Outcomes and Safety of Antithrombotic Treatment in Patients Aged 80 Years or Older With Nonvalvular Atrial Fibrillation

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Our aim was to evaluate the effectiveness of oral anticoagulation (OAC) in patients aged ≥80 years with nonvalvular atrial fibrillation in daily clinical practice. From February 1, 2000 to June 30, 2009, we enrolled all patients aged ≥80 years with nonvalvular atrial fibrillation attended at 2 outpatient cardiology clinics of a tertiary care university hospital. The patients received antithrombotic treatment according to the recommendations from scientific societies and were prospectively followed, with major events (i.e., all-cause death, stroke, transient ischemic attack, peripheral embolism, severe bleeding) analyzed according to the treatment group (OAC vs no OAC). Of 269 patients included in the present study (87 men, mean age 83 ± 3 years), 164 received OAC (61%). After 2.8 ± 1.9 years of follow-up, the raw rates (per 100 patient-years) of embolic events (1.52% vs 8.30%, p <0.0001) and mortality (6.67% vs 10.94%, p = 0.04) were lower for patients receiving OAC, with a nonsignificant greater rate of severe bleeding (3.03% vs 1.25%, p = 0.14). The probability of survival free of major embolic or hemorrhagic events at the mean follow-up was greater for patients receiving OAC (82.27% vs 66.10%, p = 0.004). After adjustment for age, gender, coronary heart disease, and embolic risk, evaluated using the $CHADS_2$ score (congestive heart failure, 1 point; hypertension [blood pressure consistently >140/90 mm Hg or hypertension medication], 1 point; age ≥75 years, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischemic attack, 2 points), only OAC was an independent predictor of embolic events (hazard ratio 0.17, 95% confidence interval 0.07 to 0.41, p <0.001). The $CHADS_2$ score (hazard ratio 1.32, 95% confidence interval 1.01 to 1.73, p = 0.04) and OAC (hazard ratio 0.52, 95% confidence interval 0.31 to 0.88, p = 0.01) were independent predictors of mortality. In conclusion, OAC according to the scientific societies' recommendations is effective and safe in daily clinical practice, even in patients aged ≥80 years. **(Am J Cardiol 2011;xx:xxx)**

The aim of the present study was to evaluate the effectiveness and safety of oral anticoagulation (OAC) as thromboembolic prophylaxis for patients aged ≥80 years with nonvalvular atrial fibrillation (NVAF) in daily clinical practice.

Methods

We included in the present study all consecutive patients with permanent NVAF attended from February 1, 2000 to June 30, 2009 at a general outpatient cardiology clinic of a university hospital. The cardiology clinics receive patients from primary care physicians, from the emergency department, and from hospitalization for cardiology and internal medicine. In every patient, cardioversion was considered, with those who finally achieved sinus rhythm excluded. The present analysis included all patients aged ≥80 years who were included in the study.

Our thromboembolic prophylaxis protocol has been described in previous publications[1–3] and was established by consensus among investigators, after reviewing the guidelines of the Spanish Society of Cardiology for antithrombotic treatment in cardiology[4] that had been published before the design of our study and the scientific evidence available at that time. During the course of the study, the guidelines from the Spanish Society of Cardiology on cardiac arrhythmias[5] and the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for atrial fibrillation[6,7] became available. After reviewing these documents, the protocol was not changed, because it was consistent with the basic principles of the 3 guidelines. In brief, each patient was examined for cardioembolic risk factors (CERFs) and contraindications for anticoagulation. The following CERFs were identified and prospectively included in the database: age ≥75 years (all patients in the present study because of the inclusion criteria), hypertension, diabetes mellitus, previous cardioembolic event (e.g., stroke, transient ischemic attack, peripheral embolism), coronary disease, congestive heart failure, atrial enlargement (anteroposterior diameter ≥50 mm), and left ventricular dysfunction (ejection fraction ≤0.45).

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Patients with an absolute anticoagulation contraindication were treated with aspirin, other platelet aggregation inhibitors, or no antithrombotic treatment, at the discretion of the responsible physician. Patients with no contraindication for anticoagulation and with ≥1 additional CERFs (other than age ≥75 years) were offered OAC. Sufficient time was spent explaining the benefits and risks of OAC to the patients and their families to avoid treatment refusal because of incomplete or inadequate information. The decision to administer OAC was left to the cardiologist for patients with advanced age as the only CERF and no contraindications. The treatment of every patient was prospectively registered, and 2 study groups were considered: those who received OAC and those who did not, irrespective of the use of platelet aggregation inhibitors. We also considered 3 subgroup analyses: men versus women, patients aged 80 to 84 years versus those aged ≥85 years, and those with a $CHADS_2$ score of 1 (only advanced age as the CERF) versus those with a $CHADS_2$ score of ≥2 ($CHADS_2$: congestive heart failure, 1 point; hypertension [blood pressure consistently >140/90 mm Hg or hypertension medication], 1 point; age ≥75 years, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischemic attack, 2 points). We did not perform a more detailed analysis of the results for all $CHADS_2$ scores because of the small number of patients and events in each subgroup. The coagulation controls and therapeutic plan were established by expert hematologists who set a target international normalized ratio (INR) of 2 to 3 and who were unaware of the study parameters. Most patients received acenocumarol; only a minority received warfarin. Patients gave their informed consent, and the local ethics committee approved the study.

The patients were followed up annually in the clinic, and the occurrence of embolic events (e.g., stroke, transient ischemic attack, peripheral embolism), severe bleeding (bleeding that caused death or required a blood transfusion or hospital admission), and death was recorded. After every admission because of an event, the clinical history was examined for confirmation. If the patient presented with a possible cardioembolic event that had not been studied (e.g., symptoms suggestive of a transient ischemic attack), consultation with the appropriate specialist was requested. The cause of death (cardiovascular vs noncardiovascular) was established after reviewing the medical history of the patients who had died in hospital or the information given by their physicians or relatives.

All basal and follow-up data were included in a database created using the Statistical Package for Social Sciences software (SPSS, Chicago, Illinois). Quantitative data are presented as the mean ± SD, and qualitative data as proportions. The raw rates of events were calculated for 100 patient-years of follow-up. Subgroup comparisons were performed using Student's *t* test for parametric data, the Mann-Whitney *U* test for nonparametric data, and the chi-square or Fisher exact test for qualitative data. The probability of survival free of events at the mean follow-up was estimated using the Kaplan-Meier method, and the results were compared using the log-rank test. $CHADS_2$ scores[8–10] were obtained retrospectively using the data from the first visit of each patient. Multivariate analyses were performed using the Cox proportional hazards method, with cardioembolic and hemorrhagic events and all-cause mortality as dependent variables and OAC as the independent variable. The models were adjusted by all covariates that showed differences ($p < 0.20$) between patients receiving OAC and the rest of the series. p values <0.05 were considered significant. The Statistical Package for Social Sciences software (SPSS) was used for statistical analysis.

Table 1
Basal features of patients aged ≥80 years with nonvalvular atrial fibrillation (NVAF) in our series stratified by treatment

Variable	Anticoagulation		p Value
	Yes (n = 164)	No (n = 105)	
Age (years)	83 ± 3	84 ± 4	<0.01
Men	58 (35%)	29 (28%)	0.19
Hypertension	126 (77%)	69 (66%)	0.04
Diabetes mellitus	46 (28%)	20 (19%)	0.09
Heart failure	28 (17%)	17 (16%)	0.85
Previous embolic event	30 (18%)	12 (11%)	0.13
Ischemic heart disease	21 (13%)	3 (3%)	<0.01
Atrial enlargement	23 (14%)	8 (8%)	0.13
left ventricle systolic dysfunction	8 (5%)	4 (4%)	0.46
$CHADS_2$ score	2.59 ± 1.15	2.24 ± 1.05	0.01
1	23 (14%)	26 (25%)	
2	71 (43%)	46 (44%)	
3	35 (21%)	18 (17%)	
≥4	35 (21%)	15 (14%)	0.09

Data are presented as mean ± SD or absolute numbers (%).

Table 2
Event rate

Variable	Anticoagulation		p Value
	Yes (n = 164)	No (n = 105)	
Transient ischemic attack	5 (1.08)	8 (3.32)	0.07
Nonfatal stroke	1 (0.22)	4 (1.66)	0.05
Fatal stroke	0 (0)	6 (2.49)	<0.01
Peripheral embolism	1 (0.22)	2 (0.83)	0.27
All embolic events	7 (1.52)	20 (8.30)	<0.01
Nonfatal bleeding	9 (1.95)	3 (1.25)	0.76
Fatal bleeding	5 (1.08)	0 (0)	0.17
All severe bleeding	14 (3.03)	3 (1.25)	0.14
All embolic and hemorrhagic events	21 (4.55)	23 (9.55)	<0.01
Cardiovascular death	8 (1.67)	15 (5.86)	<0.01
Other causes of death	24 (5)	13 (5.08)	0.99
All-cause death	32 (6.67)	28 (10.94)	0.04

Data are presented as number of events (raw rates for 100 patient-years).

Results

From February 1, 2000 to June 30, 2009, 269 patients were included in the present study. The mean age was 83 ± 3 years, and 32% were men. Of the 269 patients, 73% were aged 80 to 84 years, 21% 85 and 89 years, and only 6% ≥90 years old. The symptoms were as follows: 78% were asymptomatic, 18% presented with dyspnea, 2% had palpitations, and 2% had chronic stable angina.

Table 3
Rate of events stratified by gender, age, and embolic risk, as estimated using $CHADS_2$ score

Variable	Anticoagulation	No Anticoagulation	p Value	HR* (95% CI)	p Value
Embolic events					
Men	2/58 (1.20)	4/29 (6.06)	0.06	0.21 (0.04–1.17)	0.08
Women	5/105 (1.70)	16/76 (9.14)	<0.001	0.18 (0.06–0.49)	0.001
Age 80–84 years	6/129 (1.56)	14/66 (9.59)	<0.01	0.14 (0.05–0.37)	<0.001
Age ≥85 years	1/35 (1.29)	6/39 (6.32)	0.13	0.29 (0.03–2.69)	0.27
$CHADS_2$ score					
1	0/23 (0)	7/26 (10.47)	0.01	0.02 (0.00–6.55)	0.18
≥2	7/141 (1.77)	13/79 (7.47)	<0.01	0.22 (0.09–0.57)	0.002
All patients	7/164 (1.52)	20/105 (8.30)	<0.01	0.17 (0.07–0.41)	<0.001
Severe bleeding					
Men	4/58 (2.40)	2/29 (3.03)	0.68	0.82 (0.15–4.66)	0.83
Women	10/105 (3.40)	1/76 (0.57)	0.06	09 (0.78–47.75)	0.09
Age 80–84 years	11/129 (2.87)	3/66 (2.06)	0.76	1.47 (0.40–5.41)	0.57
Age ≥85 years	3/35 (3.86)	0/39 (0)	0.09	103.40 (0.01–1.5 × 10^6)	0.34
$CHADS_2$ score					
1	0/23 (0)	0/26 (0)	0.99		
≥2	14/141 (3.55)	3/79 (1.7)	0.24	2.23 (0.63–7.82)	0.21
All patients	14/164 (3.03)	3/105 (1.25)	0.14	2.66 (0.76–9.32)	0.13
All embolic and hemorrhagic events					
Men	6/58 (3.59)	6/29 (9.09)	0.10	0.41 (0.13–1.30)	0.13
Women	15/105 (5.10)	17/76 (9.71)	0.08	0.51 (0.26–1.03)	0.06
Age 80–84 years	17/129 (4.43)	17/66 (11.65)	<0.01	0.35 (0.18–0.70)	0.003
Age ≥85 years	4/35 (5.15)	6/39 (6.32)	0.99	1.62 (0.37–7.20)	0.52
$CHADS_2$ score					
1	0/23 (0)	7/26 (10.47)	0.01	0.02 (0.00–6.55)	0.18
≥2	21/141 (5.32)	16/79 (6.90)	0.08	0.56 (0.29–1.08)	0.09
All patients	21/164 (4.55)	23/105 (9.55)	<0.01	0.46 (0.25–0.83)	0.01
All-cause death					
Men	14/58 (7.87)	4/29 (5.48)	0.51	2.50 (0.66–9.51)	0.18
Women	18/105 (5.94)	24/76 (13.11)	0.006	0.38 (0.20–0.72)	0.003
Age 80–84 years	24/129 (5.98)	18/66 (11.39)	0.03	0.42 (0.22–0.79)	0.007
Age ≥85 years	8/35 (10.20)	10/39 (10.23)	0.99	1.49 (0.53–4.17)	0.45.
$CHADS_2$ score					
1	2/23 (3.00)	6/26 (8.73)	0.27	0.25 (0.04–1.63)	0.15
≥2	30/141 (7.26)	22/79 (11.76)	0.07	0.60 (0.34–1.85)	0.08
All patients	32/164 (6.67)	28/105 (10.94)	0.04	0.52 (0.31–0.88)	0.01

Data are presented as number of events/number of patients in each subgroup (raw rates for 100 patient-years).

* HR for anticoagulant treatment (obtained from multivariate models adjusted for age, gender, presence of coronary artery disease, and embolic risk evaluated using $CHADS_2$ score, with absence of anticoagulation as reference category).

CI = confidence interval.

A total of 164 patients received anticoagulants (61%). This proportion was greater among the patients aged 80 to 84 years than among those aged ≥85 years (66% vs 47%, $p < 0.01$) and among those with a $CHADS_2$ score of ≥2 than among those with a $CHADS_2$ score of 1 (64% vs 47%, $p = 0.03$). The reasons for not prescribing anticoagulants were a high perceived risk of therapeutic noncompliance ($n = 44$), decision by the responsible physician ($n = 26$), patient refusal ($n = 14$), severe anemia ($n = 5$), gastrointestinal disease with a high risk of severe bleeding ($n = 4$), severe recent bleeding ($n = 4$), a high risk of severe or frequent trauma ($n = 3$), severe uncontrolled hypertension ($n = 3$), and other reasons ($n = 2$).

The patients prescribed OAC were younger than the other patients and had presented with a greater frequency of hypertension and coronary heart disease and a greater $CHADS_2$ score than the nonanticoagulated patients (Table 1). No significant differences were found between the 2 groups with respect to the frequency of the other risk factors. Most nonanticoagulated patients received antiplatelets (95%), mainly aspirin (87% of all nonanticoagulated patients).

After 2.8 ± 1.9 years of follow-up, 1 patient was lost to follow-up (0.37%) and 736 patient-years of observation had been accumulated. A total of 27 embolic events (13 transient ischemic attacks, 11 strokes, and 3 cases of peripheral embolism), 17 cases of severe bleeding, and 60 deaths had occurred. The raw rates of events are listed in Tables 2 and 3. The raw embolic event rate was significantly lower in the patients who had received OAC, with a nonsignificantly greater rate of bleeding events. The combined embolic and hemorrhagic event rate and all-cause mortality was also lower in this subgroup. We found lower raw rates of nonfatal stroke, fatal stroke, and cardiovascular death among the OAC group, with nonsignificant trends toward lower rates of transient ischemic attacks and peripheral embolism and toward greater rates of nonfatal and fatal severe bleeding. The probability of survival free of major embolic or

hemorrhagic events at the mean follow-up point was greater for patients in the OAC group (82.27% vs 66.10%, p = 0.004).

Women presented with findings similar to those for the whole series; however, the differences in events among anticoagulated and nonanticoagulated men did not reach statistical significance (Table 3). The results were similar when considering the $CHADS_2$ score subgroups (≥2 vs 1), although the differences in the raw rates of all-cause mortality did not reach statistical significance in each subgroup (Table 3). Patients aged 80 to 84 years presented with the same findings as the whole series; however, those patients aged ≥85 years who had received OAC showed a nonsignificant trend toward lower raw rates of embolic events and a greater risk of severe bleeding, with a neutral effect on the combined embolic and hemorrhagic event rate and all-cause mortality (Table 3).

Most embolic events were strokes in the nonanticoagulated patients (10 of 20, 50%) and transient ischemic attacks in anticoagulated patients (5 of 7, 71%). The mean INR at admission for the 7 anticoagulated patients with embolic events was 1.69 ± 0.42 (range 1.22 to 2.04). Most nonfatal severe bleeding was gastrointestinal in origin in both groups (8 of 12, 67%). However, we had 2 cases of nonfatal intracranial hemorrhage, both in anticoagulated patients. Five patients died from bleeding (three from digestive hemorrhage and two from intracranial bleeding), all in anticoagulated patients. The mean INR at admission for the 14 anticoagulated patients with severe bleeding was 6.17 ± 2.5 (range 1.6 to 8.8).

On multivariate analysis (Table 3), after adjusting for age, gender, $CHADS_2$ score, and coronary heart disease, OAC independently predicted embolic events (hazard ratio [HR] 0.17, 95% confidence interval 0.07 to 0.41, p <0.001) and all-cause mortality (HR 0.52, 95% confidence interval 0.31 to 0.88, p = 0.01). None of the other covariates showed independent predictive power for embolic events; however, the $CHADS_2$ score independently predicted all-cause mortality (HR 1.32, 95% confidence interval 1.01 to 1.73, p = 0.04). We did not observe an association between anticoagulant treatment and severe bleeding (HR 2.66, 95% CI 0.76 to 9.32, p = 0.13). Indeed, we could not find any association among the covariates tested and hemorrhagic complications.

Discussion

Other than a small randomized trial[11] that mainly focused on safety and only included 75 patients aged ≥80 years, 2 main clinical trials have studied OAC in older patients with NVAF. In the Stroke Prevention in Atrial Fibrillation II trial,[12] 385 patients with a mean age of 80 ± 3 years were randomized to OAC (target INR 2 to 4.5) or aspirin. After a follow-up of 2 years, a nonsignificant reduction in the stroke and peripheral embolism rate (3.6% vs 4.8%, p = 0.39) was nearly offset by the increase in the intracranial hemorrhage rate (1.8% vs 0.8%), which was thought to have been caused by the high INRs in the study.[13] Recently, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study[14] randomized 973 patients aged ≥75 years (mean age 81.5) to receive warfarin, with a target INR of 2 to 3, or aspirin 75 mg/day. The outcomes confirmed a significant risk reduction in the embolic event rate (1.8% vs 3.8%, p = 0.003), without an increase in the bleeding rate (1.4% vs 1.6%).

However, the population of clinical trials is often selected and can be unrepresentative of patients attended in daily clinical practice. The BAFTA trial[14] only included 21% of the patients with atrial fibrillation scrutinized for the study; interestingly, the main reason for not randomizing was the physicians' opinion that the patients should receive anticoagulants. Thus, information from observational studies can be valuable to fully evaluate this issue in "real world" patients.

Other observational studies have addressed the effectiveness of OAC in NVAF in daily clinical practice[15,16]; however, to the best of our knowledge, the present study is the largest prospective series of patients aged ≥80 years with NVAF that has focused on the outcomes of anticoagulant treatment. Several points are worth noting. First, OAC was the only independent predictor of embolic events, and age, gender, and $CHADS_2$ score were not independent predictors after adjusting for anticoagulant treatment in this elderly population. Second, as others have noted,[17,18] we not only found a lower embolic risk for anticoagulated patients, but also less severe events in these patients than in those not receiving anticoagulants (mainly transient ischemic attacks vs strokes). Third, we found nonsignificantly greater raw rates of severe bleeding among the anticoagulated patients. This finding invites us to carefully stratify not only the thromboembolic, but also the hemorrhagic, risk in this frail population of elderly patients. Perhaps, new tools such as the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly [>65 years], Drugs/alcohol concomitantly) score, recently recommended by the most recent European guidelines,[19] could be useful in this setting. Fourth, in our study, we found a significant and independent effect of OAC on overall mortality in patients aged ≥80 years that appeared to be related to a reduction in cardiovascular death. All-cause mortality is a major end point, and it has been not fully studied in trials of OAC in patients with NVAF.[20] Finally, our study, as have other investigators,[21] also found the $CHADS_2$ score to be an independent predictor of overall mortality in this population.

Recently, new drugs such as dabigatran and rovarixaban have shown very promising results in thromboembolic prevention in patients with NVAF. However, the clinical trial[22] that evaluated dabigatran versus warfarin in this setting did not separately describe the results for elderly patients. A large trial that analyzed rovarixaban versus warfarin in patients with NVAF has been communicated at the 2010 American Heart Association scientific sessions, but the full article has not yet been published. Thus, further information is needed to evaluate the role that these new drugs will play in thromboembolic prevention in elderly patients with NVAF.

Our study had some limitations. First, we had no data on the INRs during the study; thus, the duration of a therapeutic INR was not available. This information would have been important to evaluate the quality of anticoagulation in our setting. The duration of therapeutic INR is not the same at

all anticoagulation clinics and is related to the effectiveness of OAC.[23] However, the embolic and bleeding outcomes in the anticoagulated patients in our series suggest good overall anticoagulation control at our institution. Second, only 74 patients were ≥85 years in our series, with few events; thus, little information could be obtained for this particularly poorly studied age subgroup. Third, the relatively small sample size precluded a more detailed analysis of events in each stratum of the $CHADS_2$ score, which would have been of great interest. It is possible that we did not found statistical significance in the different rates of events between the anticoagulated and nonanticoagulated patients in other subgroups (e.g., men) because of this limitation. Fourth, we did not find any independent predictor of severe bleeding, but we could not test the recently described bleeding scores, such as the HAS-BLED score, because some of the variables needed for the calculation of the score were not prospectively collected in our database. Finally, the results of events during follow-up must be seen as those of a prospective observational cohort study, subject to possible biases (e.g., sicker patients might not have received OAC) and inaccuracy in the effect estimates, although our results are concordant with randomized trial-based evidence and the results of other observational studies of patients aged ≥75 years.[15,16]

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