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Research Article

Atrial Fibrillation and Cognitive Impairment: A Growing Association. Occurrence of Death among Chronic Complex Outpatients

Clua-Espuny JL[1], González-Henares[2]*, Queralt-Tomas MLL[3], Panisello-Tafalla A[4], Campo-Tamayo W[5], Muria Subirats E[5], Gil-Guillen VF[6], and Lasaga-Heriz A[7]

[1]EAP Tortosa 1-Est, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Temple, 43500 Tortosa, Spain.

[2]EAP-Camarles-Aldea-Ampolla, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Ampolla, 43895, Spain.

[3]EAP Tortosa-2-Oest, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Xerta, 43592, Spain.

[4]EAP Aldea-Camarles-Ampolla, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Aldea, 43520, Spain

[5]EAP Tortosa Est. Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya. Family and Community Specialty Resident. CAP Temple, 43500 Tortosa, Spain.

[6]Universidad Miguel Hernández. Cátedra Medicina de Familia. 03202 Elche, Spain. Clinical Evidence Based Medicine and Emotional Department, Miguel Hernández University, Family and Community Specialty

[7]EAP Tortosa-1-Est, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Temple, 43500 Tortosa, Spain

***Corresponding Author**: González Henares, EAP-Camarles-Aldea-Ampolla, Institute Català Salut, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, CAP Ampolla, 43895 Tortosa, Spain.

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Abstract

Introduction: In the developed countries, around 3 - 4% of the people could be identified as chronic complex patient and they are increasingly at risk of atrial fibrillation and cognitive impairment. The main objective of this study was to evaluate association of atrial fibrillation and mortality risk among chronic complex outpatients.

Materials and Methods: We carried out a multicenter and prospective cohort study of mortality incidence from 01.01.2013 to 30.09.2016 in a sample of 932 adult patients registered as Chronic Complex Outpatient (CCP). To predict hazard ratios, mean survival time, and survival probabilities used a multivariate Cox regression.

Results: The overall mortality among the CCP people with atrial fibrillation was 40.9% [CI95% 35.4 - 46.4] and 56.9% if it associates to cognitive impairment ($p < 0.001$). The long-term survival was not different between the group of CCP with AF and without AF (p 0.463). In the survival analyses, the outcome independent factors were: Pfeiffer score [HR 1.07 CI95% 1.005 - 1.146, $p < 0.036$], the Barthel score [HR 0.99 CI95% 0.98 - 0.99, $p < 0.019$], Charlson index [HR 1.17 CI95% 1.03 - 1.33, $p < 0.015$], and Heart Failure [HR 1.91 CI95% 1.33-2.74, $p < 0.001$]. The cognitive impairment was found to increase the mortality by 2-fold (Relative Risk: 1.69; CI95%: 1.31-2.17). Our results showed higher stroke incidence, but fewer and poor quality (c-TTR <60%) treatment with oral anticoagulants among those with cognitive impairment and Barthel score < 60 ($p < 0.001$).

Conclusion: Therefore, persons with AF should be investigated for the presence of cognitive impairment and heart failure given their higher prevalence and prognostic importance and should be a major priority in the treatment of atrial fibrillation.

Keywords: *Atrial Fibrillation; Cognitive Impairment; Chronic Complex Patient; Mortality; Disability; Heart Failure*

Abbreviations

AF: Atrial Fibrillation; CCP: Chronic Complex Patient; HF: Heart Failure; HR: Hazard Risk; IDIAP: Primary Care Research Institute Jordi Gol I Gurina; NOACs: Novel Oral Anticoagulants; SD: Standard Deviation; c-TTR: Time in Therapeutic Range

Introduction

We face an epidemic of multi-morbidity and rising complexity of health needs [1-3] resulting from changing demographics and global circumstances. With the aging of the population, chronic illness is increasingly common, leading to increasingly complex patient populations in primary care: common geriatric issues such as frailty, polypharmacy, and multi-morbidity are encountered more frequently. Atrial fibrillation and cognitive impairment are both strongly related to aging.

Recent research supports atrial fibrillation as a risk factor for incident dementia, independent of clinical stroke [4-6]. With the aging of the population, the number of patients with AF is expected to increase 150% in the next four decades with more than 50% of patients being over the age of 80 [7]. Elderly patients with atrial fibrillation have high incidence of thromboembolic complication and increasing age is associated with stroke severity. AF and their subsequent outcomes are likely to remain a major health care cost for all European countries for the foreseeable future.

Long-term studies suggest that 15 to 20 percent of those aged 65 and older may have mild cognitive impairment and have an increased risk of eventually developing Alzheimer's or another type of dementia [8]. The number of people living with dementia worldwide in 2015 was estimated at 47.47 million, reaching 75.63 million in 2030 and 135.46 million in 2050 [9]. For all studies combined, the incidence of dementia doubled with every 5.9 year increase in age, from 3.1/ 1000 person years at age 60 - 64, to 175.0/ 1000 person years at age ≥ 95 years [10].

The prevention and treatment of all both are of major importance because they engender significant morbidity and mortality becoming into major issues for health and social care providers [11-13].

The purpose of this report was to examine the association of atrial fibrillation with cognitive impairment among Complex and Chronic Patients in a longitudinal study of community. In the developed countries, around 3 - 4% of the people could be identified as chronic complex patient and they are increasingly at risk of atrial fibrillation and cognitive decline.

Materials and Methods

We carried out a multicenter and prospective cohort study of mortality incidence from 01.01.2013 to 30.09.2016 among out-of-hospital patients over 65 years old attending primary care teams in the Terres de l'Ebre health area in Catalonia (Spain). All people included were managed by the Public Health System in Catalonia. The overall number of CCP registered was 3,490 people. We included a randomized sample of 932 adult patients registered in the electronic health record of Primary Care as Chronic Complex Outpatient (CCP) in the period 01/01/2013-31/12/2014. Patients were excluded if they resided in a long-term institutional setting. Alpha Risk = 5%; Beta Risk = 20%; Power = 80,0%.

Patient outcome was followed until death or study end (30.09.2016) since date of report as CCP in the electronic health record. Data included demographics, functional, comorbidity, cognitive and social assessment, and were collected directly from the Shared Individual Intervention Plan [Pla d'intervenció individualitzat compartit (PIIC)] written and managed by Nursing service in Primary care. In the PIIC, determinants related to the personal factors, social and physical environment are described as well as a tailored personal approach according the patient's preferences in case of hospital readmission o emergency use, and main caregiver. The report is updated automatically to ensure that relevant information is shared across the electronic health record. Currently 82% of people registered as CCP have this basic information in their PIIC.

Definitions

Chronic Complex Patient (CCP) definition [14,15]: Those who meet at least four of the next criteria: Age (≥ 65-year-old). Chronic comorbidities (≥ 4). Psychosocial disorders (cognitive impairment or psychological disorder with functional disability). Geriatric conditions such as functional disability (Barthel score < 60, living to assisted living, nursing home, or in-home caregivers) or recurrent falls or fall risk. Previous high health care utilization (two hospitalizations no programmed for exacerbation of chronic pathologies or three emergency department visits in last year). Number of active medications last six months (≥ 4 active medications). Living alone or with caregiver ≥ 75-year-old. "They defined the "Chronic Complex Patient" [15] as those who have chronic illness and also complex clinical situations which make their management significantly far more difficult.

The independent variables were:

Sex: woman (0) man (1)
Age: <80-year-old (1), ≥80-year-old (2).
Number CCP criteria: <4 (0) ≥4 (1).
Charlson comorbidity index [16]. Short version.

Polypharmacy (defined as four or more daily medications): <5 (0), entre 5-9 (1), and ≥10 (2). Oral anticoagulants (acenocumarol or warfarina) with control TTR ≥60% (1), si TTR <60% (2) or New Oral Anticoagulants NOACs (0). The TTR for individual patients was estimated by Rosendaal method, using linear interpolation to assign an INR value to each day between two successively observed INRs [17]. We considered the average time in therapeutic range (TTR) to be lower if it was < 60%. Antidepressants and/or, sedating or other drugs affecting the neurologic system: man (1), woman (2).

Atrial fibrillation (any type of): no (0), yes (1).
Hypertension not controlled by therapy (≥ 160/90 mmHg): no (0), yes (1).
Alcoholism abuse vs dependence: no (0), yes (1)

Presence de cognitive impairment: a disease-specific diagnosis of cognitive impairment, without specification of sub-type or severity, was used and measured by Pfeiffer test [18]: [0-2 errors] = Intact Intellectual Functioning (1); [≥3 errors] = Mild to severe Intellectual Impairment (2)].

Presence de disability: score in [Barthel ≥60 (1) <60 (2)] or in [Rankin <4 (1) 5(2)].
Sociofamiliar risk: score in Gijon [19] scale 10 - 14 (1) ≥15 (2)]

Demographic data were summarized using mean and SD or median and quartiles for continuous variables and percentages for categorical data. Data analysis information extracted was the adjusted risk estimates and 95% confidence intervals (CI). Statistical tests of homogeneity were performed using Cochran's Chi-squared test for homogeneity (Q) and the percentage of total variation across studies attributable to heterogeneity (I^2). To predict hazard ratios, mean survival time, and survival probabilities used a multivariate Cox regression. The variables were included in a multivariable model Cox to identify their influence on the mortality. In the survival analyses of risk factors for death, follow-up began at the start of the study, and patients were censored when follow-up ended for reasons other than death. A graphical presentation of the survival of fallers versus non-fall risk was made using an adaptation of the Kaplan–Meier product-limit estimator.

Ethics approval was granted by Ethics Committee Research Institute Primary Care Jordi Gol i Gurina (IDIAP), Health Department, Generalitat de Cataluña.

Results

932 CCP cases were included as CCP [52.3% CI95% 49.1 - 55.6, women]. 325 [34.8% CI95% 31.7 - 37.9] were diagnosed of AF [46.5% CI95% 40.8 - 52.0, women]. The basal characteristics are showed in table 1.

CCP People (N 932)	Without AF (n_1 607)	With AF (n_2 325)	P
N (%)	607	325 (34.87%)	
Age (average ± SD)	81.8 ± 10.86	83.9 ± 7.51	0.002
Percentage > 80-year-old n (%)	408 (67.2%)	247 (76.0%)	0.003
Women n (%)		151 (46.5%)	0.005
CCP criteria number (average ± SD)	3.81 ± 1.21	3.95 ± 1.12	0.076
Charlson score (average ± SD)	2.44 ± 1.38	2.68 ± 1.36	0.014
Hypertension n (%)	500 (82.4%)	274 (84.3%)	0.256
Diabetes mellitus n (%)	345 (56.8%)	149 (45.8%)	0.001
Dyslipidemia n (%)	354 (58.3%)	167 (51.4%)	0.025
Active smoking n (%)	50 (8.2%)	22 (6.8%)	0.253
Alcoholism active n (%)	12 (2.0%)	11 (3.4%)	0.137
Ischaemic Heart Disease n (%)	120 (19.8%)	76 (23.4%)	0.114
Peripheral arterial occlusive disease n (%)	98 (16.1%)	51 (15.7%)	0.468
Failure Heart n (%)	131 (21.6%)	172 (52.9%)	< 0.001
Daily medications number (average±SD)	8.49 ± 3.68	9.58 ± 3.31	< 0.001
CHADSVASC score (average±SD)	5.31 ± 1.85	5.00 ± 1.26	0.344
Stroke risk/year (average±SD)	6.11 ± 2.53	6.55 ± 2.41	0.485
HAS-BLED (average±SD)	3.38 ± 1.20	2.96 ± 1.09	0.147
Major Bleeding rate %/year (average±SD)	6.06 ± 4.38	4.89 ± 3.57	0.207
Oral Anticoagulant treatment n (%)	30 (4.9%)	240 (73.9%)	< 0.001
Labile INR (TTR < 60%)	53.16 ± 28.4	53.08 ± 27.31	0.988
Hypertension no controlled n (%)	79 (13.0%)	28 (8.6%)	0.026
Stroke before CCP register n (%)	123 (20.3%)	77 (23.7%)	0.129
Stroke after CCP register n (%) /1000 people	41 (6.8%) 0.675	25 (7.7%) 0.769	0.701
Cognitive Impairment n (%)	236 (38.9%)	102 (31.4%)	0.014
Pfeiffer Test Score (average ± SD)	3.34 ± 3.47	2.54 ± 2.80	< 0.001
Barthel score (average ± SD)	63.91 ± 33.63	70.2 ± 28.09	0.004

Percentage Barthel score <60 Moderate dependence n (%)	241 (39.7%)	102 (31.4%)	0.007
Gijón score (average ± SD)	10.28 ± 4.86	9.35 ± 4.16	0.377
Platelet anti-aggregants n (%)	306 (50.4%)	79 (24.3%)	< 0.001
Statins treatment n (%)	24 (30.8%)	23 (35.4%)	0.342
Inhibitor proton pump n (%)	394 (64.9%)	249 (76.6%)	< 0.001
Antidepressants and/or sedating or similars n (%)	346 (57.6%)	168 (51.7%)	0.069
Falls risk report n (%)	134 (22.1%)	54 (16.6%)	0.028
Death n (%)	186 (30.6%)	133 (40.9%)	0,.001
Average survival time (days) (average ± SD)	971.71 ± 1462.9	1066.01 ± 2455.4	0.463

Table 1: *Baseline characteristics of Complex and Chronic Patients with Atrial Fibrillation.*

The patients with AF were on average older, a larger proportion was male and aged ≥80 years, and they had a lower prevalence of diabetes, dyslipidemia, but higher prevalence of heart failure (HF), higher Barthel score, higher Charlson score, and higher incidence of mortality than those without atrial fibrillation (Figure 1). Average age was 82.5 yr (CI95% 81.8 - 83.2). Average number of CCP criteria was 3.83 (CI 95% 3.75 - 3.92). The global mortality was 40.9% [CI95% 35.4 - 46.4]. The average survival time was 1,066.13 ± DS 2455.0 days. In the survival analyses of risk for death, the outcome independent factors were: Pfeiffer score [HR 1.07 CI95% 1.005 - 1.146, p < 0.036], the Barthel score [HR 0.99 CI95% 0.98-0.99, p < 0.019], Charlson index [HR 1.17 CI95% 1.03-1.33, p < 0.015], and HF [HR 1.91 CI95% 1.33-2.74, p < 0.001].

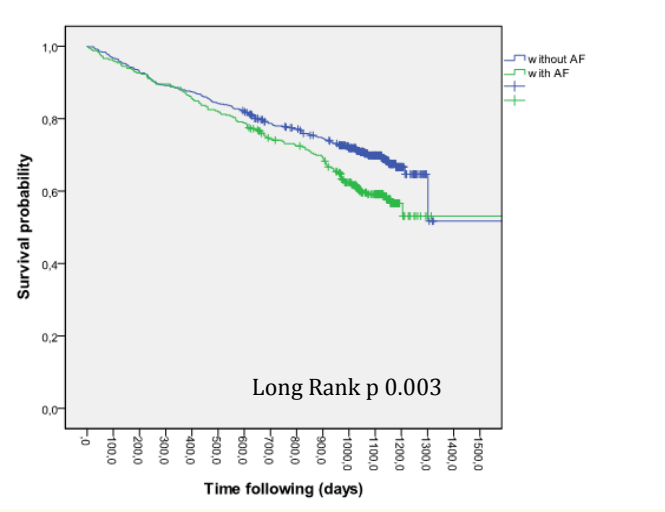

Figure 1: *Survival among PCC people: with AF vs without AF.*

102 patients [31.38 CI95% 26.1 - 36.5] with AF had been diagnosed for cognitive impairment by Pfeiffer test. The basal characteristics are showed in table 2. They were more likely to be women [54.9% CI95% 44.7 - 65.0, p < 0.008], be older age [86.45 ± SD 5.90 vs 82.86

± SD7.90, p < 0.001], have more CCP criteria [4.63 ± SD 1.19 vs 3.64 ± SD 0.94, p < 0.001]; higher score in Charlson index [3.24 ± SD 1.40 vs 2.42 ± SD1.25, p < 0.001]; higher baseline burden of functional dependence in daily activities [Barthel index [53.15 ± SD28 vs 77.9 ± SD24.08, p < 0.001] and higher mortality [56.9% vs 33.6%, p < 0.001] (Figure 2). Cognitive impairment was found to increase the mortality by 2 times (Relative Risk: 1.69; CI95%: 1.31 - 2.17). Other interesting points were: patients with cognitive impairment were more likely to be treated with Central Nervous System medications (antidepressants, sedating and others) [65.7% vs 45.3, p < 0.001], with antiplatelet agent rather than anticoagulant (p < 0.008), and had more labile INR [70% vs 53.2%, p < 0.018]; but less treatment with statins [33.3% vs 48.5%, p < 0.009] and suffered more stroke incidence. The outcome independent factors were: age [HR 1.02 CI95% 1.00 - 1.05, p < 0.048], Charlson index [HR 1.16 CI95% 1.02 - 1.32, p < 0.019], and heart failure [HR 1.83 CI95% 1.27 - 2.63, p < 0.001]. The Barthel score keeps as protector factor [HR 0.99 CI95% 0.986 - 0.998, p < 0,011]. Using a reduced model and adjusting for the strongest known predictors of mortality (age at the register CCP, sex and Charlson score), the Barthel score remained a significant factor in reduction in mortality [HR 0.984 CI95% 0.976 - 0.993, p < 0.001]. We observed a strong association between cognitive impairment and mortality that persisted even after adjustment for known mortality risk factors, such as age.

CCP People with AF (N 325)	With Out cognitive impairment (n_1 223)	With cognitive impairment (n_2 102)	P
N (%)	223	102 (31.38%)	
Age (average ±SD)	82.8±7.90	86.45±5.90	< 0.001
Percentage > 80-year-old n (%)	156 (70%)	91 (89.2%)	< 0.001
Women n (%)		58 (56.9%)	0.008
CCP criteria number (average±SD)	3.64±0.94	4.63±1.19	< 0.001
Charlson score (average±SD)	2.42±1.26	3.24±1.40	< 0.001
Hypertension n (%)	191 (85.7%)	83 (81.4%)	0.205
Diabetes mellitus n (%)	101 (45.3%)	48 (47.1%)	0.429
Dyslipidemia n (%)	125 (56.1%)	42 (41.2%)	0.009
Active smoking n (%)	21 (9.2%)	1 (1%)	0.002
Alcoholism active n (%)	11 (4.9%)	0 (0.0%)	0.115
Ischaemic Heart Disease n (%)	51 (22.9%)	25 (24.5%)	0.414
Peripheral arterial occlusive disease n (%)	39 (17.5%)	12 (11.8%)	0.123
Failure Heart n (%)	118 (52.9%)	54 (52.9%)	0.546
Daily medications number (average±SD)	9.92±3.23	8.83±3.36	0.006
CHADSVASC score (average±SD)	4.92±1.30	5.16±1.17	0.134
Stroke risk/year (average±SD)	6.40±2.47	6.87±2.27	0.115
HAS-BLED (average±SD)	2.92±1.08	3.05±1.13	0.339
Major Bleeding rate %/year (average±SD)	4.76±3.48	5.17±3.75	0.363
Oral Anticoagulant treatment n (%)	156 (70.0%)	62 (60.8%)	0.137
Labile INR (TTR < 60%)	83 (53.2%)	42 (70.0%)	0.018
Hypertension no controlled n (%)	22 (9.9%)	6 (5.9%)	0.165
Stroke before CCP register n (%)	45 (20.2%)	32 (31.4%)	0.021
Stroke after CCP register n (%) /100 people/year	16 (7.2%) 2.18/100/year	9 (8.8%) 4.18/100/year	0.231
Pfeiffer Test Score (average±SD)	0.94±1.14	6.03±2.08	< 0.001

Barthel score (average±SD)	77.9±24.08	53.15±28	< 0.001
Percentage Barthel score <60 Moderate dependence n (%)	46 (20.6%)	56 (54.9%)	< 0.001
Gijón score (average±SD)	9.89±3.34	8.50±5.24	0.372
Platelet anti-aggregants n (%)	45 (20.2%)	34 (33.3%)	0.008
Statines treatment n (%)	107 (48.8%)	34 (33.3%)	0.009
Inhibitor proton pump n (%)	175 (78.5%)	74 (72.5%)	0.152
Antidepressants and/or sedating or similar n (%)	101 (45.3%)	67 (65.7%)	< 0.001
Falls risk report n (%)	33 (14.8%)	21 (20.6%)	0.128
Death n (%)	75 (33.6%)	58 (56.9%)	< 0.001
Average survival time (days) (average±SD)	1200.4±2944.3	772.0±399.0	0.034

Table 2: *Basal characteristics Complex and Chronic Patients with Atrial Fibrillation and cognitive impairment.*

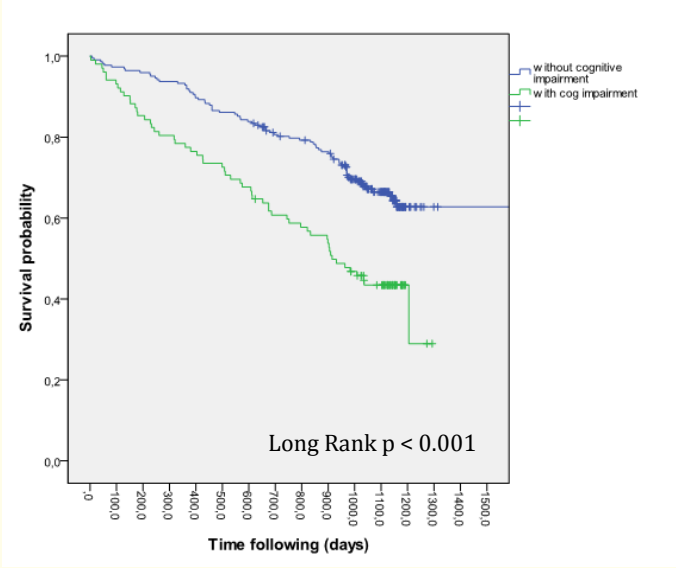

Figure 2: *Survival CPP and AF with/without cognitive impairment.*

172 patients [52.92% CI95% 47.3 - 58.5] with AF had been diagnosed for HF. The basal characteristics are showed in table 3. They were more likely to be men [51.7%, CI95% 43.9 - 59.5, p 0.282], be older age [84.9 ± SD 7.10 vs 82.98 ± SD7.85, p < 0.022], have higher score in Charlson index [2.86 ± SD 1.23 vs 2.47 ± SD1.45, p < 0.009]; higher score in CHA2DS2-VASc [5.28 ± SD 1.20 vs 4.68 ± SD1.26, p < 0.001] and higher mortality [50.6% vs 30.1%, p < 0.001] (Figure 3). The HF remained the strongest outcome independent factor associated to mortality after adjustment for other risk factors. The heart failure was found to increase the mortality by 2 times (Relative Risk: 1.68; CI95%: 1.26 - 2.23).

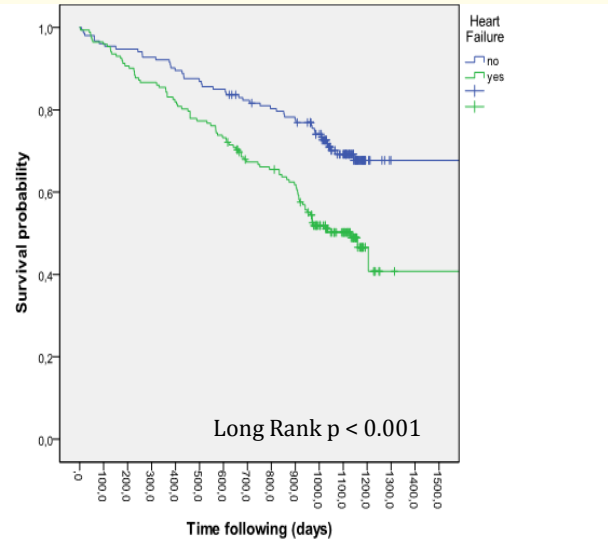

Figure 3: *Survival in CPP with AF and Heart Failure.*

CCP People with AF (N 325)	Without Heart Failure (n_1 153)	With Heart Failure (n_2 172)	P
N (%)	153	172 (52.92%)	
Age (average ±SD)	82.9±7.85	84.9±7.10	0.022
Percentage >80-year-old n (%)	109 (71.2%)	138 (80.2%)	0.039
Women n (%)	68 (44.4%)		0.282
CCP criteria number (average±SD)	3.91±1.21	3.99±1.04	0.524
Charlson score (average±SD)	2.47±1.45	2.86±1.23	0.009
Hypertension n (%)	133 (86.9%)	141 (82.0%)	0.142
Diabetes mellitus n (%)	78 (49.7%)	73 (42.4%)	0.116
Dyslipidemia n (%)	83 (54.2%)	84 (48.8%)	0.194
Active smoking n (%)	12 (7.8%)	10 (5.8%)	0.306
Alcoholism active n (%)	10 (6.5%)	1 (0.6%)	0.003
Ischaemic Heart Disease n (%)	34 (22.2%)	42 (24.2%)	0.369
Peripheral arterial occlusive disease n (%)	27 (17.6%)	24 (14.0%)	0.223
Daily medications number (average±SD)	9.36±3.34	9.78±3.27	0.255
CHADSVASC score (average±SD)	4.68±1.26	5.28±1.20	< 0.001
Stroke risk/year (average±SD)	6.03±2.47	7.00±2.28	< 0.001
HAS-BLED (average±SD)	2.94±1.07	2.99±1.12	0.687
Major Bleeding rate %/year (average±SD)	4.80±3.59	4.97±3.57	0.666
Oral Anticoagulant treatment n (%)	111 (72.6%)	129 (74.0%)	0.395
Labile INR (TTR < 60%)	54 (55.1%)	71 (60.2%)	0.270

Hypertension no controlled n (%)	15 (9.8%)	13 (7.6%)	0.300
Stroke before CCP register n (%)	40 (26.1%)	37 (21.4%)	0.198
Stroke after CCP register n (%) /100 people/year	16 (10.5%) 3.36/100/year	9 (5.2%) 1.90/100/year	0.134
Pfeiffer Test Score (average±SD)	2.59±2.95	2.48±2.66	0.719
Cognitive Impairment (Peiffer score ≥4)	48 (31.4%)	54 (31.4%)	0.546
Barthel score (average±SD)	72.03±28.33	68.55±27.86	0.265
Percentage Barthel score <60 Moderate dependence n (%)	43 (28.1%)	59 (34.3%)	0.140
Gijón score (average±SD)	9.89±3.34	8.50±5.24	0.372
Platelet anti-aggregants n (%)	40 (26.1%)	39 (22.7%)	0.275
Statins treatment n (%)	65 (42.5%)	76 (44.2%)	0.422
Antidepressants and/or sedating or similars n (%)	76 (49.7%)	92 (53.5%)	0.282
Falls risk report n (%)	23 (15.0%)	31 (18.0%)	0.284
Death n (%)	46 (30.1%)	87 (50.6%)	< 0.001
Average survival time (days) (average±SD)	1136.4±2402	1003.0±2507.0	0.627

Table 3: *Basal characteristics Complex and Chronic Patients with Atrial Fibrillation and Heart Failure.*

The compared basal characteristics in the different groups are showed in table 4. Cognitive impairment is particularly common (31.4%) among those with HF and exerts significant effects on mortality of patients with HF (Figure 4). Our results showed higher stroke incidence, but less treatment with oral anticoagulants mainly among those with Barthel score < 60 ($p < 0.001$) and poor quality (c-TTR < 60%) among those with cognitive impairment.

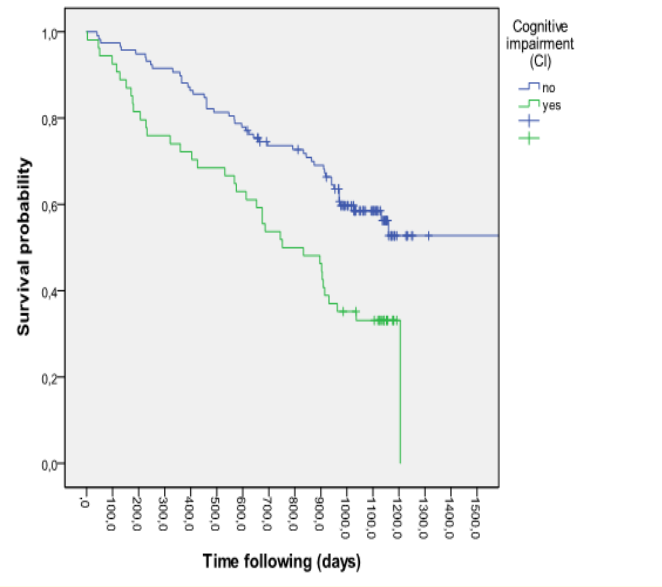

Figure 4: *Survival in [AF and heart failure] with cognitive impairment.*

CCP People with AF (N 325)	Atrial Fibrillation (All)	FA+Cognitive Impairment	FA+Heart Failure
N (%)	325 (34.87%)	102 (31.38%)	172 (52.92%)
Age (average ±SD)	83.9±7.51	86.45±5.90	84.9±7.10
Percentage >80-year-old n (%)	247 (76.0%)	91 (89.2%)	138 (80.2%)
Women n (%)	151 (46.5%)	58 (56.9%)	68 (44.4%)
CCP criteria number (average±SD)	3.95±1.12	4.63±1.19	3.99±1.04
Charlson score (average±SD)	2.68±1.36	3.24±1.40	2.86±1.23
Hypertension n (%)	274 (84.3%)	83 (81.4%)	141 (82.0%)
Diabetes mellitus n (%)	149 (45.8%)	48 (47.1%)	73 (42.4%)
Dyslipidemia n (%)	167 (51.4%)	42 (41.2%)	84 (48.8%)
Active smoking n (%)	22 (6.8%)	1 (1%)	10 (5.8%)
Alcoholism active n (%)	11 (3.4%)	0 (0.0%)	1 (0.6%)
Ischaemic Heart Disease n (%)	76 (23.4%)	25 (24.5%)	42 (24.2%)
Peripheral arterial occlusive disease n (%)	51 (15.7%)	12 (11.8%)	24 (14.0%)
Daily medications number (average±SD)	9.58±3.31	8.83±3.36	9.78±3.27
CHADSVASC score (average±SD)	5.00±1.26	5.16±1.17	5.28±1.20
Stroke risk/year (average±SD)	6.55±2.41	6.87±2.27	7.00±2.28
HAS-BLED (average±SD)	2.96±1.09	3.05±1.13	2.99±1.12
Major Bleeding rate %/year (average±SD)	4.89±3.57	5.17±3.75	4.97±3.57
Oral Anticoagulant treatment n (%)	240 (73.9%)	62 (60.8%)	129 (74.0%)
Labile INR (TTR < 60%)	125 (57.9%)	42 (70.0%)	71 (60.2%)
Hypertension no controlled n (%)	28 (8.6%)	6 (5.9%)	13 (7.6%)
Stroke before CCP register n (%)	77 (23.7%) 8.11/100/year	32 (31.4%) 14.86/100/year	37 (21.4%) 7.85/100/year
Stroke after CCP register n (%) /100 people/year	25 (7.7%) 2.63/100/year	9 (8.8%) 4.18/100/year	9 (5.2%) 1.90/100/year
Pfeiffer Test Score (average±SD)	2.54±2.80	6.03±2.08	2.48±2.66
Barthel score (average±SD)	70.2±28.09	53.15±28	68.55±27.86
Percentage Barthel score <60 Moderate dependence n (%)	102 (31.4%)	56 (54.9%)	59 (34.3%)
Gijón score (average±SD)	9.35±4.16	8.50±5.24	8.50±5.24
Platelet anti-aggregants n (%)	79 (24.3%)	34 (33.3%)	39 (22.7%)
Statins treatment n (%)	23 (35.4%)	74 (72.5%)	76 (44.2%)
Antidepressants and/or sedating or similars n (%)	168 (51.7%)	67 (65.7%)	92 (53.5%)
Falls risk report n (%)	54 (16.6%)	21 (20.6%)	31 (18.0%)
Death n (%)	133 (40.9%)	58 (56.9%)	87 (50.6%)
Average survival time (days) (average±SD)	1066.01±2455.4	772.0±399.0	1003.0±2507.0

Table 4: *Differential characteristics of CCP people with Atrial Fibrillation and Cognitive Impairment.*

The overall mortality among the CCP people with atrial fibrillation was 40.9% and 56.9% if it associates to cognitive impairment (p 0.001). The long-term survival was not different between the group of CCP with AF and without AF (p 0.463). In unadjusted analysis, patients who had AF were at a significantly higher risk of death if were older ≥80-year-old, with cognitive impairment or Barthel score < 60.

Discussion

This study is one of the few prospective studies to examine the significance of atrial fibrillation associated to cognitive impairment and their longitudinal outcome mortality among individuals identified as Chronic Complex Patients. These patients are among the highest-cost users of health organization and they constitute an important source of growth in expenditures and increasing the number of co-morbidities induces a multiplicative rather than an additive cost structure. This suggests that disease management and care coordination programs will face a difficult challenge in coping with the heterogeneity of patient health conditions [20].

The mean of CCP is similar to frailty, a novel concept that is not yet well defined in the literature [21]. Frailty is a complex entity that encompasses a range of clinical conditions such as limited mobility with a high falls risk, polypharmacy, comorbidity, low social status, nutritional impairment and cognitive impairment.

It is known the AF incidence in cognitively impaired persons is significantly higher than those without cognitive impairment [22]. Our results added a strong association between AF, cognitive impairment and heart failure for mortality. Also, the AF was described as the strongest risk factor for cognitive impairment in patients with congestive heart failure [23] and its development in patients without previous AF or stroke predicted a faster cognitive decline [6,24,25]. Like our results, several studies have demonstrated that cognitive impairment is particularly common among 30% to 80% of patients with HF [26]. Presence of cognitive impairment may interfere with self-care and may be related to increased mortality [27] and the treatment adherence may be obviously influenced by self-care and compromise patients' capacity to make appropriate decisions about their health care exerting significant effects on quality of life, disability, morbidity, and mortality. Also, it could contribute with social and behavioral problems. The challenges for clinicians will be not only the treatment of cardiac disease itself but also the identification and the management of associated conditions such as cognitive impairment, in order to prevent major complications.

Therefore, persons with AF should be investigated for the presence of cognitive impairment and HF given their higher prevalence and prognostic importance and should be a major priority in the treatment of atrial fibrillation. Health professionals should become familiar with assessment of cognitive performance in their routine evaluations. At present, the best treatment to prevent progression of AF-associated cognitive impairment is unknown. Patients should be encouraged to participate in cognitive, physical, and social activities in order to improve their cognitive performance.

The available data on the benefit of warfarin are controversial. According to guidelines [1], if a c-TTR of more than 60% cannot be maintained, treatment with NOACs should be considered. Internationally, studies of the quality of OAC treatment in general practice have consistently shown poor results [7,28], but we found a mean c-TTR < 60% of 70.0% in the group with cognitive impairment and 60% in those with HF, which suggests that OAC treatment is of poor quality.

The risk scores, HA2DS2VASC and HAS-BLED, rise with age up to 85 years, but, as the risk of stroke increases, the rate of anticoagulation use does not differ or decrease in group with cognitive impairment. This may be due to the concerns of providers regarding the risk of bleeding and the risk-benefit trade-off of treatment for higher-risk populations. The reasons for the underuse of anticoagulation are poorly understood and these findings suggest that providers are using factors other than clinical risk stratification tools to guide anticoagulation decisions [7]. Despite the clear indication for anticoagulation treatment according to established risk scores, in practice this treatment is often withheld from geriatric AF patients because of comorbidities (21%), cognitive impairment (15%) and bleeding risk (12%) [29]. The CCP assessment along with CHADS-VASc and HAS-BLED score can provide fine resolution for predicting mortality in older atrial fibrillation patients [30]. Our results also showed this association between CHADS-VASc and mortality but only among patients with HF. Finally, a small number of studies provided valuable evidence that specific medications used in HF such as ACE inhibi-

tors and digoxin may have beneficial effects on cognitive performance of HF patients [31]. Effective control of vascular risk factors and therapeutic goals in anticoagulant use should be achieved. Long-term studies are needed to determine if strict TTR control or use of the novel oral anticoagulants can influence progression of AF-associated cognitive impairment.

These results confirm that cognitive deficits detected on clinical assessment among people with AF are associated with an increased mortality risk in community. A diagnosis of AF in people with cognitive impairment may even represent a reliable risk factor for cognitive decline and is a useful indicator of the risk mortality. It has been described [9] that these patients are older, suffer more chronic diseases and have poorer functional status at baseline and functional deterioration which could explain the higher mortality. It would appear as a worsening factor in any CCP condition. The Isolation and loneliness has been shown to be an added risk factor. The percentage in our study was 22.3% among people ≥ 75-year-old. Those who are unaided constitute a high priority group for preventive interventions.

Conclusion

In summary, in our CCP cohort with atrial fibrillation the heart failure is present in 52.9%, and the cognitive impairment in 31.4%. We report an independent positive association between them and mortality risk. The long-term survival was significantly lower when were introduced the cognitive impairment and the HF. Also, they got the worse results in the quality of anticoagulant treatment. Therefore, persons with AF should be investigated for the presence of cognitive impairment and heart failure given their higher prevalence and prognostic importance and should be a major priority in the treatment of atrial fibrillation.

There is a need for a large multicenter study to provide additional data to implement strategies to treat or even prevent cognitive decline in elderly patients with HF and to examine the effects of novel oral anticoagulants on long-term cognitive function.

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