Adherence to guidelines and mortality in atrial fibrillation

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Contributor statement

We assure that all authors included on a paper fulfill the criteria of authorship. J. Díez-Manglano designed the study. J. Díez-Manglano, J. Gomes-Martín, P. Al-Cheikh-Felices, S. Isasi de Isasmendi Pérez, R. Díez-Angulo, and C. Clemente-Sarasa performed data collection. Data analysis was performed by J. Díez-Manglano. The manuscript was drafted by J. Díez-Manglano, and J. Gomes-Martín, P. Al-Cheikh-Felices, S. Isasi de Isasmendi Pérez, R. Díez-Angulo, and C. Clemente-Sarasa helped with its revision and gave final approval of this version.

ABSTRACT

Objective: Determining the adherence to ACC/AHA/ESC 2006 guidelines and its influence on the survival of patients with atrial fibrillation.

Methods: Prospective observational study of patients discharged during 2007 from an Internal Medicine department with a main or secondary diagnose of atrial fibrillation. The stroke risk was estimated with the $CHADS_2$ score. The follow-up was carried out in outpatients medical office or via telephone.

Results: We included 259 patients (mean age 80.9 years); 73% of them had a high risk of stroke. Oral anticoagulants were administered to 134 (51.7%), and antiplatelet drugs to 71 (27%) patients. A rate control strategy was chosen for 155 (59.8%) patients and a rhythm control one for 28 (10.8%). In 100 (38.6%) patients, treatment was adherent to the guidelines. Adherence to guidelines was associated with age (0.95 95%CI 0.92-0.99; p=0.03), contraindication to the use of oral anticoagulants (0.38 95%CI 0.18-0.79; p=0.01) and mitral valve heart disease/valvular prosthesis (2.21 95%CI 1.10-4.43; p=0.03). The median follow-up was 727 days, and 191 patients died. Patients treated according to the guidelines had a higher rate of survival during the first three years (0.47 vs. 0.36; p=0.049). The use of oral anticoagulants was associated to a higher probability of survival over a 5 year period (0.34 vs 0.21; p=0.001) and the rate control strategy during the first year (0.69 vs 0.57; p=0.04).

CONCLUSIONS: In the real world, treatment of atrial fibrillation according to guidelines is associated to improved survival for up three years during follow-up.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia among the population[1], and it has been associated with an increase in the occurrence of stroke[2]. The risk of AF-related stroke grows with age[3]. Other factors contributing to a higher risk are feminine gender, hypertension, valvular heart disease, impaired left ventricular function, previous myocardial infarct and previous thromboembolic events[4-6]. It has been shown that oral anticoagulants (OA) reduce the risk of AF-related stroke[7]. Despite that, they are still underused in real practice[8].

Several systems have been developed to stratify the risk of stroke in patients with AF. In a multivariate analysis from the Framingham Heart Study, age, feminine gender, history of stroke or transient ischemic attack (TIA) and diabetes were associated with the onset of stroke[9]. Another stratification system is $CHADS_2$, which assigns 2 points for previous stroke or TIA, and one point for each of the following factors: age over 75, hypertension, diabetes or heart failure[10]. Patients are considered low risk with zero points, moderate risk with one point and high risk with two or more points[10].

The American College of Cardiology (ACC) / American Heart Association (AHA) / European Society of Cardiology (ESC) 2006 guidelines for AF management recommended treating with aspirin those patients with no risk factors, with aspirin or OA those with moderate risk and with OA those with high risk[11]. Platelets under 100 $x10^9$/L, alcoholism, recent (less than a month) surgery or trauma and major

hemorrhage (that is, one that puts life at risk or causes hospitalization) during the previous month are considered contraindications (CI) for OA[12].

The meta-analysis of randomized clinical trials on AF patients comparing rate control and rhythm control strategies has shown no differences in mortality[13]. The drugs used for chronic rate control were beta blockers, non-dihydropyridine calcium antagonists and digoxin; for rhythm control, they were amiodarone, dofetilide, flecainide, ibutilide, propafenone and quinidine[11].

In the prevention of cardiovascular diseases, adherence to guidelines is associated to substantial benefits in terms of morbidity and mortality[14]. Patients admitted to Internal Medicine wards are different from those included in clinical trials; usually, they are older and have more comorbidity. Consequently, patterns of practice for these patients differ from those applied in clinical trials and guidelines.

This study aimed to determine whether treatment of AF at the time of hospital discharge is in agreement with guidelines, and whether in the real world, adherence to guidelines recommendations is associated to longer patient survival.

MATERIAL AND METHODS

A prospective observational study of patients admitted to an Internal Medicine unit during 2007 was carried out. All patients with paroxysmal, persistent or permanent AF as main or secondary diagnosis in their discharge report were included, so if they experienced one or more AF episodes, if that was the first detected AF, or if more than one AF episode had already been documented, and if they were in sinus rhythm or in AF at time of discharge. Patients who died during hospitalization were excluded. We define previous AF when this was not the first detected episode of AF.

Measurements

The following variables were gathered: age; sex; presence of hypertension; diabetes; heart failure; previous stroke or TIA; moderate or severe mitral valve heart disease; valve prosthesis; chronic kidney failure; chronic liver disease; antithrombotic treatment, rhythm at discharge, rate or rhythm control strategy at discharge; hemoglobin, albumin, cholesterol and creatinine values. All data were collected at discharge. The stroke risk was estimated using the $CHADS_2$ score[10]. Risk was considered low for a $CHADS_2$ score of 0, intermediate for a score of 1 and high for a score ≥ 2. Even though the ATRIA score had not yet been developed at the time we began the study, we used this stratifying system in hindsight to assess the risk of OA-associated hemorrhage[15]. Three risk levels were considered: low (0-3 points), medium (4 points) and high (5-10 points).

Adherence to guidelines criteria

As a baseline, we took the ACC/AHA/ESC 2006 guidelines for management of patients with atrial fibrillation, current in 2007[11]. Antithrombotic treatment was defined as adequate in the following circumstances: use of OA in patients with mitral valve disease or valve prosthesis, use of OA in patients with high risk of stroke but no CI for OA use, use of antiplatelet agents (APA) in patients with high risk and CI for OA use, use of OA or APA in patients with moderate risk but no CI for OA use, use of APA in patients with moderate risk and CI for OA use. Antithrombotic treatment was defined as inadequate in the following circumstances: use of OA in patients with moderate or high risk and CI for it, use of APA in patients with high risk and no CI for OA use, use of OA in patients with low risk. The strategy for rhythm control was deemed to be the use of amiodarone, dofetilide, flecainide, ibutilide, propafenone and quinidine, while for rate control it was the use of beta blockers, non-dihydropyridine calcium antagonists and digoxin[11]. Adherence to guidelines was defined as the use of OA or APA following the previous criteria, along with a strategy for rhythm control, rate control or both.

Follow-up

The patients were followed-up for 5 years. The follow-up was carried out in outpatients medical office or by telephone whenever the patient was unable to attend to consultation. The date of death was checked in the Spanish National Death Index

(https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/IND_TipoDifusion.htm) and causes of death were ascertained in medical history.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Clinical Investigation Ethics Committee of Aragón. An informed consent was obtained from each patient (or from their caregivers, in case of cognitive impairment).

Statistical analysis

Assuming that patients without adherence to guidelines have a survival of 36% after three years, a 5% type I error and a difference >10% in survival for adherence to guidelines, a sample size of 247 patients was calculated.

Qualitative variables are expressed as absolute frequencies and percentages, and quantitative ones as mean and standard deviation (SD). Comparisons between groups of patients were made by applying the chi-squared test for the former and the Student's t-test for independent samples for the latter. In the multivariate analysis, in order to determine which variables were associated with the different treatment strategies and with adherence to guidelines, a logistic regression model was constructed using those variables associated with a $p<0.1$ in the univariate analysis. To determine the variables associated with mortality, we used a Cox proportional regression model. 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. In the end, 259 patients with a first admission with AF during 2007 were included. Their mean (SD) age was 80.9 (8.5) years.

Risk of stroke and bleeding

The risk of suffering a stroke applying the $CHADS_2$ score is presented in figure 2. Risk was high for 73% of the patients. The risk of OA-associated hemorrhage is presented in figure 2. The risk was low in 44.8% of the patients and high in 45.9% of them.

Treatment strategies

Baseline characteristics of patients and treatment strategies are presented in table 1. OA were used on 134 (51.7%) patients, and APA on 71 (27%). A rate control strategy was used on 155 (59.8%) patients, and a rhythm control one on 28 (10.8%). In the multivariate analysis, older age (odd ratio [OR] 0.90 95% confidence interval [CI] 0.86-0.94; p=0.0007), sinus rhythm at discharge (OR 0.24 95%CI 0.11-0.54; p=0.0005) and the existence of CI for anticoagulant treatment (OR 0.27 95%CI 0.13-0.54; p=0.0003) were associated with a lesser use of OA. Diabetes mellitus (OR 2.35 95%CI 1.19-4.62; p=0.01) and the existence of a significant mitral valve disease or a valve prosthesis were asscciated with a greater use of OA (OR 4.84 95%CI 2.21-10.61; p=0.0008). Rate control strategy was associated with the presence of heart failure (OR 2.02 95%CI 1.05-3.90;

p=0.03) and diabetes (OR 1.98 95%CI 1.0.3-3.81; p=0.04) and with the absence of anemia (OR 0.50 95%CI 0.28-0.89; p=0.02), and rhythm control strategy with a history of stroke/TIA (OR 3.84 95%CI 1.49-9.92; p=0.005), and with sinus rhythm at discharge (OR9.56 95%CI 3.91-23.39; p=0.0008). Do not use neither rate nor control strategy was associated with the absence of heart failure (OR 2.08 95%CI 1.09-3.99; p=0.03).

There was an obvious association between choosing a rate control strategy or a rhythm control one and the use of OA. OA were more used on patients with a rate strategy (58% vs 44%; p=0.01) and less used on those with a rhythm strategy (32% vs 54%; p=0.03).

Adherence to guidelines

In 100 (38.6%) patients, AF treatment was adherent to guidelines. Table 2 shows the characteristics of these patients. On 121 (46.7%) no antithrombotic treatment was applied, and on 89 (34.4%) neither rate nor rhythm control strategy were followed. There was lesser adherence to guidelines with older patients, men, patients with previous stroke/TIA, anemia, CI for OA use or higher bleeding risk as per ATRIA score, and more adherence with patients with mitral valve disease or valve prosthesis. There were no differences in their $CHADS_2$ score. In the multivariate analysis, adherence to guidelines was associated to younger age, absence of CI for OA use and the existence of mitral valve disease or valve prosthesis (table 3).

Survival

Patients were followed up for five years. The median duration of the follow-up was 727 days, and 191 (73.7%) patients died. The cause of death was neoplasm in 25 patients, infection in 23, end stage heart failure in 20, ischemic stroke in 13, sudden death in 9, bleeding in 8 (cerebral in 4, digestive in 3, and renal in one), and acute myocardial infarction in 6. Old age was the main factor associated with mortality (hazard ratio 1.08 95%CI 1.06-1.11; p=0.0003). Table 4 and figure 3 show the survival of patients under different treatment strategies. Patients treated according to guidelines had a higher survival during the three first years. Use of OA was associated to a higher survival along the full five years, and the rate control strategy during the first year. The rhythm control strategy was not associated with the probability of survival. Patients who were neither at rate nor at rhythm control had a lesser survival during the first year.

DISCUSSION

The main findings of our study were that at the time of discharge only for 38.6% of the patients the treatment of AF was adherent to the guidelines, and that patients treated according to the guidelines survived longer during the first three years of the follow-up.

At the time of their discharge, somewhat more than half the patients received antithrombotic treatment conforming to the guidelines. These results substantially match those of other studies[16]. Even though vitamin K antagonists have proved beneficial for stroke prevention in patients with AF, their use is still below guidelines recommendations. In the Euro Heart Survey on Atrial Fibrillation[17], an observational study on 5,333 patients attended to in cardiology units of 182 hospitals in 35 European countries, OA were prescribed to 67% of patients with indications and to 49% of patients with CI. Other studies carried out in hospitals and primary health care centers in the USA[8, 18], Japan[19], Taiwan[20] and Europe[21, 22] showed a low use (52-55%) of OA. In a systematic review of 54 studies on AF patients in the real world, Ogilvie et al[23] found treatment levels under 60%. This indicates that OA are not properly used on patients with AF by neither internists nor cardiologists or family practitioners. Moreover, such underuse is a worldwide phenomenon.

OA underuse has been associated with age[24, 25], feminine gender[24, 25], previous hemorrhages, functional and cognitive impairment[8, 25, 26], falls[25], cirrhoses[8], kidney failure[8, 24], permanent AF[24] and the use of a rhythm control strategy[27]. A

study carried out among internists found that the prescription of OA was associated with the perceived risk of intracranial hemorrhage[28]. Another study carried out in Canada[29] showed that patients with AF and high stroke risk valued more avoiding a stroke and valued less avoiding a hemorrhage than their doctors. Ten years ago, a systematic survey concluded that, for the patients, doctors' fear of bleeding risk is often exaggerated and unfounded[30]. It is possible that doctors have a different perception of risks than patients with AF[31].

Adherence to treatment with OA is low too. In Italy, primary healthcare doctors, having diagnosed AF, prescribed OA to 84% of the patients, but after two years only 29.6% of them were still following the treatment[32]. Both OA underuse and low adherence in AF patients are associated with more strokes and higher mortality[24], as well as with a greater use of hospital services and higher total healthcare cost[33].

Unlike what happens with antithrombotic treatment, there are few studies on the use in the real world of rate and rhythm control strategies for AF. In ours, rate control was used for 59.8% and rhythm control for 10.8% of the patients. There was a prevailing use of the rate control strategy, just as in the ORBIT AF registry[34] and in the Euro Heart Survey[17], but in the latter rhythm control drugs were used in 40% of the patients, up to four more times. The same happened in a study by Meiltz[35]. Both showed management by cardiologists, who proceed in a totally different way than internists and primary healthcare doctors. In the ATRIUM registry, carried out in Germany with primary healthcare doctors, only 33% of the

patients received rhythm control treatment[36]. The RecordAF study, a worldwide registry, has shown geographic differences in the management by cardiologists of persistent or recently appeared paroxysmal AF, with a prevalent use of rhythm control strategies in Belarus, France, Italy, Sweden and Poland, and of rate control strategies in Denmark, South Korea, Philippines, Thailand and the United Kingdom[37].

In the Euro Heart Survey, whereas there were no differences in the chosen strategy among patients with typical symptoms, in those with atypical ones or asymptomatic there was a more extensive use of a rate control strategy for female patients[5]. In the RecordAF, the rate control strategy was more common in patients with a history of heart failure or valve heart disease, while the rhythm control was more frequent in younger patients, patients with more symptoms and those with recently diagnosed AF[37]. Our showed some of these associations. Rate control, for instance, was the preferred strategy for patients with heart failure, diabetes and with no anemia, whereas rhythm control was prevalent for patients with records of stroke/TIA or in sinus rhythm at discharge.

Old age and comorbidity probably move internists to discard rhythm control, though there are also many patients with whom neither strategy is used. This differs from the opinions found in a survey carried out among American internists, who chiefly favored rhythm control[38]. Furthermore, those who chose rhythm control believed this strategy diminished strokes and mortality and helped to

avoid anticoagulation in the long run[38]. In our study, OA were less used on patients with a rhythm control strategy also.

The survival was higher among patients with rate control in the first year as compared to rhythm control. From the second year rhythm control was numerically associated with a higher survival than rate control. The same was observed in patients in sinus rhythm at discharge. However the differences were not statistically significant. Further the presence of comorbidities was different between the groups. New studies with a larger sample size would be needed to validate these findings.

Patients included in clinical trials are different from those found in clinical practice[39]. They are usually younger and less frequently female[40]. Guidelines are based on evidence generated in clinical trials, and this raises some doubts about whether they can be applied to patients in the real world. Actually, it is frequent to fail to comply with guidelines[41]. In our study, guidelines were observed more frequently in patients with mitral valve disease and/or valve prosthesis, and less frequently in older patients and patients with CI for the use of OA. Other studies have shown that guidelines for AF are less observed in older patients[42].

Despite those limitations, the observance of AF guidelines is associated with a reduction of morbidity and mortality[14, 43], and with smaller costs[44]. In our study, old age was the main determining factor of mortality, but adherence to guidelines was associated with a higher survival over the three first years. The lack of benefit

of guideline adherence upon survival after three years of follow-up could represent a cohort bias and might be explained by older age of patients. The mean age of patients included in our study was 80.9 years and an increase of 9% in survival probability after three years is an important outcome. The reduction of mortality was sustained up to five years in patients treated with OA regardless of their risk of stroke. This benefit of OA has been observed in overtreated patients[24] and even in pluripathological ones without functional impairment[26]. Unlike other studies, we have found that a rate control strategy is associated with lesser mortality during the first year. Rhythm control was not associated with benefits in mortality, but the number of patients to whom this treatment strategy was assigned was small. Furthermore, the absence of benefits might be conditioned by the lesser use of OA on these patients.

We think there is a need to implement guidelines and discuss the benefits and risks of the treatments with the patients. A study carried out in Spain has verified that the use of prospective protocols effectively increases the use of OA in patients with AF[46]. Implementing integrated programs of chronic cares managed by nurses has also improved the adherence to guidelines[47].

Our study has several limitations. In the first place, it was carried out in a single center and in an internal medicine service, so the results cannot be generalized to patients treated in primary healthcare or cardiology units. Nevertheless, in Spain AF is a diagnosis codified in 20% of discharges in internal medicine departments[48], a figure similar to that of our study. In addition, the rates of OA

use are consistent with the studies carried out in the real world[23]. Secondly, we have taken the ACC/AHA/ESC 2006 guidelines as a reference. Currently, guidelines recommend the use of the CHA_2DS_2-VASC score to stratify the risk of stroke[49]. With this system, a higher percentage of the patients should be treated with OA, and applying it to our patients would have yielded a greater level of undertreatment. The current recommendations include new oral anticoagulants (NOA). In Spain, dabigatran, the first NOA, was authorized in November 2011, four years after the inclusion of patients in our study, and currently NOA are prescribed only to 9% of subjects with AF. However, the increase in their use could change the results of the study. As a strong point of the study, we can point out that the follow-up was long and only 9 patients were lost. Furthermore, both the patients and the doctors who take part in clinical trials are different from those found in real life[39], which is why it is essential to carry out observational studies that might allow translating the results of research to everyday clinical activity. Therefore, the application of guidelines recommendations to this cohort may not represent the focus of the guidelines themselves, but there are no specific AF guidelines for internal medicine patients and in Spain 36% of patients with cardiac arrhythmias were admitted to internal medicine departments[50].

In conclusion, it is capital to implement the observation of guidelines for the management of AF, particularly so with older patients. It is also necessary to know the behaviors and profiles of the doctors attending to them, and probably to design different implementation strategies to fit the diverse profiles of both patients and clinicians.

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Table 1. Baseline characteristics of atrial fibrillation patients according to treatment

	Total group (n=259)	Oral anticoagulants (n=134)	Rate control (n=155)	Rhythm control (n=28)	Neither rate nor rhythm control (n=89)
Age*	80.9 (8.5)	78.4 (9.0)	80.4 (8.8)	80.4 (9.8)	81.7 (8.0)
Sex					
Male	120 (46)	57 (42)	62 (40)	15 (54)	50 (56)
Female	139 (54)	77 (57)	93 (60)	13 (46)	39 (44)
Previous AF	175 (68)	102 (76)	114 (73)	14 (50)	55 (62)
Rhythm at discharge					
Sinus	47 (18)	13 (10)	24 (15)	16 (57)	14 (16)
AF	212 (82)	121 (90)	131 (84)	12 (43)	75 (84)
Comorbidities					
Heart failure	78 (30)	49 (37)	57 (37)	5 (18)	19 (21)
Hypertension	162 (62)	87 (65)	104 (67)	16 (57)	50 (56)
Diabetes	78 (30)	51 (38)	56 (36)	5 (18)	21 (24)
Stroke/TIA	55 (21)	28 (21)	27 (17)	11 (39)	21 (24)
Mitral valve disease or valve prosthesis	59 (23)	46 (34)	44 (28)	3 (11)	13 (15)
Chronic kidney failure	98 (38)	57 (42)	54 (35)	11 (39)	61 (36)
Chronic liver disease	9 (3)	4 (3)	4 (3)	0 (0)	5 (6)
Anemia	133 (51)	59 (44)	68 (44)	16 (57)	57 (36)
Contraindications for OA	64 (25)	21 (16)	32 (21)	5 (18)	29 (33)
Thrombopenia	13 (5)	8 (6)	5 (3)	2 (7)	6 (7)
Alcoholism	4 (2)	3 (2)	3 (2)	0 (0)	1 (1)
Trauma/recent surgery	10 (4)	0 (0)	5 (3)	2 (7)	5 (6)
Recent major hemorrhage	39 (15)	11 (8)	21 (13)	1 (4)	17 (19)
Analytical parameters*					
Cholesterol (mg/dL)	149 (41)	148 (41)	148 (40)	150 (38)	148 (43)
Albumin (g/dL)	3.4 (0.5)	3.5 (0.4)	3.4 (0.5)	3.31 (0.6)	3.3 (0.4)
Hemoglobin (g/dL)	11.9 (2.2)	12.3 (2.3)	12.2 (2.31)	12.0 (1.9)	11.5 (2.3)
Creatinine (mg/dL)	1.1 (0.6)	1.2 (0.7)	1.1 (0.6)	1.1 (0.6)	1.2 (0.6)

CHADS2 score*	2.5 (1.3)	2.5 (1.4)	2.5 (1.3)	2.4 (1.4)	2.3 (1.3)
ATRIA score*	4.2 (2.2)	3.9 (2.1)	3.9 (2.1)	4.1 (2.4)	4.8 (2.1)

Data are presented as n (%) or *mean (standard deviation)

Table 2. Adherence to guidelines			
	Yes (n=100)	No (n=159)	p
Age*	79.4 (9.0)	81.8 (8.0)	0.02
Sex			
Male	36 (36)	84 (53)	0.008
Female	64 (64)	75 (47)	
Previous AF	74 (74)	101 (63)	0.08
Rhythm at discharge			
Sinus	13 (13)	34 (21)	0.09
AF	87 (87)	125 (79)	
Comorbidities			
Heart failure	37 (37)	41 (26)	0.05
Hypertension	66 (66)	96 (60)	0.36
Diabetes	36 (36)	42 (24)	0.10
Stroke/TIA	15 (15)	40 (25)	0.05
Mitral valve disease or valve	36 (36)	23 (14)	<0.0001
prosthesis	39 (39)	94 (59)	0.002
Anemia	35 (35)	63 (40)	0.45
Chronic kidney failure	1 (1)	8 (5)	0.08
Chronic liver disease			
Contraindications ACO	10 (10)	51 (32)	0.0005
Thrombopenia	3 (3)	10 (6)	0.24
Alcoholism	0 (0)	4 (2)	0.11
Trauma/recent surgery	1 (1)	9 (6)	0.06
Recent major hemorrhage	10 (10)	29 (18)	0.07
Analytical parameters*			
Cholesterol (mg/dL)	155 (40)	146 (41)	0.09
Albumin (g/dL)	3.5 (0.4)	3.3 (0.5)	0.0004
Hemoglobin (g/dL)	12.4 (2.2)	11.7 (2.2)	0.007
Creatinin (mg/dL)	1.1 (0.6)	1.2 (0.6)	0.47
CHADS2 score*	2.4 (1.3)	2.5 (1.4)	0.86
ATRIA score*	3.6 (1.9)	4.6 (2.2)	0.0002
Data are presented as n (%) or *mean (standard deviation)			

Table 3. Factors associated with the adherence to AF guidelines

	Univariate analysis		Multivariatea nalysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.97 (0.94-0.99)	0.03	0.95 (0.92-0.99)	0.03
Female sex	1.99 (1.19-3.33)	0.009	1.61 (0.88-2957)	0.12
Previous AF	1.63 (0.94-2.84)	0.08	1.45 (0.77-2.73)	0.24
Sinus rhythm at discharge	0.56 (0.27-1.10)	0.09	0.63 (0.29-1.36)	0.24
Stroke/TIA	0.52 (0.27-1.01)	0.05	0.62(0.30-1.29)	0.20
Mitral valve disease or valve prosthesis	3.33 (1.82-6.07)	0.0009	2.10 (1.04-4.25)	0.04
Anemia	0.44 (0.26-0.74)	0.002	0.68 (0.38-1.24)	0.21
Contraindicationfor OA	0.32 (0.16-0.62)	0.0008	0.38 (0.18-0.81)	0.01
Albumin	3.39 (1.84-6.21)	0.0008	1.72 (0.85-3.49)	0.13

CI: confidence interval. OA: oral anticoagulants. OR: odd ratio. TIA: transient ischemic attack

Table 4. Probability of survival of atrial fibrillation patients according to treatment					
	One-year	2-years	3-years	4-years	5-years
Oral anticoagulants					
Yes	0.74	0.60	0.51	0.41	0.34
No	0.54	0.40	0.29	0.24	0.21
p	0.002	0.001	0.0002	0.0006	0.001
HR (95% IC)	0.51 (0.34-0.78)	0.56 (0.40-0.80)	0.54 (0.39-0.75)	0.59 (0.44-0.80)	0.62 (0.47-0.83)
Rate control					
Yes	0.69	0.53	0.43	0.34	0.31
No	0.57	0.46	0.37	0.30	0.23
p	0.04	0.13	0.20	0.24	0.10
HR (95% IC)	0.65 (0.43-0.97)	0.77 (0.54-1.08)	0.81 (0.59-1.12)	0.83 (0.61-1.13)	0.78 (0.59-1.05)
Rhythm control					
Yes	0.64	0.57	0.50	0.39	0.39
No	0.64	0.49	0.39	0.32	0.26
p	0.95	0.58	0.43	0.52	0.30
HR (95% IC)	1.02 (0.53-1.97)	0.84 (0.47-1.53)	0.80 (0.46-1.39)	0.85 (0.51-1.40)	0.76 (0.46-1.26)
Rate or rhythm control					
No strategy	0.55	0.45	0.36	0.30	0.21
Any strategy	0.69	0.53	0.43	0.34	0.31
p	0.02	0.08	0.11	0.19	0.05
HR (95% CI)	1.62 (1.07-2.44)	1.37 (0.96-1.95)	1.30 (0.94-1.81)	1.23 (0.90-1.68)	1.34 (0.99-1.80)
Adherence to guidelines					
Yes	0.73	0.57	0.47	0.36	0.32
No	0.58	0.46	0.36	0.31	0.25
p	0.02	0.04	0.049	0.12	0.09
HR (95% IC)	0.59(0.38-0.93)	0.69 (0.48-0.99)	0.72 (0.51-1.00)	0.78 (0.52-1.07)	0.77 (0.57-1.04)

Figure legends

Figure 1.Flow chart CONSORT of patients considered in the study. AF: atrial fibrillation.

Figure 2. Stroke ($CHADS_2$ score) and bleeding (ATRIA score) risks.

Figure 3. Kaplan-Meier survival curves.