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Original Study

Atrial Fibrillation in Older Patients with Syncope and Dementia: Insights from the Syncope and Dementia Registry

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A B S T R A C T

Objectives: To evaluate the clinical characteristics and the long-term outcome of atrial fibrillation (AF) patients with dementia and history of syncope or falls.
Design: Observational: analysis of a prospective registry.
Setting and Participants: Between 2012 and 2016, the Syncope and Dementia Registry enrolled patients in 12 geriatric departments. Follow-up evaluation was at 12 months.
Measures: Clinical, functional, and cognitive assessment.
Results: Of the 522 patients (women, 62.1%; Mini-Mental State Examination 17 ± 6), 26.4% have or presented an AF history. Patients with AF were older (85 ± 6 vs 83 ± 6 years, $P = .012$), with higher heart rate (78 ± 17 vs. 73 ± 14 bpm, $P < .001$), prescribed drugs (6.9 ± 2.9 vs 5.9 ± 2.7, $P < .001$), and an increased number (3.9 ± 2.0 vs 3.0 ± 1.8, $P < .001$) and severity of comorbidities. Oral anticoagulant therapy was underprescribed (39.9%). Cardiac syncope was more frequently diagnosed (18.8 vs 4.9%, $P < .001$). At multivariate analysis, AF patients were characterized by advanced age, a higher severity of comorbidities, a greater number of prescribed drugs, an increased heart rate, and a more frequent presence of cardiac symptoms. One-year mortality differed little between patients with and without AF (27.7 vs 22.1%, $P = .229$). In the arrhythmia group, multivariate predictors of prognosis were disability (number of lost BADLs; $P = .020$) and a higher heart rate ($P = .006$).
Conclusions and Implications: AF and postural stability-related issues often co-exist in persons with dementia. This complex of conditions is associated with an intricate clinical picture, underprescription of oral anticoagulants, and high long-term mortality. Future studies are needed to evaluate the effects of therapy optimization in this population.

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Syncope and falls are dramatic events in the clinical history of older patients. They can be responsible for severe trauma with loss of autonomy, disability development, hospitalizations, and, ultimately, death.[1] Furthermore, syncope and falls can complicate the course of dementia, and the interaction among these conditions can contribute to the development of frailty.[2] Atrial fibrillation (AF) is one of the arrhythmias that can be often found in patients with a history of cardiac syncope or orthostatic hypotension.[3] AF prevalence significantly increases in old individuals. A link between the arrhythmia and disability development was established, with dementia correlating with the presence of AF, especially if oral anticoagulant treatment is not prescribed.[4] Importantly, syncope and falls can frequently prevent the use of vitamin K antagonists or direct oral anticoagulants for fear of major bleeding secondary to traumatic events.[5] All these factors can interact, potentially compromising patients' clinical conditions.

Aims of this study were to identify, in older patients with dementia with a syncope or a history of falls, the clinical and pharmacologic features associated with the presence of AF, to evaluate the influence of the arrhythmia on 1-year survival, and the predictors of mortality in the population with AF.

Methods

The Syncope and Dementia (SYD) Registry includes patients recruited from acute care settings or outpatient clinics of 12 geriatric departments. Methods and baseline data have been published elsewhere.[6] Briefly, between 2012 and 2016, the SYD Registry enrolled patients aged ≥65 years with a diagnosis of dementia (following the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision*) and 1 or more suspected transient loss of consciousness and/or unexplained falls during the previous 3 months. There were no clinical exclusion criteria. All individuals underwent the initial evaluation protocol proposed by the European Society of Cardiology guidelines on syncope, including history, physical examination, blood pressure measurement in the supine and standing position, electrocardiogram (ECG) and carotid sinus massage in the supine position.[1] When needed, a second level neuro-autonomic (Tilt Test and upright carotid sinus massage), neurologic, or cardiologic assessment was undertaken.[1]

Baseline assessment also included measurement of functional status at 1 month before the event. For this purpose, we used the basic activities of daily living (BADL; including bathing, dressing, using the toilet, transferring, bowel and bladder control, and eating) and the instrumental activities of daily living (including using the telephone, shopping, cooking, house-keeping, washing clothes, using transport, management of own money, and independently taking medications).[6] For cognitive assessment, we used the Mini-Mental State Examination.[7] The presence and the weight of comorbidities were assessed with the Cumulative Illness Rating Scale (CIRS), a quantitative measure of physical illness burden, including the count of the organ system with moderate to greater impairment (CIRS-comorbidity).[8] The degree of dysfunction in the 13 explored systems is rated from 1 (no impairment) to 5 (extremely severe impairment, life threatening condition), with CIRS-severity, as a summary score, based on the average rating of all items.[8] We recorded also the pharmacologic treatment at baseline. Follow-up was closed at the 12-month evaluation. For the purposes of the present analysis, patients were stratified according to AF status, characterized by the presence of the arrhythmia at the baseline ECG, and/or previous episodes in the clinical history, as documented in hospital charts or medical reports (ie, medical visits by cardiologists, primary care physicians, or other specialists based on ECG and ECG Holter reports).

The study was approved by the ethics committee of the coordinating center, and, subsequently, by the local committees of each of the participating centers. A written informed consent was signed by all patients or their legal representatives.

Statistical Analysis

Continuous and categorical variables are presented as means ± standard deviation (SD) and as absolute numbers and percentages, respectively. Student's *t* test was used for comparisons of continuous variables between groups (ie, AF present/absent; surviving or not patients). In the case of a not normal distribution, the analogous nonparametric test, the Mann-Whitney test, was chosen. Different distributions of discrete variables were assessed using the χ^2 test and the related tests. In every case, the Monte Carlo Method was employed to increase the accuracy of the analysis. Multivariate logistic regression analysis models were built to identify the clinical variables associated with the presence of AF and with mortality at the 1-year follow-up. In each model, all univariate predictors significantly correlated with the endpoint were entered at the beginning, and iteratively deleted in the subsequent steps, basing on the least statistically significant *P* value. In the case of collinearity, we used only the variable characterized by the highest association with the endpoint. Odd ratios (ORs) and 95% confidence intervals (CIs) were also provided for multivariate models. SPSS for Windows v 25.0 (IBM, Armonk, NY) was used for statistical analysis. A *P* value of $<.05$ was considered to indicate statistical significance.

Results

Clinical Characteristics of Patients According to the Presence of AF

During the study period, 522 patients (mean age: 83 ± 6 years; women: 324, 62.1%; Mini-Mental State Examination 17 ± 6) entered in the SYD Registry. Of these, 138 (26.4%) have or presented a history of AF. Clinical characteristics and drug therapy of the enrolled patients are reported in Table 1. Patients with AF were more often enrolled in an acute care setting. Sex did not differ in those with or without AF. Patients with arrhythmia were older, had a higher heart rate, and a more complex clinical picture, characterized by an increased number and severity of comorbid conditions. In particular, the prevalence of diabetes, heart failure, valvular heart disease, and a previous stroke/transient ischemic attack was higher in patients with the arrhythmia, in whom mean CHA_2DS_2-VASc (the risk score for stroke and systemic embiolism in AF patients: C, congestive heart failure; H, hypertension; A_2, age ≥75; D, diabetes; S_2, stroke (doubled), TIA, systemic thromboembolism; V, vascular disease; A, age 65–74; Sc, sex category, female; each item equals 1 with the exception of A_2 and S_2, which ≥ 2) was 4.5 ± 1.4. Alzheimer and vascular dementia were the most frequent types of dementia, and they were equally distributed independently of the presence of the arrhythmia. Population with AF did not show a higher degree of neurocognitive impairment, disability, and greater burden of depressive symptoms. Patients with arrhythmia received more drugs, for the larger use of anticoagulants, diuretics, and nitrates, and rate- and rhythm-control therapies. In patients with AF, 15.9% of the patients did not take any antithrombotic drug; this proportion significantly decreased for higher values of CHA_2DS_2-VASc score. Remarkably, although the use of oral anticoagulants (39.9% in the population with AF) did not change by thrombotic risk, antiplatelet prescription was directly related to the score and was equal to 72.7% in patients graded 6–8 (Figure 1). Interestingly, the proportion of patients who used antipsychotics and antidementia drugs was higher among individuals without AF. With the exception of a more frequent occurrence of cardiac symptoms in arrhythmia patients (AF - no: 1.8% vs yes: 5.1%; $P = .043$), the daytime distribution of events, the prevalence of syncope-related factors and symptoms, and the incidence of fractures and other injuries did not differ between patients

Table 1
Clinical Characteristics of the SYD Registry Patients and Baseline Therapy by AF Status

(N = 522)	AF (n = 138)	No AF (n = 384)	*P*
Age (y)	84.6 ± 5.6	83.1 ± 6.4	.012
Women (n, %)	84 (60.9)	240 (62.5)	.735
Heart rate (bpm)	78.4 ± 16.7	72.9 ± 13.6	<.001
Acute care setting (n, %)	109 (79.0)	242 (62.8)	.001
Alzheimer disease (n, %)	60 (43.5)	193 (50.3)	.172
Vascular dementia (n, %)	66 (47.8)	151 (39.3)	.082
Parkinson/Lewy body dementia (n, %)	10 (7.2)	31 (8.1)	.757
MMSE (score)	17.6 ± 4.6	16.5 ± 5.8	.056
BADL lost (n)	3.0 ± 2.0	2.9 ± 1.9	.793
IADL lost (n)	6.1 ± 2.5	6.3 ± 2.3	.346
CIRS comorbidity (n)	3.9 ± 2.0	3.0 ± 1.8	<.001
CIRS severity (n)	1.8 ± 0.3	1.6 ± 0.4	<.001
CAD (n, %)	33 (23.9)	67 (17.4)	.098
Depression (n, %)	43 (31.2)	125 (32.6)	.764
Diabetes (type II) (n, %)	39 (28.3)	77 (20.1)	.047
Heart failure (n, %)	19 (13.8)	28 (7.3)	.023
Hypertension (n, %)	103 (74.6)	286 (74.5)	.971
Stroke or TIA (n, %)	36 (26.1)	68 (17.7)	.035
Valvular heart disease (n, %)	31 (22.5)	42 (10.9)	.001
Number of drugs (n)	6.9 ± 2.9	5.9 ± 2.7	<.001
Anticoagulants (n, %)	55 (39.9)	16 (4.2)	<.001
Antiplatelets (n, %)	69 (50.0)	223 (58.1)	.101
ACE inhibitors (n, %)	45 (32.6)	131 (34.1)	.748
Sartans (n, %)	22 (15.9)	71 (18.5)	.502
Beta blockers (n, %)	56 (40.6)	84 (21.9)	<.001
Ca-channel blockers (n, %)	34 (24.6)	62 (16.1)	.027
Diuretics (n, %)	70 (50.7)	127 (33.1)	<.001
Nitrates (n, %)	27 (19.6)	32 (8.3)	<.001
Antiarrhythmics (n, %)	27 (19.6)	12 (3.1)	<.001
Digoxin (n, %)	25 (18.1)	8 (2.1)	<.001
Statins (n, %)	34 (24.6)	96 (25.0)	.933
Antidementia (n, %)	12 (8.7)	95 (24.7)	<.001
Antidepressive drugs (n, %)	47 (34.1)	134 (34.9)	.859
Antipsychotics (n, %)	18 (13.0)	106 (27.6)	.001
Benzodiazepines (n, %)	31 (22.5)	77 (20.1)	.549

ACE, angiotensin-converting enzyme; antidementia, cholinesterase-inhibitors and memantine; CAD, coronary artery disease; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack.

with AF and the other part of the enrolled population. Indeed, 48.7% (n = 254/522) of patients reported some trauma after the event.

At discharge, 68.0% and 23.6% of the SYD Registry patients were diagnosed to have had a syncope or a fall, respectively. A cardiac syncope was more frequently observed in patients with AF of both arrhythmia (AF - yes: 12.3% vs no: 3.4%; $P < .001$) and structural cause (AF - yes: 6.5 vs no: 1.6%; $P = .006$). In particular, brady- and tachyarrhythmias were found in 3.6% and in 8.7% of patients with AF, respectively. Structural causes of syncope in patients with

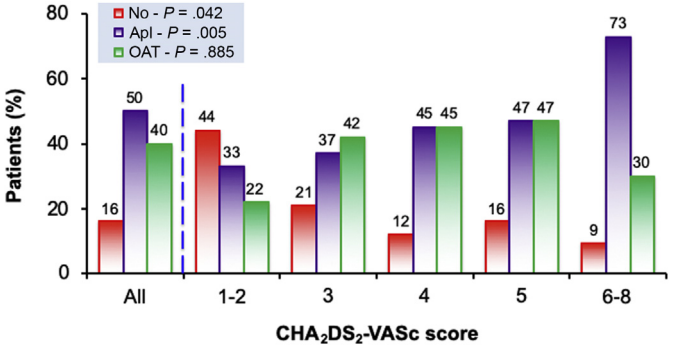

Fig. 1. Antithrombotic therapy by CHA_2DS_2-VASc score in the SYD Registry. The use of antiplatelet agents (Apl) is directly related to the score, whereas oral anticoagulant therapy (OAT) prescription does not show any association with thrombotic risk.

arrhythmia were aortic stenosis (2.9%), acute myocardial infarction (2.2%), pulmonary embolism (0.7%) and severe left ventricular dysfunction (0.7%). The proportion of patients with AF and with a reflex or an orthostatic event was 15.2% and 30.4%, respectively, not statistically different from that observed in patients without the arrhythmia (20.6% and 33.6%). Logistic regression analysis found that the presence of AF in the SYD Registry population was directly associated with age, severity of comorbidities, as evaluated with CIRS, heart rate, number of prescribed drugs, and presence of cardiac symptoms (Table 2).

AF and Mortality at the Follow-Up

At the 1-year evaluation, we had no data of 21/522 (4.0%) patients; among these, 8/138 (5.8%) and 13/384 (3.4%) individuals were with and without AF, respectively. Mortality was slightly different according to arrhythmia presence (AF - no: 22.1% vs yes: 27.7%; $P = .229$). Limiting analysis to the population with AF (clinical characteristics by vital status are reported in Table 3), we found that age and sex were not related to survival. In univariate analysis, mortality was higher in those hospitalized in acute care settings, and it was associated with heart rate, severity of comorbid conditions, and loss of BADL. CHA_2DS_2-VASc score did not differ according to vital status at the follow-up (survival - yes: 4.5 ± 1.5 vs no: 4.5 ± 1.3, $P = .891$). Patients who survived were more often prescribed with statins and less frequently showed dyspnea both before (0% vs 11.1%, $P = .001$) and after (1.1% vs 8.3%, $P = .032$) the event. No other differences were observed by prognosis in the population with AF. In logistic regression analysis (overall predictivity: 74.4%), heart rate ($OR_{\Delta.bpm} = 1.03$, 95% CI 1.00–1.06; $P = .045$) and the number of lost BADL ($OR_{\Delta.BADL} = 1.26$, 95% CI 1.01–1.57; $P = .039$) were predictors of mortality at the follow-up.

In patients without AF, univariate predictors of mortality were the same of those observed in patients with the arrhythmia, with the exception of age and male sex, higher in those who did not survive (Table 3).

Discussion

Persons with dementia who experience syncope and/or a fall represent a challenging population with a 1-year mortality rate of approximately 25%. AF was present in over one-quarter of these individuals and was associated with older age and greater clinical complexity but only a small and statistically insignificant difference in 1-year mortality.

The large proportion of patients with the arrhythmia in the SYD Registry can be explained by the advanced age of the enrolled population. Patients with AF showed a prevalence of diabetes, heart failure, valvular heart disease, and a previous stroke/transient ischemic attack higher than in individuals without arrhythmia. On the whole, SYD Registry population with AF presented also a higher burden of disease severity, confirming previous experiences.[9]

Our results did not show any difference in the type of dementia in patients with or without the arrhythmia. The prevalence of dementia in the general population is higher in patients with AF and each new arrhythmic event can accelerate cognitive decline.[10] Interestingly, the arrhythmia seems to be related not only to the incidence of vascular dementia, but also to a 50% higher risk of having Alzheimer disease, with AF burden possibly correlating with the reduction of cerebral perfusion.[11]

Our results show that the use of oral anticoagulation in patients with AF and severe thrombotic risk is low, without any association with the CHA_2DS_2-VASc score. Several considerations can explain this finding. Undertreatment of older individuals is still present in the real world. The EUROObservational Research Programme in AF (EORP)

Table 2
Variables Associated With Presence of AF in the SYD Registry. Results of the Logistic Regression Analysis (Overall Predictivity: 75%; $P < .001$)

	β ± Standard Error	OR (95% CI)	*P*
Age (Δ . y)	0.04 ± 0.02	1.038 (1.002–1.076)	.041
CIRS severity (Δ . score)	1.24 ± 0.31	3.461 (1.871–6.402)	<.001
Heart rate (Δ . bpm)	0.02 ± 0.01	1.021 (1.007–1.036)	.004
Number of drugs (Δ . number)	0.09 ± 0.04	1.096 (1.015–1.184)	.020
Cardiac symptoms (yes vs no)	1.24 ± 0.63	3.450 (1.003–11.864)	.049

Δ, change of the dependent variable per unitary increase of the independent variable. Variables excluded from the model: heart failure ($P = .918$); diabetes (type II) ($P = .711$); CIRS comorbidity ($P = .460$); acute care setting ($P = .220$); valvular heart disease ($P = .219$); stroke or TIA ($P = .097$).

General Pilot Registry demonstrated that advanced age was associated with a reduction in the prescription of oral anticoagulants.[12] Moreover, the SYD Registry population had a severely altered health status; in the Frailty, Stroke Risk and Bleeding Risk on Anticoagulation in the Elderly with AF (FRAIL-AF) study, which enrolled frail older individuals, about 25% of missing prescriptions were not justified by any clinically relevant reason.[5] Our population always presented a history of syncope or falls. In a survey by the European Heart Rhythm Association (EHRA), about 30% of respondents thought that falls were a valid reason not to prescribe an oral anticoagulant drug in a frail individual,[13] even if a subanalysis of the Effective aNticoaGulation with factor Xa next GEneration in AF-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) demonstrated the higher benefit of edoxaban, compared with warfarin, in terms of bleeding risk and survival, in individuals at high risk of falling.[14] Non–vitamin K antagonist oral anticoagulants (NOACs) seem also to have a lower impact on health-related quality of life than warfarin.[15] Importantly, the researchers involved in the Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail) consensus survey concluded that, despite the high bleeding risk and the cost of treating a population with poor function and cognition, the discontinuation of oral anticoagulants could be inappropriate because of the high risk of stroke, an unfavorable outcome also in frail individuals with a limited life expectancy.[16] Confirming previous experiences, in our registry, the use of antiplatelet agents was greater in those patients showing the higher thrombotic risk. Importantly, guidelines recommendations strongly discouraged this behavior.[17]

In the patients with AF of the SYD Registry, mortality at the 1-year follow-up was associated with an increased heart rate at the baseline evaluation: to each increase of 10 bpm corresponded a 30% higher risk of dying. A higher heart rate may be secondary to an increased sympathetic drive and to the presence of heart failure, and it can be associated with an accelerated atherosclerotic process.[18,19]

In the SYD Registry, mortality was higher in those who presented a greater functional decline as evaluated with BADL assessment independently of cardiac rhythm. A more pronounced loss of functional capacity may hamper homeostatic reserve and physical function, significantly contributing to frailty development. These considerations help to interpret the lack of differences in prognosis in patients with and without AF in our registry.

Study Limitations

This was a prospective, observational study. We showed only possible associations and, for causative relations, it will be necessary to wait for specifically designed studies. We could not differentiate our population based on arrhythmia burden (ie, history of AF, and paroxysmal, persistent, and permanent forms of AF). However, the history of the arrhythmia can often be seen as a continuous time-dependent progression, extending from isolated to never-ending episodes. Furthermore, we decided to have a relatively short length of

Table 3
Clinical Characteristics and Baseline Therapy of Patients With and Without AF by Vital Status at Follow-Up

	AF		*P*	No AF		*P*
	Alive (n = 94)	Deceased (n = 36)		Alive (n = 289)	Deceased (n = 82)	
Age (y)	84.3 ± 5.6	84.9 ± 5.7	.588	82.7 ± 6.5	84.4 ± 6.0	.026
Women (n, %)	58 (61.7)	19 (52.8)	.354	192 (66.4)	42 (48.8)	.004
Heart rate (bpm)	76.2 ± 15.5	85.1 ± 17.2	.006	71.6 ± 12.8	76.7 ± 14.5	.003
Acute care setting (n, %)	69 (73.4)	34 (94.4)	.014	159 (55.0)	72 (87.8)	<.001
Alzheimer disease (n, %)	39 (41.5)	18 (50.0)	.382	140 (48.4)	44 (53.7)	.453
Vascular dementia (n, %)	45 (47.9)	16 (44.4)	.726	122 (42.2)	27 (32.9)	.160
Parkinson/Lewy body dementia (n, %)	8 (8.5)	2 (5.6)	.572	20 (6.9)	10 (12.2)	.165
MMSE (score)	18.0 ± 4.5	16.2 ± 4.9	.061	16.8 ± 5.5	15.8 ± 6.4	.200
BADL lost (n)	2.8 ± 1.9	3.7 ± 2.3	.020	2.8 ± 2.0	3.4 ± 2.0	.013
IADL lost (n)	5.8 ± 2.5	6.7 ± 2.5	.076	6.2 ± 2.4	6.5 ± 2.2	.346
CIRS comorbidity (n)	3.8 ± 1.7	4.2 ± 1.8	.195	3.0 ± 1.8	3.1 ± 1.7	.419
CIRS severity (n)	1.8 ± 0.3	1.9 ± 0.4	.024	1.5 ± 0.4	1.6 ± 0.3	.017
CAD (n, %)	22 (23.4)	11 (30.6)	.402	49 (17.0)	17 (20.7)	.513
Depression (n, %)	33 (35.1)	6 (16.7)	.040	101 (34.9)	19 (23.2)	.046
Diabetes (Type II) (n, %)	28 (29.8)	9 (25.0)	.588	55 (19.0)	21 (25.6)	.215
Heart failure (n, %)	11 (11.7)	7 (19.4)	.253	19 (6.6)	8 (9.8)	.338
Hypertension (n, %)	71 (75.5)	27 (75.0)	.950	215 (74.4)	63 (76.8)	.669
Stroke or TIA (n, %)	24 (25.5)	9 (25.0)	.950	48 (16.6)	19 (23.2)	.193
Valvular heart disease (n, %)	18 (19.1)	11 (30.6)	.162	34 (11.8)	8 (9.8)	.697
Number of drugs (n)	7.0 ± 3.0	7.1 ± 2.7	.839	5.9 ± 2.7	5.9 ± 2.7	.961
Anticoagulants (n, %)	34 (36.2)	14 (38.9)	.774	11 (3.8)	5 (6.1)	.539
Antiplatelets (n, %)	51 (54.3)	18 (50.0)	.664	165 (57.1)	53 (64.6)	.253
ACE inhibitors (n, %)	29 (30.9)	15 (41.7)	.244	103 (35.6)	24 (29.3)	.295
Sartans (n, %)	17 (18.1)	5 (13.9)	.568	56 (19.4)	13 (15.9)	.523
Beta blockers (n, %)	39 (41.5)	13 (36.1)	.575	68 (23.5)	13 (15.9)	.173
Ca-channel blockers (n, %)	19 (20.2)	13 (36.1)	.060	42 (14.5)	19 (23.2)	.090
Statins (n, %)	29 (30.9)	5 (13.9)	.049	81 (28.0)	13 (15.9)	.030

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack.
The use of diuretics, nitrates, antiarrhythmics, digoxin, antidementia and antidepressive drugs, antipsychotics, and benzodiazepines was not related to survival in patients with and without AF.

the follow-up (1 year) because the weight of frailty and comorbidities continuously change, usually worsening, over time.

Conclusions and Implications

The findings of the SYD Registry demonstrated that patients with dementia and AF, who have a syncope or a fall, are older, present a more complex clinical picture than patients without the arrhythmia, and are undertreated with anticoagulants. Little difference in mortality was found according to cardiac rhythm. In patients with AF, prognosis was related to disability. Future studies should evaluate the effects of therapy optimization in this challenging population. In particular, the consequences of a wider use of anticoagulation on bleeding, worsening of disability, and mortality, and on caregiver burden should be assessed.

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