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Cognitive impairment in patients with atrial fibrillation: Implications for outcome in a cohort study

Vincenzo Livio Malavasi [a], Cristina Zoccali [a], Maria Chiara Brandi [a], Giulia Micali [a], Marco Vitolo [a], Jacopo Francesco Imberti [a], Chiara Mussi [b], Renate B. Schnabel [c,e], Ben Freedman [d], Giuseppe Boriani [a,*]

[a] Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy
[b] Geriatrics, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Civil Hospital, Modena, Italy
[c] University Heart and Vascular Center Hamburg, Clinic for Cardiology, Hamburg, Germany
[d] Heart Research Institute, Charles Perkins Centre, Concord Hospital Cardiology, University of Sydney, Australia
[e] DZHK (German Center for Cardiovascular Research), partner site Hamburg/Kiel/Luebeck, Australia

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ABSTRACT

Background: The impact of cognitive status on outcomes of patients with atrial fibrillation (AF) is not well defined.
Aims: To assess the prevalence of cognitive impairment in AF patients and evaluate its association with: i) all-cause mortality; ii) a composite endpoint of death, stroke/systemic embolism, hemorrhages, acute coronary syndrome, pulmonary embolism, new/worsening heart failure.
Methods: In a cohort study, cognitive status was assessed at baseline by the Mini Mental State examination adjusted for age and education (aMMSE). aMMSE <24 was considered indicative of cognitive impairment.
Results: The cohort included 437 patients (61.3% male, mean age 73.4 ± 11.7 years). Sixty-three patients (14.4%) had cognitive impairment at baseline aMMSE. Permanent AF (odds ratio [OR] 1.750; 95%CI 1.012–3.025; $p = .045$), haemoglobin levels (OR 0.827; 95%CI 0.707–0.967; $p = .017$) and previous treatment with antiplatelet drugs only, without oral anticoagulation, (OR 4.352; 95%CI 1.583–11.963; $p = .004$) were independently associated with cognitive impairment at baseline.
After a median follow-up of 887 days (interquartile range 731–958) 30 patients died (7.1%), and 97 (22.9%) reached the composite endpoint. After adjustment for Elixhauser Comorbidy Measure, aMMSE <24 was significantly associated with all-cause mortality (hazard ratio [HR] 2.473, 95%CI 1.062–5.756, $p = .036$) and with the composite endpoint (HR 1.852, 95%CI 1.106–3.102, $p = .019$).
Conclusions: In patients with AF, cognitive impairment (aMMSE <24) is associated with worse outcomes, and the association of adverse outcomes with previous treatment with antiplatelet drugs only, without oral anticoagulation, highlights the potential role of appropriate antithrombotic treatment for improving patient prognosis.

1. Introduction

Several studies have shown a significant impact of atrial fibrillation (AF) on cognitive status and on the risk of dementia and AF has been associated with an accelerated cognitive decline [1,2].

AF and cognitive decline share some common risk factors, with aging being the most important, since the prevalence of dementia after age 65 seems to double every five years [3]. Other risk factors linked to the development of cognitive impairment (CImp) are hypertension, heart failure and diabetes, all included in the CHA_2DS_2-VASc score [4] and associated with the risk of developing AF. Multiple mechanisms can contribute to the association between AF and CImp/dementia, either related to the risk of stroke or totally independent of this risk [5]. Also the role of antithrombotic therapies is still controversial, probably due to the multifaceted pathophysiology and severity of CImp and little is known about anticoagulation in patients with overt dementia and AF [6].

Mini-mental state examination (MMSE), due to its simple application, is a valuable and valid screening tool for measuring cognitive status, and it may be used to classify the severity of CImp, although it does not constitute the sole criterion for diagnosing dementia or for differentiating specific forms of dementia. In practice, it is a useful tool for cognitive assessment in the clinician's office or at the bedside. Among inpatients of a general medical ward, a value <24 indicate cognitive impairment with a reported sensitivity and specificity of 87% and 82%, respectively [7]. Despite these data, the prognostic implications of MMSE in relatively unselected patients with AF in daily cardiology practice are not defined.

* Corresponding author at: Cardiology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Largo del Pozzo 71, 41121 Modena, Italy.
E-mail address: giuseppe.boriani@unimore.it (G. Boriani).

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The aim of this prospective cohort study was to identify the prevalence of CImp in AF patients using MMSE as a diagnostic tool, to explore which risk factors and patients' characteristics are independently associated with CImp in AF patients. We also aimed to investigate the relationship between CImp and adverse outcomes at long-term follow-up, in terms of all-cause mortality and a composite endpoint, constituted by death, stroke/systemic embolism, hemorrhages, acute coronary syndrome, pulmonary embolism, new/worsening heart failure.

2. Methods

This prospective single-centre observational study was approved by the Local Medical Ethical Committee and patients gave written informed consent for participation. In- and outpatients consecutively referred to the Cardiology Division of our tertiary hospital during a 1-year period were enrolled in a prospective cohort study. Inclusion criterion was at least one episode of ECG-documented AF within 1 year from admission or office visit. AF at the time of enrolment was not necessarily required for enrolment. Other inclusion criteria were: (i) age older than or equal to 18 years; (ii) feasibility of the MMSE. A previous diagnosis of dementia was an exclusion criterion.

For each patient, demographic, clinical, laboratory, and echocardiographic data were collected, as well as drug prescriptions. Moreover, information about AF pattern, time since the first episode, symptoms and co-morbidities were acquired.

3. Mini mental state examination (MMSE)

The test was administered during the enrollment visit. MMSE includes 10 domain items that measure orientation to time (5 points), orientation to place (5 points), registration (3 points), attention and calculation (5 points), recall (3 points), naming and repetition (3 points), comprehension (3 points), reading ability (1 point), writing ability (1 point) and design copy (a brief measure of visual construction; 1 point). One point is awarded for each successfully completed item on the MMSE up to a maximum of 30 points and the higher the score, the better the cognitive performance.

In this study MMSE score was adjusted (aMMSE) for age and educational status [8], according to ethnicity. Since adjustment is related to patients between 65 and 89 years of age, patients below 65 were considered as having 65 years and patients above 89 were considered as aged 89 years.

Any score greater than or equal to 24 points (out of 30) was assumed as indicating a normal cognitive status and any value below 24 was considered indicative of CImp [7].

4. Follow-up data and study endpoints

Information about clinical status, laboratory analysis and medications at follow-up were obtained through the Hospital database, or during office visit or by telephone interview. The primary end-point of this study was all-cause mortality. The secondary endpoint was a composite endpoint including death and admissions for stroke/systemic embolism, hemorrhages, pulmonary embolism, acute coronary syndrome and new or worsening heart failure.

4.1. Definitions

Anemia was defined using a cut-off value of Hb <10 g/dl (i.e. at least moderate anemia). Chronic kidney disease (CKD) was defined as abnormalities of kidney structure or function, present for >3 months, with implications for health, using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [9]. An estimated glomerular filtration rate (eGRF) <60 ml/min/1.73 m2 identified CKD according to KDIGO recommendations [10]. Heart failure was considered if typical clinical features were present or an ejection fraction (EF) ≤ 40% was found at echocardiographic examination. Left atrial (LA) dilation was classified according to 2015 American Society of Echocardiography recommendations [11]. Valvular heart disease (VHD) was defined as presence of at least moderate aortic stenosis or regurgitation and/or at least moderate mitral or tricuspid regurgitation/stenosis, or any valvular disease that required surgical or percutaneous correction. Bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria [12].

Thromboembolic and haemorrhagic risks were calculated (CHA_2DS_2-VASc and HAS-BLED score) according to European Society of Cardiology guidelines [13]. Briefly, we stratified thromboembolic risk by means of CHA_2DS_2-VASc score: Congestive heart failure (1 point), Hypertension (1 point), Age 65–74 years (1 point) or Age ≥ 75 (2 point), Diabetes (1 point), Stroke/transient ischemic attack(TIA)/thrombo-embolism (2 point), Vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.) (1 point), female sex (1 point) [13]. The bleeding risk was estimated according to HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, each item leads to 1 point).

The Elixhauser Comorbidity Measure (ECM) [14] was calculated to obtain information on patient's status. The index is characterized by not including cognitive impairment, unlike the Charlson Comorbidity index in which dementia is an item of the index [15].

5. Statistics

Continuous variables were expressed as median and interquartile [IQ] range. Categorical variables were reported as number of patients and percentages. Among-group comparisons were made using Mann-Withney *U* test for continuous variables and χ^2 test for categorical variables.

To evaluate the variables associated with cognitive impairment (aMMSE ≥24 and aMMSE <24), a logistic univariate and multivariate regression analysis was performed. Results were expressed as odds ratio (OR), 95% confidence interval (CI) and *p* value. Variables that at univariate analysis had a p value $< .10$ were inserted in the multivariable regression analysis. Age or a categorization of age were not included since MMSE adjusted for age and education was considered. CHA_2DS_2-VASc and HAS-BLED scores were not included in the multivariable analysis, in order to allow to consider separately the variables included in these scores, avoiding collinearity.

Survival curves for aMMSE categories were built with Kaplan Meier method and compared with log-rank test. To test the prognostic significance of aMMSE combined with other clinical baseline variables, a Cox regression analysis was performed and aMMSE unadjusted and ECM-adjusted hazard ratios (HR) with 95% confidence intervals (95%CI) were calculated. Moreover, aMMSE HR were adjusted for ECM and clinical covariates with a p value $< .10$ at univariate Cox regression analysis. The proportionality of the Cox models was checked through visual procedures and by plotting partial (Schoenfeld) residuals of variables entered in the models against the time to event. As reported above, CHA_2DS_2-VASc and HAS-BLED scores were not included in the multivariable Cox regression analysis to avoid collinearity.

Specificity and sensitivity of ECM vs all-cause mortality and the composite endpoint by means of receiver operating characteristic (ROC) curves and area under the curve (AUC) were also evaluated, by comparing the two curves by means of Delong test [16].

A p value $< .05$ was considered statistically significant. All evaluations were conducted using SPSS v.21 (IBM Corp Armonk, NY).

6. Results

A total of 437 patients were enrolled, 61.3% male, with a mean age of 73.4 ± 11.7 years.

Before enrolment 317 patients (72.5%) were already on treatment with oral anticoagulants (OACs), 106 (24.5%) with antiplatelet drugs and 45 (10.3%) were taking antiarrhythmic medications. Among those treated with antiplatelet drugs, 11.9% overall were on these drugs alone, without an OAC (Table 1).

Patients characteristics according to antithrombotic regimen prescribed before enrollment (OAC only, antiplatelet only or OAC + antiplatelet) are shown in Web Table 1. Sixty-three patients had an aMMSE suggestive of CImp (14.4%). An aMMSE <18 was present in 13 patients (3.0% of the whole population). Clinical features of the patients according to presence or absence of CImp are shown in Table 1. All items of the aMMSE showed lower values in patients with CImp but visuo-spatial praxis (−50% vs patients without CImp), delayed recall (−52.2%) and attention and calculation (−65.9%) were halved or even lower when compared with scores of the patients without CImp (Web Table 2).

Patients with and without CImp did not show important or significant differences with regard to a series of variables, including adoption of a rhythm control strategy before enrolment or anticoagulation regimen before enrolment.

As a result of the enrolment visit, OACs were prescribed to 89.7% of the patients (16% with additional antiplatelets) and antiplatelets alone to 4.3% of the patients. Patients with and without CImp did not differ with regard to rate of prescription of OACs at the enrolment visit (61 [87.1%] vs 331 [90.2%]; OR 0.737; 95% CI 0.338–1.608; $p = .442$). However, there was significantly great proportion with CImp prescribed antiplatelet alone (21% vs 10% OR 2.432; 95%CI 1.252–4.727; $p = .007$).

Table 1
Clinical features at baseline for the patients enrolled in the study and univariate binary logistic regression analysis. Data are shown as N (%) if no otherwise indicated.

Variable	Total (437)	aMMSE ≥ 24 (374)	aMMSE < 24 (63)	OR	95% CI	*p*
Female sex	169 (38.7)	133 (36.2)	36 (51.4)	1.341	0.768–2.342	0.302
Age yrs. [median (IQ range)]	74 (66–80)	74 (66–79)	81 (71–85)	1.079	1.045–1.113	<0.001
Age ≥ 75 yrs	217 (49.7)	169 (46.0)	48 (68.6)	2.556	1.483–4.407	0.001
Ward as enrolment site	166 (38%)	132 (36.0)	34 (48.6)	0.566	0.325–0.987	0.045
Risk factors and comorbidities						
Hypertension	303 (69.3)	251 (67.1)	52 (82.5)	2.334	1.143–4.768	0.020
Diabetes	75 (17.2)	61 (16.6)	14 (20.0)	1.477	0.752–2.900	0.257
Dyslipidemia	181 (41.7)	155 (42.6)	26 (27.1)	0.766	0.432–1.359	0.363
Smoke (former + active)	166 (38.1)	146 (39.9)	20 (28.6)	0.766	0.426–1.376	0.372
Alcohol >8 drinks/week	19 (4.4)	16 (4.4)	3 (4.3)	1.234	0.348–4.374	0.745
History of CAD	120 (27.5)	93 (25.3)	27 (38.6)	1.752	0.983–3.124	0.057
Heart failure (NYHA >2 or LV EF ≤ 40%)	77 (17.6)	63 (17.2)	14 (20)	1.422	0.725–2.787	0.305
Peripheral vascular disease	71 (16.2)	57 (15.5)	14 (20.0)	1.599	0.812–3.148	0.175
Valvular heart disease	109 (29.8)	92 (29.2)	17 (33.3)	1.359	0.692–2.670	0.373
History of stroke/SE	60 (13.7)	48 (13.1)	12 (17.1)	1.006	0.451–2.243	0.988
History of bleeding	38 (8.7)	29 (7.9)	9 (12.9)	1.646	1.044–2.597	0.032
History of major or intracranial bleeding	15 (3.4)	10 (2.7)	5 (7.1)	3.481	1.146–10.578	0.028
CKD-EPI ml/min/1.73 m^2 [median (IQ range)]	73.6 (55.7–86.7)	73.7 (58.4–87.2)	62.7 (46.9–81.1)	0.981	0.968–0.994	0.004
CKD (CKD-EPI < 60 ml/min/1.73 m^2)	128 (29.3)	97 (26.4)	31 (44.3)	2.397	1.364–4.214	0.002
COPD	34 (7.8)	27 (7.4)	7 (10.0)	1.446	0.572–3.661	0.436
Hb g/dl [median (IQ range)]	13.6 (12.4–14.8)	13.6 (12.5–14.5)	12.2 (11.1–14.4)	0.791	0.679–0.920	0.002
Anemia (Hb <10 g/dl)	20 (4.6)	14 (3.8)	6 (8.6)	2.289	0.799–6.557	0.123
Severe hepatic impairment	14 (3.2)	11 (3.0)	3 (4.3)	1.825	0.494–6.747	0.367
Malignancy	83 (19.0)	64 (17.4)	19 (27.5)	1.463	0.758–2.822	0.257
Clinical status at enrollment						
CHA_2DS_2VASc [median (IQ range)]	3 (2–5)	3 (2–5)	4 (3–5)	1.348	1.160–1.567	<0.001
CHA_2DS_2-VASC ≥1 (M) or ≥2 (F)	401 (91.8)	331 (90.2)	70 (100.0)	na	na	0.998
HAS-BLED [median (IQ range)]	1 (1–2)	1 (1–2)	2 (1–3)	1.566	1.206–2.033	0.001
HAS-BLED >2	63 (14.4)	43 (11.7)	20 (28.6)	3.002	1.576–5.715	0.001
EHRA_score [median (IQ range)]	1 (1–2)	1.6 ± 0.8	1.7 ± 0.9	1.184	0.887–1.180	0.251
EHRA score >2	78 (17.8)	65 (17.7)	13 (18.6)	1.396	0.712–2.734	0.331
BMI [median (IQ range)]	26.6 (23.6–29.4)	26.6 (23.6–29.4)	25.8 (23.7–29.3)	0.992	0.932–1.056	0.809
Echocardiography						
Severe LA enlargement	157 (35.9)	131 (35.7)	26 (37.1)	1.105	0.624–1.954	0.733
Left ventricular EF % [median (IQ range)]	55 (45–60)	55 (45–60)	55 (45–60)	1.005	0.981–1.029	0.688
Left ventricular EF ≤ 40%	67 (15.3)	58 (15.5)	9 (14.3)	0.881	0.392–1.981	0.760
AF features						
AF on baseline ECG	255 (58.4)	295 (55.9)	50 (71.4)	1.549	0.863–2.78	0.143
History of AF >1 month	341 (78.0)	287 (78.2)	54 (77.1)	0.779	0.412–1.473	0.443
First-detected AF	54 (12.4)	46 (12.5)	8 (11.4)	0.796	0.324–1.952	0.618
Permanent AF	175 (40.0)	136 (37.1)	39 (55.7)	1.729	0.992–3.012	0.053
CV (ECV or PhCV) prior to enrollment	182 (41.7)	161 (44.0)	21 (30.0)	0.587	0.325–1.062	0.078
Therapy						
Rhythm control strategy before enrolment	100 (22.9)	89 (23.8)	11 (17.5)	0.863	0.438–1.700	0.670
Anticoagulation before enrolment	317 (72.5)	266 (72.5)	51 (72.9)	0.746	0.412–1.350	0.333
Antiplatelet drugs before enrolment	106 (24.3)	84 (22.9)	22 (31.4)	1.963	1.091–3.532	0.024
in combination with OAC	54 (12.4)	47 (12.6)	7 (10)	0.757	0.327–1.750	0.513
without OAC	52 (11.9)	37 (10.1)	15 (21.4)	2.432	1.252–4.727	0.007

Legend: aMMSE: age and education adjusted Mini Mental State Examination; OR: odds ratio; CI: confidence interval; CAD: coronary heart disease; NYHA: New York Heart Association; LV EF: left ventricular ejection fraction; SE: systemic embolism; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; Hb: haemoglobin; EHRA: European Heart Rhythm Association; BMI: body mass index; LA: left atrium; AF: atrial fibrillation; CV: cardioversion (either electrical – ECV – or pharmacological –PhCV); OAC: oral anticoagulant therapy; AAD: antiarrhythmic drugs.

Table 2
Results of multivariable logistic regression analysis for factors independently associated with CImp.

	OR	95% CI		p
Hypertension	1.618	0.950	2.754	0.076
CAD	1.057	0.579	1.928	0.857
History of bleeding	1.195	0.512	2.790	0.680
Hb	0.846	0.722	0.992	0.039
Permanent AF	1.806	1.043	3.126	0.035
Antiplatelet drugs treatment before enrolment (without OAC)	4.352	1.583	11.963	0.004
CKD (CKD-EPI < 60 ml/min/1.73 m^2)	1.594	0.897	2.831	0.112

Legend: OR: odds ratio; CI: confidence interval; CAD: coronary heart disease; Hb: haemoglobin; AF: atrial fibrillation; CKD: chronic kidney disease; OAC: oral anticoagulation.

6.1. Factors associated with CImp

Table 1 shows the results of univariate binary logistic regression analysis. At a multivariable logistic regression analysis (Table 2) antiplatelet treatment alone (without OAC) before enrolment, Hb and having permanent AF at enrolment were independently associated with CImp, as measured by aMMSE.

6.2. Follow-up data and relationship with CImp

Eleven (2.5%) patients were lost to follow-up and 3 patients withdraw their consent for participation in the study. Therefore, follow-up was analysed in 423 patients.

After a median follow-up of 887 days (interquartile range 731–958) 30 patients died (7.1%), and 97 (22.9%) achieved the composite endpoint. Other clinical events that occurred during the follow-up are shown in Web Table 3. The results of univariate Cox proportional hazard regression with regards to all-cause mortality, and the composite endpoint are shown in Web Table 4.

The results of multivariate survival analysis by means of Cox proportional regression model with a complete set of covariates, selected for a p value < .10 at univariate Cox regression (excluding comorbidities considered in ECM such as diabetes, heart failure, VHD, peripheral vascular disease, anemia, CKD, liver disease, cancer, BMI, and those with risk of collinearity such as permanent AF and rate control strategy) are shown in Table 3. CImp, as expressed by aMMSE <24 and co-morbidities, as expressed by ECM, were significantly and independently associated with all-cause mortality. Moreover, CImp, as expressed by aMMSE <24, co-morbidities, as expressed by ECM, coronary artery disease (CAD) and first-detected AF were significantly and independently associated with the composite endpoint.

Table 3
Results of multivariable Cox proportional hazard regression models for the primary end point (all-cause mortality) and for the secondary composite endpoint (death and admissions for stroke/systemic embolism, hemorrhages, pulmonary embolism, acute coronary syndrome and new or worsening heart failure).

	HR	95% CI		p value
All-cause mortality (N = 30 events)				
aMMSE <24	2.819	1.324	6.000	0.007
ECM	1.608	1.284	2.015	<0.001
AF at enrolment ECG	2.670	0.989	7.206	0.053
Severe LA enlargement	0.916	0.421	1.992	0.824
CAD	1.286	0.571	2.895	0.544
APT alone at discharge	2.007	0.661	6.090	0.219
Composite endpoint (N = 97 events)				
aMMSE <24	2.121	1.334	3.372	0.001
ECM	1.215	1.069	1.381	0.003
AF at enrolment ECG	1.379	0.866	2.198	0.176
First-detected AF	2.145	1.273	3.614	0.004
Severe LA enlargement	1.183	0.754	1.858	0.465
CAD	1.985	1.261	3.123	0.003
APT alone at discharge	1.320	0.634	2.748	0.458

Legend: HR: hazard ratio; CI: confidence interval; ECM: Elixhauser Comorbidity Measure; aMMSE: age and education adjusted Mini Mental State Examination; ECG: electrocardiogram; AF: atrial fibrillation; LA: left atrium; CAD: coronary heart disease, APT: antiplatelet therapy.

Survival curves of freedom from all-cause mortality and freedom from the composite end-point, according to presence or absence of CImp at baseline,are shown in Fig. 1 (Panel a and b, respectively).

A aMMSE <24 significantly predicted all-cause mortality (unadjusted HR 3.989, 95% CI 1.921–8.281, p < .001; ECM adjusted HR 2.473, 95%CI 1.062–5.756, p = .036) (Fig. 1, panel a) and the composite endpoint (unadjusted HR 2.236, 95%CI 1.481–3.653, p < .001; ECM adjusted HR 1.852, 95%CI 1.106–3.102, p = .019) (Fig. 1, panel b).

Adjusting for ECM, CAD, severe LA enlargement (>48 ml/m^2) and presence of AF at enrolment ECG, an aMMSE <24 was associated with all-cause mortality (HR 3.057; 95%CI 1.464–6.682; p = .003): Moreover, after adjustment for the same variables and first detected AF, aMMSE <24 was also associated with the composite endpoint (HR 2.185; 95% CI 1.387–3.444; p = .001).

The evaluation of the specificity and sensitivity of MMSE and ECM in predicting all-cause death and the composite endpoint (Web Figs. 1 and 2) showed that the AUC of ECM was slightly, but not significantly, better than the AUC of MMSE. An ECM > 4 and an aMMSE <24 showed very high negative predictive value for all-cause death (ECM 96.4%, MMSE 94.9%) with lower values for the composite endpoint ECM (81.7% MMSE 80.3%). A value of ECM > 4 had low sensitivity (55%) but high specificity (91%) in characterizing patients who died.

7. Discussion

The relationship between AF and dementia and cognitive decline is gaining growing interest. The field is complex in view of the many factors involved and the need for long periods of observations. Retrospective and longitudinal observational studies suggest an association between AF and dementia or cognitive impairment [1,17–21], although a more valuable demonstration of causality would require a randomized controlled trial showing an effect on dementia through a targeted intervention. Several prospective studies and two meta-analyses [2,22] showed an increased risk of dementia and CImp in AF also independently from AF-related overt ischaemic stroke. The recent Swiss-AF study [23] clearly showed through MRI that patients with AF have a high burden of large cerebral arge noncortical or cortical infarcts, that most of these lesions are clinically silent and are associated with worse cognitive function. This may be potentially related to a series of factors, such as silent cerebral infarcts, microbleeds and cerebral hypoperfusion, that are likely to play a role in the association of AF and cognitive decline or dementia.

In our cohort study the prevalence of CImp was 14.4%, lower than the value of 23% reported by Cacciatore et al. [24], as evaluated by MMSE <24, in a cross sectional study of Italian patients with a similar mean age of 73.9 years, with AF present in only 5.6% of the population. In that study heart failure, sex and age, but not AF, were associated with CImp [24]. Also in another study from Italy, with a slightly older patient population [25], the prevalence of CImp, as evaluated by MMSE, was higher than in our cohort suggesting that many factors related to clinical status and clinical history, but also to social status and education may contribute to the prevalence of CImp and dementia [2,26,27]. In a more general view it is clear that the different tests used for qualifying patients as affected by CImp and dementia and the variable settings and patient characteristics included in the different studies reported in literature suggest the need for more focused, standardized and validated approaches to this topical epidemiological issue [28].

In our analysis, focused on in- and outpatients with AF, the variables significantly associated with CImp were hypertension, Hb values (for each more unit of Hb, the likelihood of CImp decreases up to about 17%) and diagnosis of permanent AF present at enrolment. All these factors

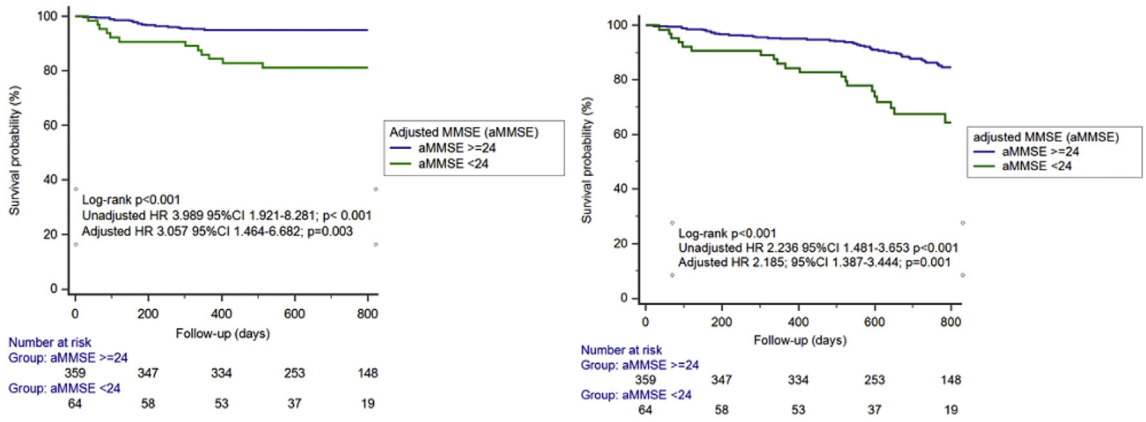

Fig. 1. The two panels depict survival curves according to CImp for the two endpoints considered. In panel (a) freedom form all-cause mortality; in panel(b) freedom from the composite end point (death and admissions for stroke/systemic embolism, hemorrhages, pulmonary embolism, acute coronary syndrome and new or worsening heart failure). In panel (a) HR is adjusted for Elixhauser Comorbidity Measure, coronary artery diasease, severe (>48 ml/m^2) left atrial enlargement and the presence of AF on ECG at enrolment while in the panel (b) adjustment was made for Elixhauser Comorbidity Measure, coronary artery disease, presence of AF on ECG at enrolment, first detected AF, and severe (>48 ml/m^2) left atrial enlargement.

are compatible with the hypothesized mechanisms that condition the pathophysiology of dementia and CImp [27,29].

Appropriate prescription of OAC is a key factor in management of AF patients [[4],30] and antiplatelet drugs can no longer be considered a valid alternative for stroke prevention. In recent years a series of observational studies showed an increased implementation of anticoagulation in patients at risk of stroke, probably related to increased awareness and availability of NOACs [31,32]. In our study prescription of antiplatelet drugs only, without OACs, occurred in a minority of patients, but was independently associated with CImp at enrolment, reflecting a different clinical profile in terms of vascular risk. However, it is noteworthy that in our series the rate of prescription of OAC was not lower in patients with CImp as compared with patients without CImp, differently from what reported in the ORBIT-AF cohort [33].

OAC is also valuable in secondary prevention of ischemic stroke in patients with dementia, although when applied with warfarin is associated a small increase in hemorrhages [34]. Since warfarin was found to have a low rate of implementation among patients with dementia, additional gains in stroke prevention appear feasible [34].

Appropriate prescription of OAC in AF may be important, apart for stroke prevention, for reducing the occurrence and the progression of CImp, according to a series of observational data, elaborated in a meta-analysis [35] suggesting that the effect of direct oral OACs may be superior to that of vitamin K inhibitors for reducing CImp at long term. In view of the limitations of observational studies, this finding needs to be confirmed in a properly designed randomized controlled trial.

In our study we found that at 2.4 years follow up an aMMSE <24 was independently associated with death and a composite endpoint (death, admissions for stroke/systemic embolism, hemorrhages, pulmonary embolism, acute coronary syndrome and new or worsening heart failure) also after adjustment for comorbidities using ECM, which was used to better define the patient clinical profile [36]. ECM presents some differences as compared with Charlson Comorbidity Index (CCI), since it is based on administrative data, but was found to be comparable with CCI in predicting mortality in patients with acute myocardial infarction [37]. In the setting of CImp, CCI may be less preferable since includes dementia in its set of variables, thus raising concerns about collinearity.

CImp was previously found an independent indicator of poor prognosis in older adults [38–41], acute coronary syndrome [42] or heart failure [43]. Our findings indicate that aMMSE, apart its diagnostic value, has also prognostic implications in the setting of AF, that may be taken into account in the clinical setting, in addition to other scores [44]. We also evaluated Elixhauser Comorbidity Measure, a clinical score for predicting likelihood of mortality, that incorporates administrative-collected clinical comorbidities [14] and we found that an ECM > 4 had a high specificity for death during follow up. According to these findings, cardiologists treating elderly patients with AF should become familiar with both aMMSE and ECM, two scores that may be of value for improved patient characterization, as well as for prognostic purposes.

There is an actual need to improve outcome prediction for patients with AF, in order to better guide clinical decision making. In this perspective our data suggest that aMMSE and ECM should be included in AF patient assessment. These scores give the chance for a more holistic approach to patients with AF, taking into account also comorbidities, and cognitive impairment. A more comprehensive approach, also including these scores, may apply not only to survival prediction but also to a series of outcomes, included in our composite end-point (death and admissions for stroke/systemic embolism, hemorrhages, pulmonary embolism, acute coronary syndrome and new or worsening heart failure) with great impact in a patient perspective, as well as in a health care system perspective, in view of AF epidemiology [45] and growing impact on resources and costs [46].

In a recent analysis of patients with AF, CImp or dementia were found significantly related to death (adjusted HR 1.34; 95%CI 1.05–1.72: $p = .0198$) [33]. However in this analysis, diagnosis of CImp or dementia was documented by treating physician and not with aMMSE, thus without a standardized measurement of neurocognitive status. Differently from our study this report from ORBIT AF included patients with cognitive impairment at enrolment, including dementia, while our study excluded patients with an overt dementia and explored the implication of an abnormal cognitive status, as measured by aMMSE <24.

The factors that might explain the relationship between CImp and all-cause mortality are multifaceted. In fact, CImp in AF patients could be the result of haemodynamic impairment related to irregular pulse, leading to cerebral hypoperfusion, hypoxia and silent cerebral infarcts and/or shared vascular risk factors, likely causative factors of CImp. Patients with CImp are older and prescribed with polypharmacy that can favor a reduced compliance [47].

According to our results, the prospective and serial assessment of the degree of cognitive impairment with aMMSE or other validated scores [28] would allow us to evaluate with better granularity the potential impact on outcomes of OACs, antihypertensive treatment, rhythm control strategies and specifically AF ablation with the aim to overcome the limitations of assessments based on subjective diagnosis or retrospective analysis of administrative data [1,27,48]. Initiatives based on screening

for AF in different patient population should also consider cognitive impairment as a criterion for patient targeting, as well as an important outcome for assessing the effectiveness of screening programmes vs no screening [49].

Moreover, our data further stress the adverse prognostic implications of first-detected AF [31], indirectly supporting the potential favorable impact of initiatives for AF screening targeted to an early recognition of undiagnosed or unknown AF [49,50].

8. Limitations

Our study has some limitations linked to its observational nature. We cannot exclude the presence of some residual confounding, persisting despite adjustment for a series of variables, due to unmeasured factors, or binarily categorized variables.

The number of patients in our cohort is limited but in daily practice is difficult to obtain such a comprehensive and complete set of prospectively collected data on CImp. Indeed, the evaluation of CImp could be potentially more challenging if a high number of patients or a multicenter- registry is considered [33].

Given the observational nature of our study, a multiparameter measurement of CImp was not possible in our patient population, in view of the necessity to reduce time-consuming visits. We, therefore, followed usual practice, which considers MMSE as a reasonable tool for clinical screening of CImp [27]. A recent document from the European Heart Rhythm Association also suggests that cognitive assessment should be performed in AF patients when there is suspicion of CImp [27] and this could be extended according to our study because also mild cognitive impairment, without overt dementia and thus not clinically obvious may have adverse outcomes.

Another limitation could be represented by the physicians administrating MMSE who were not specialized in administering such tests, but physicians were easily trained following Folstein's instructions [51].

9. Conclusions

In a cohort of AF patients with a mean age of 72 years and around half aged >75, cognitive impairment, as measured through aMMSE <24, had a prevalence of 14% at baseline. Permanent AF, Hb levels and previous treatment with antiplatelet drugs only, without OACs, were independently associated with cognitive impairment. The latter finding highlights the potential role of appropriate antithrombotic treatment for improving patient prognosis.

Cognitive impairment was also an independent predictor of death and vascular complications at long-term follow-up, in association with Elixhauser Comorbidity Measure. Future studies assessing the impact on outcome of various AF treatments or of AF screening, should include a measurement of CImp for patient characterization and for evaluating the impact of adopted interventions.

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Declaration of Competing Interest

RBS reports lecture fees and advisory board fees from BMS/Pfizer outside this work; BF reports prior fees and/or advisory board honoraria from Bayer Pharma AG, Boehringer Ingelheim, Daiichi-Sankyo, Omron, and Pfizer/BMS, and grants to the institution for investigator-initiated studies from BMS and Pfizer outside this work; GB reports speaker's fees from Boehringer Ingelheim, Boston, Biotronik, Medtronic outside this work. The other authors do not report any conflict of interest.

Appendix A. Supplementary data

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