Oral anticoagulation in patients with atrial fibrillation and medical non-neoplastic disease in a terminal stage

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Contributor statement
We assure that all authors included on a paper fulfill the criteria of authorship. J. Díez-Manglano, M. Bernabeu-WIttel, J. Murcia-Zaragoza and C. Hernández-Quiles designed the study. J. Díez-Manglano, M. Bernabeu-WIttel, J. Murcia-Zaragoza, B. Escolano-Fernández, G. Jarava-Rol, C. Hernández-Quiles, M. Oliver and S. Sanz-Baena performed the data collection. Data analysis was performed by J. Díez-Manglano. The manuscript was drafted by J. Díez-Manglano, and M. Bernabeu-WIttel, J. Murcia-Zaragoza, B. Escolano-

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Conflict of interest
None.

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Short title
Oral anticoagulation in terminal disease

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ABSTRACT

Background: Many patients with non-neoplastic disease develop atrial fibrillation in advanced stages of their disease.

Aim: Determining the factors associated with the use of oral anticoagulants in patients with atrial fibrillation and non-neoplastic medical disease in a terminal stage and whether their use is associated to longer survival.

Design: Prospective, observational, multicentre study

Participants: Patients with atrial fibrillation and non-neoplastic disease (severe not reversible organ insufficiency) in a terminal stage were included between February 2009 and September 2010. A six months follow-up was carried out.

Results: We included 314 patients with a *mean (SD)* age of 82.6 (7.0) years. Their *mean (SD)* scores in CHADS2 and ATRIA scales were 3.4 (1.2) and 4.7 (2.0), respectively. Anticoagulants were prescribed to 112 (37.5%) patients. The use of anticoagulants was associated to age (OR 0.96 95%CI 0.93-0.99, p=0.046) and to Barthel index (OR 1.01 95%CI 1.00-1.02; p=0.034). After performing a propensity score matching analysis, 262 patients were included in survival analysis. After 6 months 133 (50.8%) patients were dead. Mortality was higher among patients who were not treated with oral anticoagulants (57.1% vs. 39.4%; p=0.006), but it was independently associated only with the Barthel index score (HR 0.99 95%CI 0.98-1.00; p=0.039), delirium (HR 1.60, 95%CI 1.08-2.36; p=0.018), anorexia (HR 1.58 95%CI 1.05-2.38; p=0.027) and with the use of calcium channel blockers (*HR* 0.50 95%CI 0.30-0.84; p=0.009).

Conclusions: In patients with atrial fibrillation and non-neoplastic disease in a terminal stage, the use of oral anticoagulants wasn´t independently associated with a higher probability of survival.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrythmia among the general population, and its frequency increases with age [1,2]. Patients with AF have an increased risk of suffering a stroke or thromboembolic events. The use of antivitamin K drugs and the direct oral anticoagulants is associated with a decrease in the onset of stroke, in mortality and in disability [3,4]. Clinical practice guidelines recommend the use of oral anticoagulants (OA) in patients with AF and a high risk of stroke [5]. Following these recommendations is accompanied by a decrease in mortality [6]. The same benefit has been observed in patients with AF and comorbidity and polypathology [7]. There is no evidence, however, about when not to start the treatment with OA or when to interrupt their use.

With the progressive aging of the population and the advances in healthcare, it is becoming more and more frequent for patients with chronic diseases to live longer and eventually develop an organ failure. At present, patients with pulmonary chronic obstructive disease, heart failure, kidney failure, chronic liver disease or advanced neurologic disease have a long survival and develop AF in advanced stages of their disease [8,9]. When the patients have an expected survival of less than 6 months, they are considered to be in the terminal stage of their disease.

The aim of this study was to determine which characteristics were associated with the use of OA in patients with AF and medical non-neoplastic disease in a terminal stage and whether these patients benefitted or not from such treatment.

MATERIAL AND METHODS

Study design

In this study we present the analysis of the patients with AF included in the PALIAR study. The design of the PALIAR study has been previously described [10]. It was an observational, prospective and multicentre study in which researchers from Internal Medicine and Geriatrics departments of 41 Spanish hospitals took part (**Appendix**). Its main objective was to develop a prognostic tool to determine the risk of death within 6 months in patients with advanced medical non-neoplastic diseases. Between February 2009 and September 2010 each researcher included consecutively all patients with a medical non-neoplastic disease in an advanced stage. Later on, a follow-up was carried out during 6 months. The main result was all cause mortality. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by Ethics Committee of the university hospitals Virgen del Rocío of Seville in Spain. Every patient, or their relatives in case of cognitive impairment or delirium, signed informed written consent forms.

Inclusion criteria

To be included in the PALIAR study, patients had to be over 18 years of age and present any of the following diseases: heart failure with basal dyspnea III or IV by the New York Heart Association, chronic respiratory failure with basal dyspnea stage 3 or 4 of the modified Medical Research Council scale and/or basal arterial oxygen saturation < 90% and/or home oxygen therapy, chronic kidney failure in stages 4 or 5 of the National Kidney Foundation (glomerular filtration rate <30 mL/min and/or basal creatininaemia ≥ 3 mg/dL), chronic liver disease with clinical or analytical or endoscopic or ecographic data indicating portal hypertension and/or hepatocellular failure with a Child-Pugh score > 7, chronic neurological disease with established cognitive impairment (7 or more errors in the Short Portable Mental Status Questionnaire and/or ≤ 18 points in the Mini-mental State Examination) and/or functional impairment for basic activities of daily living (Barthel index < 60 points) [10-16]. Patients in a waiting list for a heart, liver and/or kidney transplantation, with an active neoplasia other than localized prostate adenocarcinoma on hormone therapy and basocellular or spinocellular skin carcinomas, those in a situation of death throes and those who did not give their consent were excluded.

The subgroup of patients with paroxysmal, persistent or permanent AF and disease in a terminal stage was included in this analysis. Disease in a terminal stage was defined according to the criteria of the National Hospice Organization [17]. The patient should meet all the following criteria: (i) the patient´s condition is life limiting (expected survival lower than 6 months) and the patient and/or family know this; (ii) the patients and/or family have elected treatment goals

directed to relief of symptoms, rather than the underlying disease, and (iii) the patient has documented clinical progression of the disease or documented recent impaired nutritional status related to the terminal process.

Measurements

The following data were gathered for each patient: age, sex, residence, advanced disease type, comorbidity, drugs used (OA, antiplatelet agents, angiotensin-converting enzyme inhibitors/angiotensin receptors blockers, calcium channel blockers, beta-blockers, diuretics, statins), ability to carry out basic activities of daily living, risk of stroke, risk *of* hemorrhage, symptoms and signs of advanced disease (cachexia defined as a body mass index < 20 kg/m^2, anorexia, edemas, delirium, dyspnea, refractory pressure skin ulcers, asthenia, chronic pain, insomnia, diarrhea), laboratory data (creatinine, hemoglobin) and hospital admissions in the 12 previous months. OA was referred to vitamin K antagonists only. Comorbidity was calculated with the Charlson index [18], which takes 19 diseases into account. A score ≥ 2 indicates high comorbidity. The ability for activities of daily living was measured with the Barthel index [16]. It scores between 0 and 100, lower score indicating higher disability. The risk of stroke was assessed by the CHADS2 score [19]. The risk was considered low for a score of 0, intermediate for a score of 1 and high for a score of ≥ 2. The risk of hemorrhage associated with OA was assessed by the ATRIA score [20]. The risk was considered low for a score of 0-3, intermediate for a score of 4 and high for a score of 5-10. The authors calculated both CHADS2 and ATRIA scores for this analysis.

Statistical analysis

Reported 6-month all-cause mortality in AF patients treated with or without OA was 31% and 20% respectively [6]. Assuming a 5 % type I error and a 5 % precision, a sample size of 245 patients was calculated.

Categorical variables were expressed as absolute frequencies and percentages and quantitative variables as mean and standard deviation. Qualitative variables were compared with the chi-square test and quantitative variables with the Student's t-test. In the multivariate analysis, a logistic regression model was constructed to determine which variables were associated with the use of OA, applying those variables associated with a $p<0.1$ in the univariate analysis.

A propensity score matching analysis was performed to correct for the imbalance among the groups of patients who were treated with OA or not. The variables selected as possible confounders were all baseline covariates that were associated with the use of OA (age, terminal disease type, Barthel index, presence of delirium, use of beta-blockers and diuretics). The matching was 2:1. To determine the variables associated with mortality, a Cox proportional regression model was used. The comparison of survival curves was carried out with the long-rank test. Statistical significance was established at $p<0.05$.

RESULTS

Figure 1 shows the flowchart of included patients. PALIAR project included 645 patients with AF and advanced non-neoplastic medical disease and 314

(48.7%) were in terminal stage. Their average age (standard deviation) was 82.6 (7.0) years, and 182 (58.0%) of them were male.

Type of disease and risk of stroke and bleeding

Heart, neurological and respiratory diseases were the most frequent (54.8%, 47.8% y 35.3% respectively), and 46.2% of the patients had more than one terminal illness. The mean CHADS2 score was 3.4 (1.2). Risk of stroke was low in 1 (0.3%) patient, intermediate in 15 (4.8%) and high in 298 (94.9%). Their mean ATRIA score was 4.7 (2.0). Risk of bleeding was low in 89 (28.3%) patients, intermediate in 11 (3.5%) and high in 214 (68.1%).

Use of anticoagulants

OA were prescribed to 112 (35.7%) patients. Table 1 presents the characteristics of patients treated with and without OA. Patients treated with OA were younger [80.8 (6.3) vs. 83.6 (7.2); p=0.0005], scored higher on the Barthel index [39 (33) vs. 21 (25); p=0.0003], had heart, neurological (both p<0.0001) and respiratory (p=0.005) diseases more frequently and with less delirium (p=0.001). They also were more frequently treated with beta-blockers and diuretics. There were no differences in the CHADS2 and ATRIA scores.

In the multivariate analysis (table 2), a younger age (OR 0.96 95%CI 0.93-0.99; p=0.046) and a higher score in Barthel index (OR 1.01 95%CI 1.00-1.02; p=0.034) were associated with a greater use of OA. Kidney disease (OR 2.707 95%CI 1.286-5.695; p=0.009) and use of statins (OR 2.712 95%CI 1.412-5.209; p=0.003) were associated with receiving calcium channel blockers.

Mortality

After performing a propensity score matching analysis we included 262 patients in survival analysis, 94 treated and 168 not treated with OA. *Several baseline characteristics were still unbalanced between the two groups.* During the 6 months follow-up 133 (50.8%) patients died. Figure 2 shows the Kaplan-Meier survival curves. Survival was higher in those patients treated with OA (60.6% vs. 42.9%; p=0.01) and with calcium channel blockers (68.5% vs. 44.2%; p=0.004). Deceased patients were older, had neurological diseases more frequently and heart or respiratory diseases less frequently. They also scored lower on the Barthel index and presented symptoms of terminal illnesses such as delirium, pressure ulcers and anorexia. The use of OA and of calcium channel blockers was greater among the survivors (table 3). There was not association between antiplatelets agents and survival.

In the Cox proportional regression model (table 4), only a higher score on the Barthel index (HR 0.99 95%CI 0.98-1.00; p=0.039) and the use of calcium channel blockers were associated with a lower mortality (HR 0.50 95%CI 0.30-0.84; p=0.009). The presence of delirium (HR 1.60 95%CI 1.08-2.36; p=0.018) and cachexia (HR 1.58 95%CI 1.05-2.38; p=0.027) were associated with higher mortality. There was not any association between the Charlson comorbidity index and the survival (HR 0.97 95%CI 0.89-1.06; p=0.524).

DISCUSSION

The main findings of our study were that in patients with non-neoplastic disease in a terminal stage and AF, OA were more frequently used in younger patients with less functional dependence, and that OA were not independently associated with a longer survival, but calcium channel blockers were.

Practically all our patients had a high risk of stroke, measured by the CHADS2 score, and only one third of them were treated with OA in that advanced stage of their chronic disease. The risk of bleeding was intermediate or high in 70% of the patients, though there were no differences in their hemoglobin values. The oldest and more disabled were less treated. This lesser use of OA in the elderly, even though they have higher risk of suffering an stroke and of dying, had been previously described [21,22].

Clinical practice guidelines recommend treating with OA any patient with AF and a high risk of suffering a thromboembolic event, unless the risk of bleeding is too high [23-25]. Before prescribing OA benefits and risks must always be carefully weighed, specially the risk of bleeding. However, guidelines do not mention patients with a terminal disease and limited life expectancy. It is uncertain whether OA provide any benefits in that specific group. In our study, the Kaplan-Meier curves show that patients with AF and a non-neoplastic disease in a terminal stage survived longer when they were treated with OA, but in the multivariate analysis there was no independent association between OA

and survival. The difference in survival reached 17% after 6 months, which is clinically very appreciable. Hence the dilemma of whether to treat those patients with OA. We consider that new factors must be introduced in the clinical judgement in order to answer the question. Recently, Granziera et al. presented a practical algorithm to help thromboembolic prevention in fragile patients with FA, and they recommend not to treat with OA patients with a life expectancy under 6 months [26]. In our study, mortality within 6 months was associated with dependence for the activities of daily living and with certain symptoms of terminal disease, such as delirium and anorexia. Our opinion is that patients with severe disability, delirium or anorexia should not be treated with OA. Arguably, the onset of stroke in these patients might be considered the last disease in their lives.

The purpose of anticoagulation is not necessarily to increase survival, and the reduction of strokes or the increase of major bleeding events might be highly relevant outcomes. Nonetheless, risk perception varies sometimes between doctors and patients [27,28]. When the time comes to decide whether to prescribe OA or not, the opinion of the patients and their relatives must always be known and respected. Patients with a terminal disease but no cognitive impairment may prefer to use OA and not have a stroke even if this will not extend their time of survival. Hence, the presence of symptoms of terminal disease should be taken into account by caregivers, patients and relatives before prescribing OA.

An important finding is the extension of survival in patients treated with calcium channel blockers. Furthermore, this difference can be seen already after the 10 first days of the follow-up, and increases in time up to 23% after 6 months. Most likely, this finding is due to the rate control effect for nondihidropyridine calcium channel blockers. It is known that there are no differences between rhythm and rate control in the prognosis of AF, but this finding leads us to pose the question of whether, for patients with AF in a terminal stage, the use of calcium channel blockers should be a treatment aim. Recently, in an observational study, we observed that rate control was associated with a higher survival in the first year [6]. New studies with a larger sample size or randomized trials would be needed to validate these findings.

Our study has one strong point: as far as we know, it is the first one to assess the usefulness of OA in patients with terminal non-oncological diseases. However, it also has some limitations. Firstly, this is a post hoc analysis: the study was not designed with the primary goal of assessing anticoagulation in the terminal stage of diseases. This accounts for the absence of data on thrombotic or hemorrhagic events, along the cause of death. Furthermore, there is the possibility that some patients were previously using OA and then had them withdrawn because of their terminal disease. Secondly, the number of patients is small, though it is true that it is not easy to carry out studies with end-stage patients, even more so if they have non-oncologic medical diseases. Clinical trials with the new direct OA in these patients are eagerly awaited [29]. In the third place, the study does not assess the quality of life or the opinions of patients or their relatives. And finally, all patients were treated con antivitamin K

drugs, since the direct OA were not being commercialized in Spain at the time of the study.

In conclusion, we consider that in the case of end-stage patients with AF who have a reduced life expectancy, prior to prescribing OA doctors must assess the presence of symptoms such as disability in basic activities of daily living, cachexia and delirium, as well as encourage the patient's involvement and that of their relatives in the decision-making.

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Table 1. Characteristics of the patients included in the study				
	Total (n=314)	With OA (n=112)	Without OA (n=202)	p
Age*	82.6 (7.0)	80.8 (6.3)	83.6 (7.2)	0.0005
Sex				
Male	182 (58.0)	61 (54.5)	121 (59.9)	0.350
Female	132 (42.0)	51 (45.5)	81 (40.1)	
Living at				
Home	273 (87.5)	101(91.0)	172 (85.6)	0.166
Nursing home	39 (12.5)	10 (9.0)	29 (14.4)	
Terminal disease				
Heart	172 (54.8)	79 (70.5)	93 (46.0)	<0.0001
Respiratory	111 (35.3)	51 (45.5)	60 (29.7)	0.005
Kidney	43 (13.7)	13 (11.6)	30 (14.8)	0.423
Liver	14 (4.5)	4 (3.6)	10 (4.9)	0.571
Neurologic	150 (47.8)	34 (30.4)	116 (57.4)	<0.0001
Charlson index*	3.8 (1.9)	3.8 (2.1)	3.9 (1.8)	0.623
CHADS2 score*	3.4 (1.2)	3.4 (1.2)	3.4 (1.3)	0.524
CHA2DS2-VASC score*	5.8 (1.5)	5.7 (1,4)	5.8 (1.5)	0.632
ATRIA score*	4.7 (2.0)	4.6 (2.1)	4.8 (1.9)	0.557
Barthel index*	27 (29)	39 (33)	21 (25)	0.0003
Delirium	85 (27.1)	18 (16.0)	67 (33.2)	0.001
Number of drugs	8.9 (3.5)	9.1 (3.0)	8.7 (3.7)	0.360
Hemoglobin (g/dL)*	11.1 (2.0)	11.5 (1.9)	11.1 (2.0)	0.138
Creatinine (mg/dL)*	1.4 (0.9)	1.4 (0.7)	1.4 (0.9)	0.638
Drugs				
Beta-blockers	96 (30.6)	42 (37.5)	54 (26.7)	0.047
ACEi/ARB	185 (58.9)	69 (61.6)	116 (57.4)	0.471
Diuretics	249 (79.3)	99 (88.4)	150 (74.2)	0.003
Calcium channel blockers	250 (79.6)	29 (25.9)	35 (17.3)	0.071
Statins	84 (26.7)	37 (33.0)	47 (23.3)	0.061
Antiplatelets agents	158 (50.3)	10 (8.9)	148 (73.3)	<0.0001
Hospital admissions in previous year*	2.6 (1.7)	2.5 (1.5)	2.6 (1.8)	0.717
Data are presented as n (%) or *mean (standard deviation) ACEi/ARB= angiotensin-converting enzyme inhibitors/angiotensin receptors blockers; OA=oral anticoagulants				

Table 2. Factors associated with the prescription of oral anticoagulants				
	Univariate analysis		Multiivariate analysis	
Variable	OR (95%CI)	p	OR (95%CI)	p
Age	0.94 (0.91-0.97)	0.0007	0.96 (0.93-0.99)	0.046
Heart disease	2.81 (1.72-4.59)	0.0004	1.95 (1.05-3.59)	0.067
Respiratory disease	1.98 (1.23-3.19)	0.005	1.45 (0.82-2.58)	0.189
Neurologic disease	0.32 (0.20-0.53)	0.0006	1.11 (0.53-2.34)	0.885
Barthel index	1.02 (1.01-1.03)	0.0001	1.01 (1.00-1.02)	0.034
Delirium	0.39 (0.21-0.69)	0.001	0.70 (0.6-1.38)	0.093
Beta-blockers	1.64 (1.00-2.69)	0.048	1.25 (0.70-2.21)	0.331
Diuretics	2.64 (1.37-5.10)	0.004	1.39 (0.65-2.94)	0.393
CI: confidence interval; OR: odds ratio				

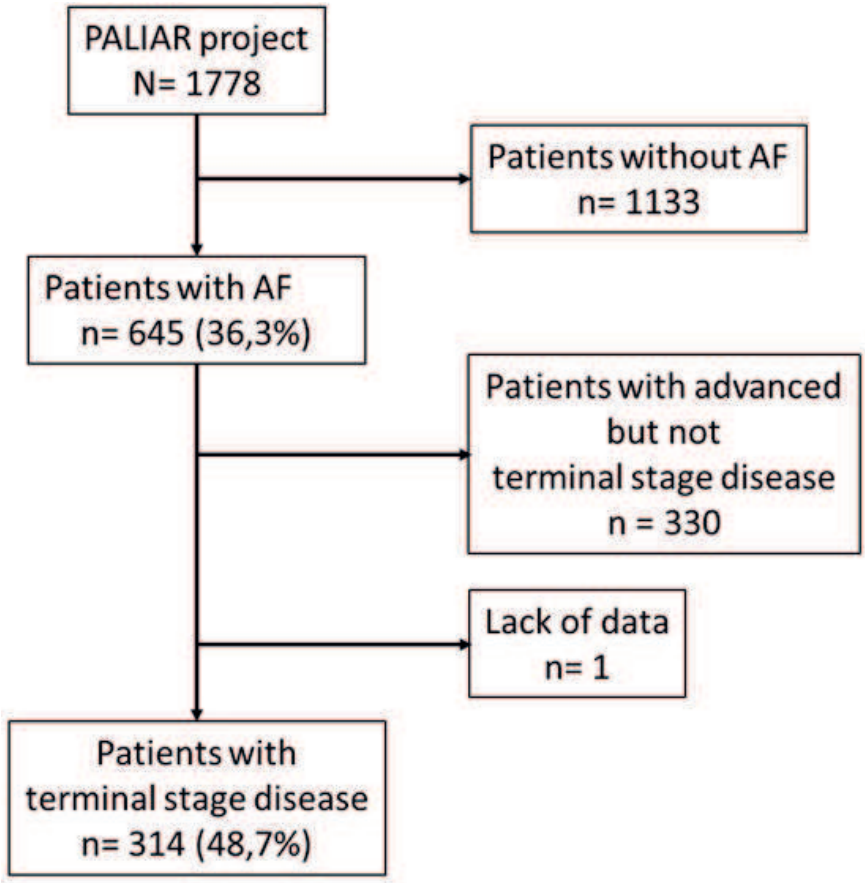
Table 3. Characteristics of patients alive and deceased at the end of the follow-up *after performing a propensity score matching analysis*			
	Alive (n=129)	Deceased (n=133)	p
Age*	81.9 (7.0)	83.9 (6.6)	0.019
Sex			
Male	50 (38.8)	58 (43.6)	0.453
Female	79 (61.2)	75 (56.4)	
Living at			
Home	114 (88.4)	110 (82.7)	0.311
Nursing home	15 (11.6)	22 (16.5)	
Terminal disease			
Heart	78 (60.5)	62 (46.6)	0.026
Respiratory	53 (41.1)	39 (29.3)	0.053
Kidney	21 (16.3)	15 (11.3)	0.283
Liver	7 (5.4)	4 (3.0)	0.371
Neurologic	54 (41.9)	79 (59.4)	0.006
Charlson index*	3.9 (2.0)	3.8 (2.0)	0.620
CHADS2*	3.3 (0.9)	3.2 (1.0)	0.752
CHA2DS2-VASC score*	5.1 (1.2)	5.1 (1.3)	0.826
ATRIA score*	5.4 (2.2)	5.3 (2.0)	0.943
Barthel index*	35 (32)	20 (25)	<0.001
Symptoms of terminal disease			
Delirium	24 (18.6)	49 (36.8)	0.001
Cachexia	6 (4.7)	14 (10.5)	0.102
Insomnia	31 (24.0)	26 (19.5)	0.454
Chronic pain	30 (23.3)	29 (21.8)	0.883
Pressure ulcers	17 (13.2)	38 (28.6)	0.002
Anorexia	25 (19.4)	54 (40.6)	<0.001
Asthenia	37 (28.7)	47 (35.3)	0.290
Nausea and/or vomiting	8 (6.2)	18 (13.5)	0.062
Diarrheas	5 (3.9)	6 (4.5)	1.000
Recurrent urinary tract infections	14 (10.9)	18 (13.5)	0.574
Edemas	57 (44.2)	51 (38.6)	0.381
Rest dyspnea	46 (35.7)	60 (45.5)	0.130
Number of drugs*	9.4 (3.6)	8.5 (3.2)	0.050
Drugs			
OA	57 (44.2)	37 (27.8)	0.007
Antiplatelets	55 (42.6)	71 (53.4)	0.085
Beta-blockers	49 (38.0)	44 (33.1)	0.440
ACEi/ARB	75 (58.1)	86 (64.7)	0.311
Diuretics	106 (82.2)	104 (78.2)	0.442
Calcium channel blockers	37 (28.7)	17 (12.8)	0.002
Statins	38 (30.9)	31 (24.2)	0.260
Admissions in previous year*	2.7 (1.7)	2.4 (1.7)	0.164
Data are presented as n (%) or *mean (standard deviation) ACEi/ARB=angiotensin-converting enzyme inhibitors/angiotensin receptors blockers; OA=oral anticoagulants			

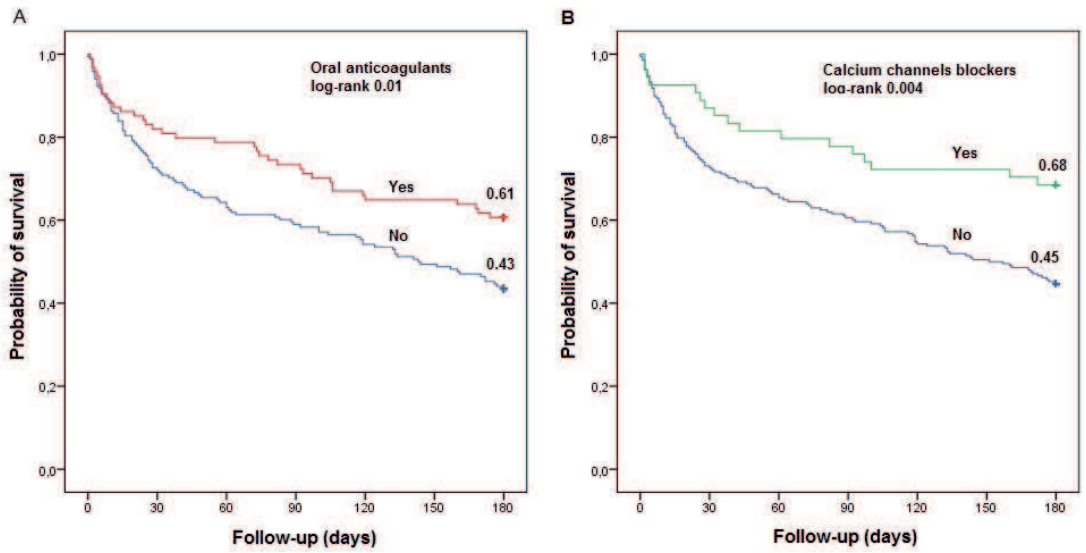
Table 4. Factors associated with mortality within 6 months				
	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	p	HR (95%CI)	p
Age	1.03 (1.01-1.06)	0.015	1.01 (0.99-1.04)	0.289
Heart disease	0.64 (0.46-0.91)	0.012	0.91 (0.59-1.41)	0.684
Respiratory *disease*	0.66 (0.45-0.96)	0.032	0.85 (0.56-1.29)	0.438
Neurologic disease	1.69 (1.19-2.39)	0.003	0.68 (0.40-1.18)	0.170
Barthel index	0.99 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	0.039
Delirium	2.06 (1.44-2.93)	<0.001	1.60 (1.08-2.36)	0.018
Cachexia	1.71 (0.98-2.97)	0.059	1.47 (0.82-2.65)	0.193
Pressure ulcers	1.90 (1.30-2.77)	0.001	1.24 (0.79-1.95)	0.345
Anorexia	2.09 (1.47-2.96)	<0.001	1.58 (1.05-2.38)	0.027
Nausea and/or vomits	1.73 (1.05-2.84)	0.032	1.09 (0.62-1.92)	0.766
Oral anticoagulants	0.61 (0.42-0.89)	0.011	0.99 (0.64-1.51)	0.948
Calcium channels blockers	0.48 (0.29-0.79)	0.004	0.50 (0.30-0.84)	0.009
CI: confidence interval; HR: hazard ratio				

Figure legends.

Fig 1. Flowchart of included patients

Fig 2. Kaplan-Meier survival curves. A: Oral anticoagulants. B: Calcium channel blockers.


PALIAR project
N= 1778
Patients without AF
n= 1133
Patients with AF
n= 645 (36,3%)
Patients with advanced
but not
terminal stage disease
n = 330
Lack of data
n= 1
Patients with
terminal stage disease
n= 314 (48,7%)


A
Oral anticoagulants
log-rank 0.01
Yes
0.61
No
0.43
Probability of survival
1,0
0,8
0,6
0,4
0,2
0,0
0
30
60
90
120
150
180
Follow-up (days)
B
Calcium channels blockers
log-rank 0.004
Yes
0.68
No
0.45
Probability of survival
Follow-up (days)