreal Cognitive Assessment (MoCA) as a global cognitive functioning test and six second-level tests for the evaluation of verbal memory (Rey Auditory-Verbal Learning immediate and delayed recall; short story recall), attention and executive functions (visual search; Color Word Stroop test), and language (semantic verbal fluency test based on animals, fruits and brands of cars; sentence construction test) [14]. Using national normative data, raw scores from the neuropsychological tests were adjusted for demographics and converted into an ordinal five-point scale according to the equivalent score (ES) non-parametric norming method widely applied in Italian normative studies [18]. ES calculation is based on percentile distributions, and scores range from ES = 0 (impaired performance, i.e., adjusted score below the outer confidence limit for the 5th centile of the normal population) to ES = 1 (borderline performance, i.e., adjusted score between the outer and inner confidence limits for the 5th centile of the normal population) and ES = 2–4 (normal performance, i.e.,

adjusted score above the inner confidence limit for the 5th centile of the normal population).

Functional status was evaluated by means of Activities of Daily Living scale (number of preserved items, score range 0–6, higher scores: less disability) and Instrumental Activities of Daily Living scale (number of impaired items, score range 0–8, higher scores: more disability) [19, 20].

Neuroimaging protocol

Brain MRI was performed on a 1.5-T MRI scanner (Ingenia; Philips Healthcare). The MRI protocol included the following sequences: sagittal T1-weighted spin-echo, coronal T2-weighted turbo spin-echo; axial fluid-attenuated inversion recovery (FLAIR); axial gradient-echo T2* fast field echo; axial diffusion-weighted imaging; sagittal magnetization prepared rapid acquisition gradient-echo 3D T1-weighted imaging, followed by multiplanar reconstruction in axial, coronal and sagittal planes.

Cerebral lesion burden was visually assessed by a trained and experienced rater using validated scales and included the following markers:

- White matter hyperintensities (WMH), rated on axial FLAIR sequences using the following scales: (i) modified Fazekas scale, which defines three grades of deep WMH severity: mild (single lesions < 10 mm; areas of "grouped" lesions < 20 mm in any diameter), moderate (single hyperintense lesions between 10 and 20 mm; areas of "grouped" lesions ≥ 20 mm in any diameter; no more than "connecting bridges" between individual lesions), and severe (single lesions or confluent areas of hyperintensity ≥ 20 mm in any diameter) [21]; (ii) van Swieten scale which evaluates anterior and posterior white matter regions and defines three grades of lesion severity: nothing or one lesion, multiple focal lesions, and multiple confluent lesions [22].
- Cerebral microbleeds (CMBs), rated on axial gradient-echo T2* sequences according to the Microbleeds Anatomical Rating Scale, which identifies "definite" microbleeds as small, rounded or circular, well-defined hypointense lesions within brain parenchyma with clear margins ranging from 2 to 10 mm in size, and classified location as deep, infratentorial, and lobar [23];
- Lacunar infarcts, which were defined as small (3–15 mm in diameter) round or ovoid, subcortical, fluid-filled cavities, usually surrounded by a hyperintense rim, and were rated on T2 and FLAIR sequences;
- Non-lacunar infarcts, which were defined as cortical or subcortical (>15 mm in diameter) lesions in vascular territories, and were rated on T1-weighted and FLAIR sequences;
- Global cortical atrophy, rated according to the 0–3-point Pasquier scale on axial T1 or FLAIR sequences [24];
- Medial temporal lobe atrophy (MTA), rated for the left and right side using the 0–4-point Scheltens visual scale on coronal T1 sequences [25].

According to the STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) criteria we considered WMH, CMBs, lacunar infarcts, and global cortical atrophy as markers of cerebral small vessel disease [26].

Statistical analyses

Descriptive statistics (frequencies and percentages, means and standard deviations) were used to describe the total cohort in terms of baseline demographics, vascular risk factors, comorbidities, history of stroke, and cognitive, functional and neuroimaging characteristics.

The ESs of the seven second-level cognitive tests of the neuropsychological battery (excluding MoCA) were used for the determination of all cognitive outcomes:

- Clinical diagnosis of cognitive impairment at baseline: defined as the presence of at least one impaired test (ES = 0; adjusted score below the outer confidence limit for the 5th centile of the normal population);
- Empirically derived cognitive phenotypes at baseline: K-means cluster analysis was performed to investigate the existence of distinctive cognitive profiles according to a data-driven exploratory approach. The seven ESs of the second-level cognitive tests were entered into the models and three models of analyses were carried out to evaluate solutions with 2, 3 or 4 clusters;
- Clinical diagnosis of cognitive worsening at follow-up: defined as the presence of at least one new impaired test (ES = 0) from the baseline evaluation.

Univariate analyses (non-parametric Mann–Whitney *U*-test or Pearson's chi-squared tests) were used to compare patients with or without cognitive impairment at baseline in terms of demographics, vascular risk factors, comorbidities, history of stroke, thromboembolic and major bleeding risk profiles, functional status, and neuroimaging characteristics. The same models of analyses were used to compare patients with or without cognitive worsening at follow-up.

Clusters were compared on baseline demographics, vascular risk factors, comorbidities, history of stroke, functional and neuroimaging characteristics by means of non-parametric Kruskal–Wallis and Pearson's chi-squared tests. The level of concordance between clinical diagnosis of cognitive impairment and classification obtained by cluster analysis was evaluated by means of Cohen's κ coefficient.

Patients who completed the study and drop-outs, and patients with or without brain MRI, were compared by means of non-parametric Mann–Whitney *U*-tests or Pearson's chi-squared tests with regard to the following baseline characteristics: demographics; cognitive and functional status; and thromboembolic and major bleeding risk profiles.

Multivariate logistic regression models were used to evaluate the independent association between cognitive worsening and those baseline variables which were significantly associated in univariate

analyses. To evaluate the association between cognitive worsening and belonging to specific data-driven cognitive phenotypes, the cluster classification was coded in dummy variables corresponding to each group separately.

For analyses purposes, neuroimaging characteristics were categorized as follows:

- Lacunar and non-lacunar infarcts were coded as absent versus present;
- WMH and global cortical atrophy were dichotomized as absent–mild versus moderate–severe (modified Fazekas score 0–1 vs. 2–3, Pasquier score 0–1 vs. 2–3, respectively);
- Definite CMBs were coded as absent versus present both globally and in two locations: "deep or infratentorial" versus "lobar";
- Mean MTA of the bilateral scores was dichotomized as normal versus abnormal according to the following age-decade-adjusted cut-offs: (i) age range 65–74 years: mean MTA ≥ 1.5, which was the cut-off to be considered abnormal; (ii) age range 75–84 years: mean MTA ≥ 2; and (iii) age ≥ 85 years: MTA ≥ 2.5 [27].

All analyses were performed using the SPSS software version 27.

RESULTS

From September 2017 to March 2019, out of the 194 subjects enrolled in the Strat-AF study, 182 (mean age 77.7 ± 6.7 years, 63% males) completed all cognitive tests of the baseline neuropsychological protocol and were included in the present study. Demographic, vascular risk factors, clinical and neuroimaging characteristics of the total cohort are shown in Tables 1 and 2. Brain MRI assessment was available for 163 patients. Compared to patients with neuroimaging information, those without were more frequently female (33% vs. 74%, chi-squared test, $p < 0.001$), while there were no other differences in terms of demographics, cognitive and functional status, and thromboembolic and major bleeding risk profiles.

Among the 182 patients, 82 (45%) received a diagnosis of cognitive impairment. The percentage distributions of normal, borderline, and impaired performances in second-level cognitive tests are shown in Figure 1. The Rey Auditory-Verbal Learning and the Color Word Stroop tests were the most difficult, with a borderline/impaired performance in at least the 25% of patients. Conversely, semantic fluency was mostly normal (94%). Compared to cognitively intact patients, those with cognitive impairment were less educated, more dependent in instrumental activities of daily living, and had a worse global cognitive efficiency (MoCA), and a higher degree of both global cortical and MTA (Table 1). Considering AF and OAC treatment characteristics, patients with cognitive impairment had a shorter duration of OAC and had less frequently received pharmacological cardioversion (Table 2).

The optimal solution of the cluster analysis resulted in three distinct groups (Figure 2). The first group ($n = 32$) was classified as mainly "dysexecutive" based on performances on the Stroop test. The second group ($n = 45$) was identified as mainly "amnestic" based on performances on the Rey Auditory-Verbal Learning test. The third group ($n = 105$) was considered as "normal" based on a cognitive profile above the normality thresholds in all cognitive tests. As reported in Tables 1 and 2, group comparisons on baseline characteristics showed the following: patients in the dysexecutive group were older and had higher thromboembolic risk as measured by the CHA_2DS_2-VASc score despite a lower frequency of smoking habits and alcohol consumption, those in the amnestic group had the worse global cognitive efficiency, more dependency in instrumental activities of daily living and more abnormal degrees of MTA. Patients in the normal group were the most educated, were mainly men, less frequently had a history of stroke or evidence of non-lacunar infarcts on neuroimaging, and had the highest duration of OAC therapy and frequency of pharmacological cardioversion.

Considering the highest duration of OAC therapy in cognitively normal patients in both clinical and cluster groups, a correlation analysis of the association between OAC duration and MoCA score was conducted separately in patients starting OACs concomitant with AF diagnosis versus patients starting OACs after AF diagnosis. As shown in Figure 3, a shorter OAC therapy duration was associated with lower global cognitive efficiency, as measured by MoCA, only in patients who started OAC after AF diagnosis.

Out of the 182 patients, 128 (70.5%) were re-evaluated at a mean time interval of 17 ± 2.2 months and completed the neuropsychological assessment, 50 (27.5%) dropped out, and four (2%) died. Compared to patients who completed the study, drop-outs were older (mean age 77.1 ± 6.6 vs. 79.4 ± 6.8 years, respectively; $p = 0.033$), less educated (mean years of education 9.9 ± 4.2 vs. 7.5 ± 3.7; $p = 0.001$), and more frequently female (33% vs. 52%; $p = 0.018$).

Among the 128 patients, 35 (27%) presented cognitive worsening. The association between cognitive impairment and worsening is shown in Figure 4: 19% (14/72) of cognitively normal patients and 37.5% (21/56) of cognitively impaired patients presented cognitive worsening (chi-squared test, $p = 0.023$). Among the groups of patients derived from cluster analysis those belonging to the normal group had lower rates of cognitive worsening (12%) compared to those belonging to the dysexecutive (45%) and amnestic (55%) groups (chi-squared test, $p < 0.001$; Figure 4).

The level of concordance between the clinical diagnosis of cognitive impairment and the classification obtained by the cluster analysis was good (Cohen's $\kappa = 0.699$). However, 11 patients clinically categorized as without cognitive impairment were classified within the dysexecutive ($n = 8$) or amnestic ($n = 3$) groups. Sixteen patients who received a clinical diagnosis of cognitive impairment were classified as normal by cluster analysis. Interestingly, looking at the association with cognitive worsening, nearly all patients (93%) classified as normal by cluster analysis and with a clinical diagnosis of cognitive impairment did not worsen, while the majority (67%) of those classified as clinically normal but not normal for the cluster analysis presented cognitive worsening (chi-squared test, $p = 0.007$).

TABLE 1 Baseline characteristics of the overall cohort and comparisons between patients with and without cognitive impairment and the cognitive groups resulting from cluster analysis.

	Overall cohort, $n = 182$	Baseline cognitive impairment			Cluster classification			
		No, $n = 100$	Yes, $n = 82$	p	Dysexecutive, $n = 32$	Amnestic, $n = 45$	Normal, $n = 105$	p
Age, years	77.7 ± 6.7	77.1 ± 6.5	78.4 ± 6.8	0.219[b]	**81.1 ± 6.3**	**77.4 ± 6.2**	**76.8 ± 6.7**	**0.003**[c]
Years of education	9.4 ± 4.2	**9.9 ± 4.2**	**8.7 ± 4.2**	**0.035**[b]	**7.3 ± 3.6**	**8.5 ± 3.7**	**10.4 ± 4.4**	**0.001**[c]
Sex: male, *n* (%)	114 (63)	66 (66)	48 (58)	0.300[d]	**14 (44)**	**26 (58)**	**74 (70)**	**0.018**[d]
MoCA (score range 0–30)	22.1 ± 3.6	**23.3 ± 3.1**	**20.5 ± 3.6**	**0.001**[b]	**21.5 ± 2.9**	**18.9 ± 3.6**	**23.5 ± 2.9**	**0.001**[c]
Activities of daily living (preserved items, range 0–6)	5.7 ± 0.6	5.8 ± 0.6	5.7 ± 0.7	0.245[b]	5.7 ± 0.5	5.7 ± 0.8	5.8 ± 0.6	0.641[c]
Instrumental activities of daily living (impaired items, range 0–8)	0.4 ± 1.1	**0.2 ± 0.5**	**0.7 ± 1.5**	**0.001**[b]	**0.4 ± 0.7**	**0.9 ± 1.6**	**0.2 ± 0.8**	**0.001**[c]
CHA_2DS_2-VASc score	3.7 ± 1.4	3.5 ± 1.3	3.9 ± 1.5	0.097[b]	**4.5 ± 1.4**	**3.9 ± 1.5**	**3.3 ± 1.2**	**0.001**[c]
HAS-BLED score	1.7 ± 0.8	1.7 ± 0.8	1.8 ± 0.8	0.320[b]	1.8 ± 0.9	1.9 ± 0.8	1.7 ± 0.8	0.309[c]
History of stroke, *n* (%)	38 (21)	17 (17)	21 (26)	0.155[d]	**8 (25)**	**16 (36)**	**14 (13)**	**0.007**[d]
Hypertension, *n* (%)	148 (81)	82 (82)	66 (81)	0.795[d]	29 (91)	34 (76)	85 (81)	0.244[d]
Diabetes, *n* (%)	23 (13)	11 (11)	12 (15)	0.463[d]	5 (16)	9 (20)	9 (9)	0.133[d]
Dyslipidemia, *n* (%)	92 (50)	47 (47)	45 (55)	0.290[d]	18 (56)	21 (47)	53 (51)	0.709[d]
Physical activity, *n* (%)	64 (35)	39 (39)	25 (30)	0.231[d]	9 (28)	12 (27)	43 (41)	0.160[d]
Smoking habits, *n* (%)	117 (64)	67 (67)	50 (61)	0.399[d]	**15 (47)**	**27 (60)**	**75 (71)**	**0.031**[d]
Alcohol consumption, *n* (%)	97 (53)	59 (59)	38 (46)	0.089[d]	**12 (38)**	**21 (48)**	**64 (61)**	**0.039**[d]
Ischemic heart disease, *n* (%)	24 (13)	13 (13)	11 (13)	0.934[d]	6 (19)	5 (11)	13 (12)	0.579[d]
White matter hyperintensities								
Modified Fazekas scale (moderate–severe)[a], *n* (%)	35 (21)	19 (22)	16 (21)	0.903[d]	6 (21)	6 (15)	23 (24)	0.441[d]
van Swieten total score (range 0–8)[a]	3.3 ± 2.9	3.1 ± 2.8	3.5 ± 3.1	0.330[b]	4.1 ± 2.7	3.2 ± 3.1	3.1 ± 2.9	0.259[c]
Non-lacunar infarcts (≥1)[a]	50 (31)	22 (25)	28 (37)	0.111[d]	**10 (36)**	**18 (44)**	**22 (23)**	**0.049**[d]
Lacunar infarcts (≥1)[a], *n* (%)	53 (32)	32 (37)	21 (28)	0.213[d]	7 (25)	15 (37)	31 (33)	0.595[d]
Cerebral microbleeds (≥1)[a], *n* (%)	28 (17)	16 (18)	12 (16)	0.660[d]	3 (11)	7 (17)	18 (19)	0.583[d]
Cortical atrophy (moderate–severe)[a], *n* (%)	128 (78)	**63 (72)**	**65 (86)**	**0.042**[d]	24 (86)	34 (83)	70 (74)	0.325[d]
Medial temporal lobe atrophy (abnormal)[a], *n* (%)	105 (65)	**50 (57)**	**55 (73)**	**0.035**[d]	**17 (61)**	**33 (82)**	**55 (58)**	**0.026**[d]

Note: Data are means and standard deviations or frequencies and percentages.

Bold indicates statistically significant results.

Abbreviation: MoCA, Montreal Cognitive Assessment.

[a]Data available in 163 patients (clinical diagnosis: without cognitive impairment $n = 87$, with cognitive impairment $n = 76$; cluster classification: Dysexecutive $n = 28$, Amnestic $n = 41$, Normal $n = 94$).

[b]Mann–Whitney *U*-test.

[c]Kruskal–Wallis test.

[d]Chi-squared test.

Comparison of baseline characteristics between patients with or without cognitive worsening are shown in Table 3. Patients with cognitive worsening belonged mainly to the amnestic group, were less educated, more frequently had a history of diabetes, stroke, non-lacunar infarcts, and a higher burden of WMH and MTA, started OAC therapy more frequently after AF diagnosis, and presented a higher thromboembolic risk (CHA_2DS_2-VASc score) and baseline worse global cognitive efficiency.

Overall, considering the impact of neuroimaging characteristics on cognitive outcomes, no statistically significant association was found for lacunar infarcts and CMBs (Tables 1 and 3). From the descriptive point of view, Figure 5 shows the distribution of CMB locations with respect to cognitive outcomes, and CMBs in deep regions seemed slightly underrepresented in patients with normal cognitive status.

Multivariate logistic regression models were computed including cognitive worsening as the dependent variable, and all the

TABLE 2 Characteristics of atrial fibrillation and oral anticoagulant therapy in the overall cohort and comparisons according to cognitive outcome: patients with or without baseline cognitive impairment, cognitive groups resulting from cluster analysis, patients with or without cognitive worsening at follow-up.

		Baseline cognitive impairment			Cluster classification				Cognitive worsening		
	Total cohort, $n = 182$	No, $n = 100$	Yes, $n = 82$	p	Dysexecutive, $n = 32$	Amnestic, $n = 45$	Normal, $n = 105$	p	No, $n = 93$	Yes, $n = 35$	p
Type of AF (paroxysmal), *n* (%)	88 (48)	49 (49)	39 (48)	0.847[a]	17 (53)	22 (49)	49 (48)	0.812[a]	45 (48)	16 (46)	0.787[a]
Duration of OAC therapy (months)	54.9 ± 54.7	**62.5 ± 59.9**	**45.8 ± 46.3**	**0.035**[b]	**33.1 ± 28.7**	**48.2 ± 49.9**	**64.5 ± 60.4**	**0.010**[c]	60.9 ± 59.9	46.8 ± 53.1	0.264[b]
Starting OAC after AF diagnosis, *n* (%)	67 (34)	38 (38)	25 (30)	0.289[a]	9 (28)	15 (33)	39 (37)	0.630[a]	**29 (31)**	**18 (51)**	**0.034**[a]
Electrical cardioversion, *n* (%)	63 (35)	39 (39)	24 (29)	0.170[a]	8 (25)	12 (27)	43 (41)	0.109[a]	38 (41)	10 (29)	0.201[a]
Pharmacological cardioversion, *n* (%)	36 (20)	**26 (26)**	**10 (12)**	**0.020**[a]	**6 (19)**	**2 (4)**	**28 (27)**	**0.007**[a]	18 (19)	5 (14)	0.506[a]
Type of OAC therapy (VKAs), *n* (%)	57 (31)	32 (32)	25 (30)	0.827[a]	8 (25)	13 (29)	36 (34)	0.563[a]	32 (34)	12 (34)	0.990[a]
	$n = 48$	$n = 26$	$n = 22$		$n = 7$	$n = 11$	$n = 30$		$n = 29$	$n = 10$	
Time in therapeutic range (VKAs)	75.9 ± 17.1	77.6 ± 18.5	73.9 ± 15.6	0.431[b]	79.9 ± 15.7	68.6 ± 16.5	77.7 ± 17.4	0.288[c]	76.4 ± 16.5	76.1 ± 20.8	0.937[b]
Time in therapeutic range ≥70 (VKAs), *n* (%)	31 (65)	17 (65)	14 (64)	0.900[a]	5 (71)	6 (54)	20 (67)	0.710[a]	19 (65)	7 (70)	0.795[a]

Note: Data are presented as means and standard deviations or frequencies and percentages.

Bold indicates statistically significant results.

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulant; VKA, vitamin K antagonist.

[a]Chi-squared test.

[b]Mann–Whitney *U*-test.

[c]Kruskal–Wallis test.

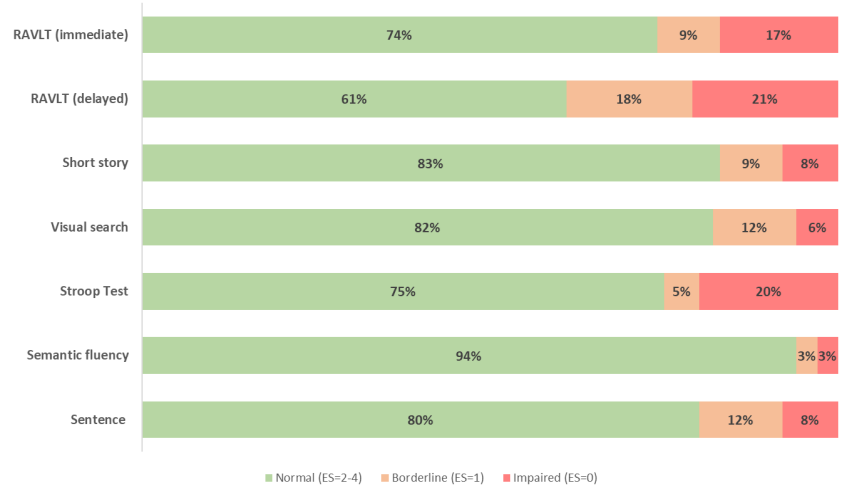

FIGURE 1 Baseline percentage distributions of normal, borderline and impaired performances in second-level cognitive tests. ES, equivalent score; RAVLT, Rey Auditory-Verbal Learning test

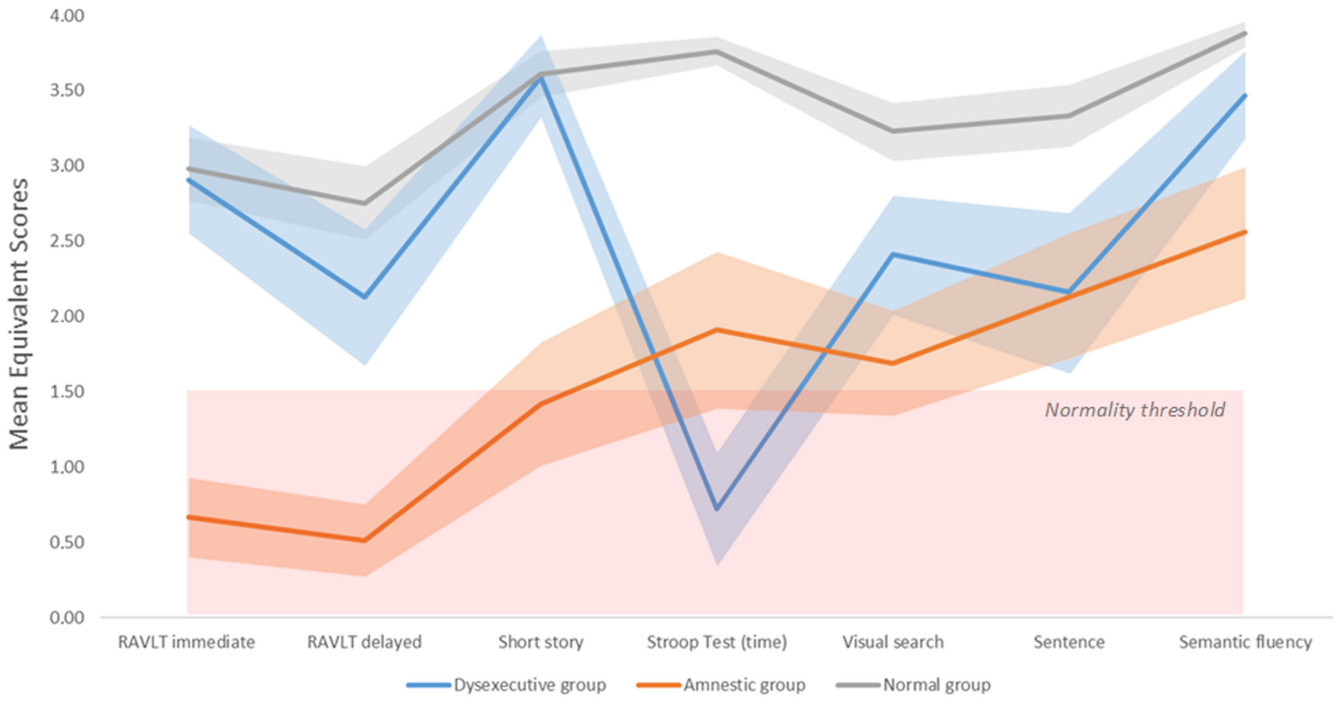

FIGURE 2 Mean and 95% confidence intervals of equivalent scores of second-level cognitive tests across groups resulting from cluster analysis. RAVLT, Rey Auditory-Verbal Learning test

above-mentioned potential predictors and either history of stroke or non-lacunar infarcts (in order to avoid multicollinearity) as independent variables. As shown in Table 3, belonging to the dysexecutive (odds ratio [OR] 17.3, 95% CI 3.2–94.7) or amnestic group (OR 9.7, 95% CI 2.4–38.7) remained significant predictors of cognitive worsening, together with history of stroke (OR 8.7, 95% CI 1.4–52.9) and delayed OAC initiation with respect to AF diagnosis (OR 0.3, 95% CI 0.1–0.9). The same results were obtained in the model adjusted for non-lacunar infarcts instead of history of stroke: belonging to the dysexecutive (OR 11.9, 95% CI 2.5–57.6) or amnestic group (OR 7.9, 95% CI 2.1–30.1) was confirmed as a predictor of cognitive worsening, together with delayed initiation of OACs with respect to AF diagnosis (OR 0.3, 95% CI 0.1–0.9). When the same multivariate logistic regression models were repeated using clinical diagnosis instead of cluster classification, baseline cognitive impairment was not significantly associated with longitudinal cognitive worsening (data not shown).

DISCUSSION

In a sample of older patients with diagnosis of AF and ongoing anticoagulant therapy, we examined the prevalence of cognitive impairment, defined either according to clinical criteria or data-driven phenotypes, the prevalence of cognitive worsening, and the clinical and neuroimaging characteristics associated with cognitive outcomes.

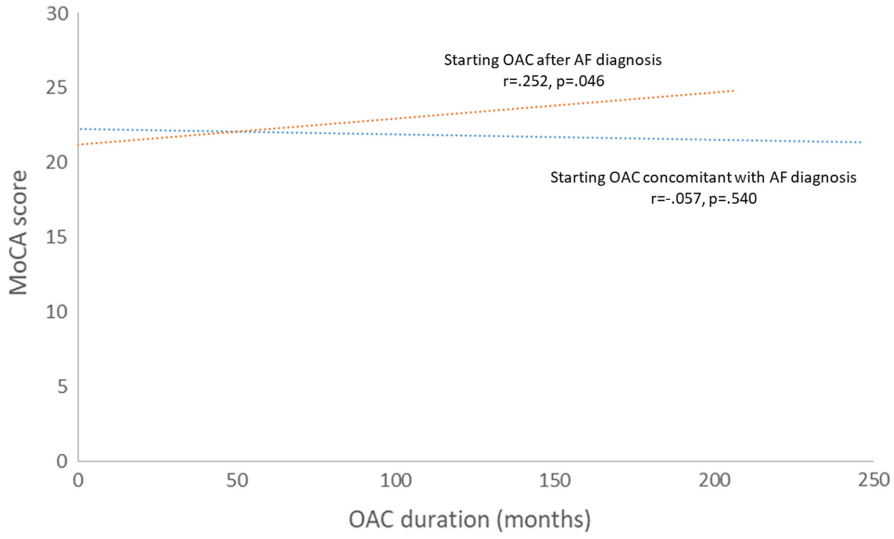

FIGURE 3 Associations between oral anticoagulant (OAC) therapy duration and Montreal Cognitive Assessment (MoCA) score in patients starting OAC concomitant with an atrial fibrillation (AF) diagnosis ($n = 119$) versus patients starting OACs after AF diagnosis ($n = 63$).

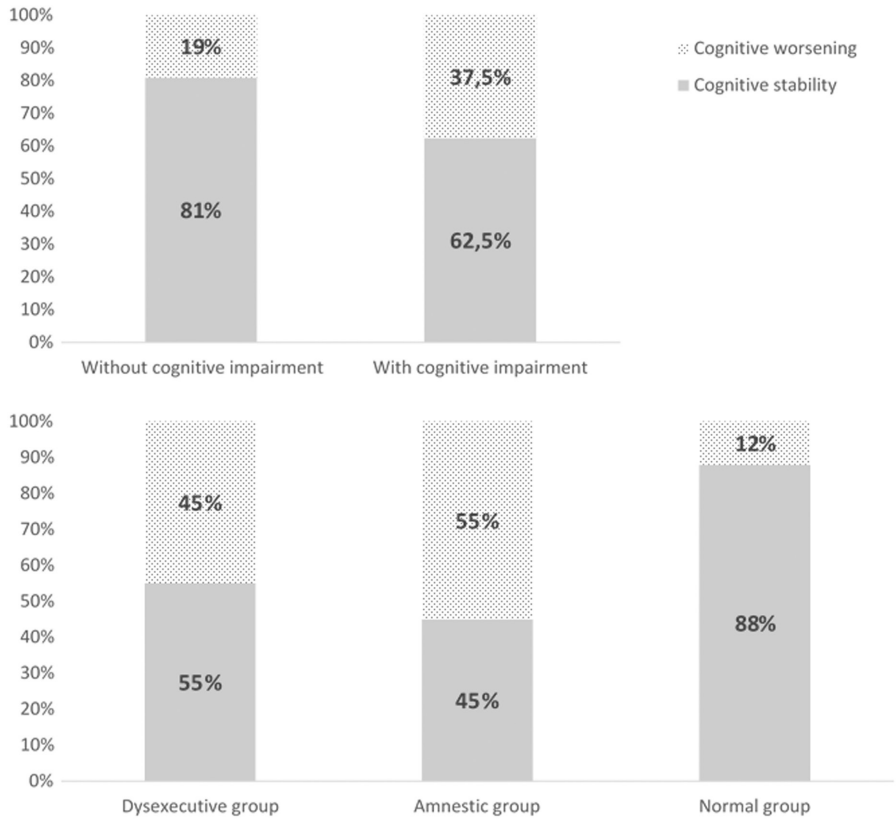

FIGURE 4 Association between cognitive worsening at follow-up and presence of baseline cognitive impairment (chi-squared test, $p = 0.023$) or belonging to clustered groups (chi-squared test, $p < 0.001$).

Overall, 45% of the study cohort had baseline cognitive impairment and 27% showed cognitive worsening during 18 months of follow-up. Our results on the prevalence of cognitive impairment in AF are in line with other cross-sectional studies, with rates of cognitive impairment ranging from 47% to 54% [9]. Presence or progression of cognitive impairment were associated with education level, global cognitive efficiency, thromboembolic risk, functional dependency, and history of stroke. Interestingly the association between CHA_2DS_2-VASc score and dementia has already been reported, stressing the importance of cognitive evaluation in AF patients with high CHA_2DS_2-VASc scores [28, 29].

Considering the possible role of OACs, in line with the hypothesis of a protective effect of treatment on cognitive outcomes, our results showed that cognitively normal patients presented a longer duration of OAC treatment than cognitively impaired patients, without an effect of OAC type (DOAC vs. VKA), and of time in therapeutic range in patients treated with VKAs [1–8]. Out results are in line with evidence from recent studies that found no difference in cognitive outcomes comparing type of OAC in older adults with AF [30–34]. Despite our sub-analyses of patients on VKAs being underpowered because of the very limited sample size, our results replicated evidence from the GIRAF trial concerning the lack of an association between time in

TABLE 3 Association between baseline characteristics and the occurrence of a cognitive worsening at the follow-up visit ($n = 128$).

	Cognitive worsening			
	No, $n = 93$	Yes, $n = 35$	p	Multivariate models, OR (95% CI)[a]
Age, years	76.8 ± 6.5	77.6 ± 6.9	0.437[b]	
Years of education	**10.4 ± 4.3**	**8.7 ± 3.6**	**0.032**[b]	ns
Sex: males, *n* (%)	64 (69)	22 (63)	0.522[c]	
MoCA (range 0–30)	**22.9 ± 3.2**	**20.6 ± 3.8**	**0.001**[b]	ns
Belonging to normal cluster, *n* (%)	**68 (73)**	**9 (25.5)**	**0.001**[c]	Reference category
Belonging to dysexecutive cluster, *n* (%)	**12 (13)**	**10 (28.5)**	**0.036**[c]	**17.3 (3.2-94.7)**
Belonging to amnestic cluster, *n* (%)	**13 (14)**	**16 (46)**	**0.001**[c]	**9.7 (2.4-38.7)**
Activities of daily living (preserved items, range 0–6)	5.8 ± 0.4	5.5 ± 0.8	0.064[b]	
Instrumental activities of daily living (impaired items, range 0–8)	0.2 ± 0.9	0.7 ± 1.6	0.058[b]	
CHA_2DS_2-VASc score	**3.4 ± 1.3**	**4.2 ± 1.5**	**0.010**[b]	ns
HAS-BLED score	1.7 ± 0.8	2.0 ± 0.9	0.073[b]	
History of stroke, *n* (%)	**15 (16)**	**14 (40)**	**0.004**[c]	**8.7 (1.4-52.9)**
Hypertension, *n* (%)	77 (83)	26 (74)	0.279[c]	
Diabetes, *n* (%)	**8 (9)**	**8 (23)**	**0.030**[c]	ns
Dyslipidemia, *n* (%)	54 (58)	17 (49)	0.335[c]	
Physical activity, *n* (%)	38 (41)	10 (29)	0.201[c]	
Smoking habits, *n* (%)	64 (69)	21 (60)	0.347[c]	
Alcohol consumption	57 (61)	16 (46)	0.113[c]	
Ischemic heart disease	11 (12)	7 (20)	0.236[c]	
White matter hyperintensities				
Modified Fazekas scale (moderate–severe)[d], *n* (%)	20 (22)	4 (12)	0.225[c]	
van Swieten total score (range 0–8)[d]	**3 ± 2.8**	**4.3 ± 2.9**	**0.023**[b]	ns
Non-lacunar infarcts (≥1)[d], *n* (%)	**23 (26)**	**17 (53)**	**0.005**[c]	
Lacunar infarcts (≥1)[d], *n* (%)	26 (29)	13 (41)	0.236[c]	
Cerebral microbleeds (≥1)[d], *n* (%)	13 (15)	7 (22)	0.342[c]	
Cortical atrophy (moderate--severe)[d], *n* (%)	69 (77)	23 (72)	0.521[c]	
Medial temporal lobe atrophy (abnormal)[d], *n* (%)	**49 (55)**	**25 (78)**	**0.022**[c]	ns

Note: Data are presented as means and standard deviations or frequencies and percentages.

Bold indicates statistically significant results.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; MoCA, Montreal Cognitive Assessment; ns, nonsignificant; OAC, oral anticoagulant; OR, odds ratio.

[a]Multivariate logistic regression model adjusted for education, MoCA, belonging to either the dysexecutive or the amnestic cluster (normal cluster: reference category), CHA_2DS_2-VASc score, history of stroke, diabetes, OAC initiation with respect to AF diagnosis (starting OAC concomitant with AF diagnosis vs. starting OAC after AF diagnosis), van Swieten total score, and medial temporal atrophy.

[b]Mann–Whitney *U*-test.

[c]Chi-squared test.

[d]Data available in 121 patients ($n = 89$ cognitively stable, and $n = 32$ cognitively worsened).

therapeutic range and cognitive outcome [30]. Similarly to the GIRAF study, a possible selection bias should be considered as a factor that limits the generalizability of our results. The Strat-AF study included a cohort of AF patients that were very well managed from the therapeutic point of view as all of them attended the Outpatient Clinic of the Atherothrombotic Diseases Department at our university hospital. In our cohort, a potential role of OAC timing also emerged: patients who started OAC therapy more than 2 months after AF diagnosis presented a higher risk of cognitive worsening over time, and their cognitive efficiency seemed to be better maintained as a function of longer OAC intake. Unfortunately, the study protocol did not include data on the reasons why patients started OAC therapy after AF diagnosis, and this further restricted our ability to clarify the role of OAC intake timing with respect to cognitive outcomes. Finally, our data appear to suggest a possible protective effect of cardioversion on cognitive decline, but this issue requires further evaluation.

In our cohort, cluster analysis identified three distinctive cognitive phenotypes: one normal profile and two characterized by

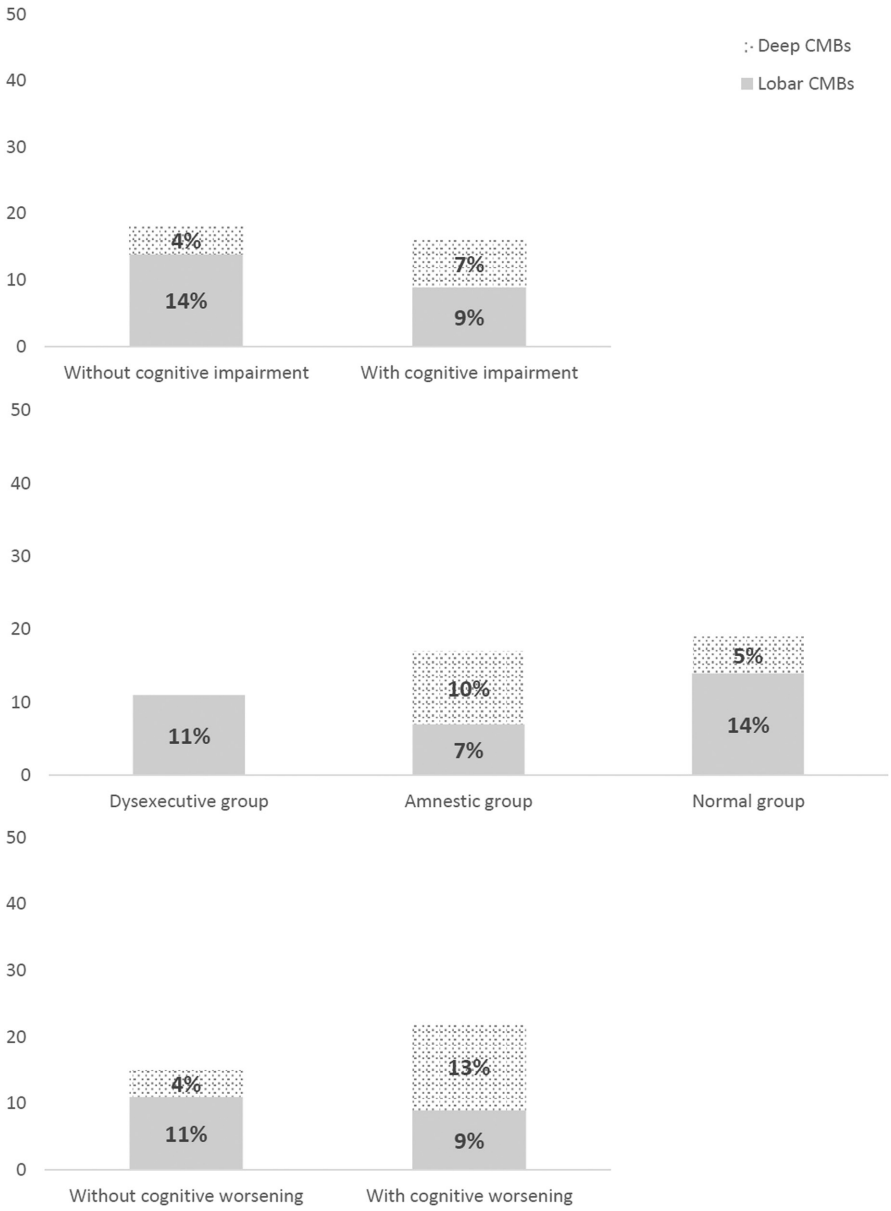

FIGURE 5 Association between cerebral microbleed (CMB) location and cognitive outcomes: presence of baseline cognitive impairment (chi-squared test, $p = 0.350$), belonging to clustered groups (chi-squared test, $p = 0.167$), cognitive worsening at follow-up (chi-squared test, $p = 0.128$).

deficits within the memory and executive function domains. To a certain extent, the two cognitive phenotypes identified in our sample may resemble the typical profiles of cognitive deficits due to cerebrovascular (dysexecutive) or neurodegenerative (amnestic) mechanisms. History of stroke and non-lacunar infarcts on brain MRI were significantly less frequent in the normal cluster, but very similar between amnestic and dysexecutive clusters. This latter phenotype seemed to be characterized by older age with a higher thromboembolic risk profile. On the other hand, the amnestic phenotype had the worst cognitive and functional status and higher burden of MTA.

The overall level of concordance between a clinical diagnosis of cognitive impairment and the empirically derived classification was acceptable, but the latter was more consistently associated with cognitive changes over time. Compared to patients with a clinical diagnosis of cognitive impairment, the empirically derived dysexecutive and amnestic groups presented higher rates of cognitive worsening (37.5% vs. 45% and 55%, respectively). Similarly, almost none of the patients classified as clinically impaired but empirically normal presented cognitive worsening. Each empirically derived cognitive phenotype was an independent predictor of cognitive worsening. Baseline normal phenotype showed a protective effect, while dysexecutive and amnestic phenotypes strongly predicted cognitive worsening, with a higher risk related to the amnestic group.

Within the debate on the empirical validity of conventional cognitive diagnostic approaches, the contribution of statistical clustering techniques in identifying cognitive heterogeneity in neurological and psychiatric patient populations is increasingly recognized [35, 36]. Considering the lack of conclusive evidence on the principal pathogenic mechanisms and clinical hallmarks of the complex relationship between AF and cognitive decline, we decided to apply a data-driven exploratory approach to empirically derive groups of patients with distinctive cognitive phenotypes. Our results seemed to highlight better clinical utility and prognostic value of the empirically derived cognitive classification compared to the conventional clinical criteria.

Overall, our results in terms of cognitive phenotypes are in line with the hypothesis of a relationship between AF and cognitive impairment mediated by cerebrovascular and/or degenerative lesion burden [1–8]. Unfortunately, the very limited associations between cognitive profiles and available MRI markers require caution in the interpretation of the possible underlying mechanisms. However, taking into account the only available marker for neurodegeneration, higher MTA burden within the amnestic group seems to support a potential homogeneity of this phenotype in terms of clinical and pathogenic expressions. From the methodological point of view, the neuroimaging assessment based on visual scales and the dichotomization of MRI markers represents a limitation that might have reduced the accuracy in the quantification of cerebral lesions burden, and thus likely underestimated its impact on cognitive outcomes. Moreover, the sub-analyses on the topography of CMBs would have the potential to underlie distinct pathophysiological mechanisms, such as amyloid angiopathy versus arterial hypertension, but our results are heavily underpowered by the limited sample size. Finally, except for MTA, no other markers of neurodegeneration, such as cerebrospinal fluid biomarkers and positron emission tomography imaging, were available. The extraction of quantitative brain volumetric and morphometric measures is ongoing, and further analyses will be conducted in this cohort to better elucidate the role of cerebrovascular and neurodegenerative mechanisms in AF-related cognitive impairment.

Further limitations of our study need to be considered. First, the sample size was small and met the minimal requirements for a cluster analysis; this was therefore applied as an exploratory approach to identify possible patterns in the data. Although the data-driven approach could also represent a strength of the study, the sample size means that caution must be applied in the interpretation and generalization of our results, and this first empirical attempt needs to be further evaluated in other populations of AF patients. Moreover, the sample size limited our ability to explore the impact of treatment type and duration extensively, as well as the impact of cardioversion.

In conclusion, in a cohort of older AF patients, our study confirms the high prevalence of cognitive impairment and highlights the existence of two cognitive phenotypes suggestive of the two most frequent subtypes of dementia, namely, vascular dementia and Alzheimer's disease, and potentially prognostic of cognitive progression over time. Deeper understanding of the potential pathological substrate may help to develop appropriate preventive and therapeutic interventions to counteract the risk of cognitive consequences in AF patients, and further studies are needed to better evaluate the interaction between presence and different phenotypes of cognitive impairment and their determinants and mechanisms.

AUTHOR CONTRIBUTIONS

Emilia Salvadori: Conceptualization; investigation; writing – original draft; methodology; formal analysis; supervision; data curation. **Eleonora Barucci:** Writing – review and editing; investigation; data curation. **Carmen Barbato:** Investigation; writing – review and editing; data curation. **Benedetta Formelli:** Investigation; writing – review and editing; data curation. **Francesca Cesari:** Investigation; writing – review and editing. **Stefano Chiti:** Writing – review and editing; data curation. **Stefano Diciotti:** Writing – review and editing; data curation. **Betti Giusti:** Writing – review and editing; supervision. **Anna Maria Gori:** Writing – review and editing; supervision. **Chiara Marzi:** Writing – review and editing; data curation. **Francesca Pescini:** Writing – review and editing. **Giovanni Pracucci:** Writing – review and editing; data curation. **Enrico Fainardi:** Writing – review and editing; supervision. **Rossella Marcucci:** Writing – review and editing; supervision. **Anna Poggesi:** Conceptualization; writing – original draft; methodology; data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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