Characteristics, management and prognosis of elderly patients in the Euro Heart Survey on atrial fibrillation

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ABSTRACT. ***Background and aims:*** *Atrial fibrillation (AF) is the most frequent sustained arrhythmia of elderly patients, in whom it determines an increase in morbidity and mortality. Aim of this study was to assess age-related differences in the characteristics, management and prognosis of patients with AF in European cardiology practices.* ***Methods:*** *The Euro Heart Survey on AF was an observational study sponsored by the European Society of Cardiology. Patients were enrolled between 2003 and 2004 in 182 hospitals of 35 countries. For the purposes of this study, they were categorized into three age-groups: <65 (n=2124), 65-80 (n=2534) and >80 years (n=671). Follow-up was closed in 2005.* ***Results:*** *Compared with general population estimates, patients >80 years were underrepresented in the Euro Heart Survey. The oldest patients were less likely to be enrolled by university or specialized centers, to receive extensive diagnostic testing, and to receive oral anticoagulation despite a worse stroke risk profile. Furthermore, the oldest patients less often received rhythm control therapy, even when presenting with palpitations and non-permanent AF. During 1 year follow-up, elderly patients more often suffered a myocardial infarction, new onset heart failure and major bleedings. They had higher all-cause and cardiovascular mortality.* ***Conclusions:*** *Elderly patients with AF are less often referred to the cardiologist and, based on current guidelines, are inadequately studied and treated, compared to younger counterparts. Education on evidence-based management and the design of randomized controlled trials specifically targeting the elderly, should improve the management and prognosis of this frail segment of the AF population.*
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INTRODUCTION

Atrial fibrillation (AF) is a signature disease of the aging population (1). It is estimated that less than 0.5% of subjects <40 years have AF, but the prevalence of the arrhythmia increases, reaching 18% in the population >85 years of age. Thus, about one every four persons older than 55 years will develop AF (2). The epidemiological burden of AF has important implications concerning quality of life and the use of medical resources (3, 4).

Moreover, the arrhythmia is independently associated with increased mortality (5). All AF associated conditions can further worsen the prognosis of patients (3, 6) and AF itself can significantly increase the incidence of complications, such as heart failure (HF) (7), stroke (8) and dementia (9). Therefore, management of AF in the elderly is complex (1). Furthermore, old patients tend to have an increased risk of adverse side effects due to antithrombotic drugs (10) and rhythm and rate control therapies (1), while the efficacy of guidelines-recommended treatments may be uncertain due to under-representation of elderly subjects in clinical trials (11).

The Euro Heart Survey (EHS) on AF offers a unique opportunity to observe age-related patterns in the characteristics, management and prognosis of AF patients in European cardiology practice (12, 13). We hypothesized that the management of elderly AF patients is less adequate according to management guidelines than that ob-

Key words: Atrial fibrillation, elderly, guidelines, management, oral anticoagulation, prognosis.

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served at younger ages, with a consequent increase in morbidity and mortality.

METHODS

Survey methods, participating centers and patient characteristics of the EHS on AF have previously been described (12). Briefly, between 2003 and 2004, 182 centers of 35 Countries of the European Society of Cardiology enrolled all consecutive AF patients (n=5333), diagnosed on ECG or ECG Holter recording, at baseline or within the preceding year. Patients entered into the registry from outpatient clinics, cardiology wards, cardiovascular surgery wards, emergency departments, electrophysiology and device implantation laboratories. At the 1-year follow-up, information about survival, incident morbidity, hospital re-admissions and AF management were specifically gathered through medical records and patient interview.

Data were collected using an electronic case report form, which provided clinical definitions and validation alerts. Additional validation checks were performed by the central data collection site (European Heart House, Sophia Antipolis, Nice, France). The Maastricht (The Netherlands) data analysis center performed the final validation of the database.

Patients were categorized into three age groups: <65, 65-80 and >80 years. While the intention to study the management of elderly AF patients was pre-specified in the original protocol, the age stratification criteria we used were not previously defined and were introduced for this study. Results of the three age groups will always be mentioned in the text in the following order: <65, 65-80, >80 years. Four patients were excluded from the present analysis because of missing data regarding age.

Statistical analysis

Data analysis was performed with SPSS statistical software (release 12.01; SPSS Inc., Chicago, Il, USA). Continuous variables are reported as mean ± standard deviation or median (25^{th}-75^{th} percentile), and categorical variables as percentage. The existence of any difference among the three age groups was tested with one-way analysis of variance or Kruskal-Wallis test for continuous variables, and with χ^2-test for categorical variables. In case of a statistically significant difference, a *post-hoc* test was performed to identify which groups exactly differed.

Table 1 - *Patients' characteristics.*

	Age <65 (n=2124)	Age 65-80 (n=2534)	Age >80 (n=671)	*p*-value
Demographics				
Age (years)	54±9	73±4	84±4	<0.001
Female (%)	31	47	61	<0.001
Cardiovascular risk factors (%)				
Current smoker	20	8	4	<0.001
Family history of CAD	21	19	16	0.038
No regular exercise	40	50	66	<0.001
Comorbidities (%)				
Cardiomyopathy	12	11	9	0.040
COPD	9	16	21	<0.001
Coronary artery disease	24	40	38	<0.001
Diabetes mellitus	13	22	18	<0.001
Heart failure	29	35	46	<0.001
Hyperlipidemia	35	39	25	<0.001
Hypertension	53	71	69	<0.001
Malignancy	2	7	11	<0.001
Peripheral vascular disease	4	10	12	<0.001
Prior major bleeding	1	2	4	<0.001
Prior stroke or TIA	6	12	18	<0.001
Prior other thromboembolism	2	3	5	<0.001
Renal failure	3	7	12	<0.001
Sick sinus syndrome	3	5	9	<0.001
Thyroid diseases	9	12	11	0.001
Valvular heart disease	23	28	34	0.001
$CHADS_2$ stroke risk score				
0	32	11	0	<0.001
1	39	33	13	
2	20	30	38	
>2	9	27	49	
Miscellaneous (%)				
Participating in clinical trial	13	11	9	0.008

Results are presented as mean ± standard deviation or proportion within the column. COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack.

Table 2 - *Information on admission/consultation and instrumental data.*

	Age <65 (n=2124)	Age 65-80 (n=2534)	Age >80 (n=671)	*p*-value
Admission/consultation reason (%)				
AF only	48	37	30	<0.001
AF and other reason	40	43	44	0.166
Other reason only	12	21	27	<0.001
Length of stay in hospital (days)	5 (2-10)	5 (1-10)	7 (3-11)	<0.001
Type of AF (%)				
1st detected AF	19	19	17	<0.001
Paroxysmal AF	36	26	20	
Persistent AF	24	23	17	
Permanent AF	21	32	47	
AF related symptoms (%)	75	67	61	<0.001
Dyspnoea	29	32	34	0.038
Palpitations	61	46	32	<0.001
Other symptoms	55	55	55	0.965
HF functional class				
NYHA I	18	19	20	<0.001
NYHA II	44	36	32	
NYHA III	32	38	36	
NYHA IV	6	7	12	
Physical examination				
Weight (kg)	77±14	71±15	66±15	<0.001
Body Mass Index (kg/m^2)	28±6	28±6	26±12	<0.001
SBP (mmHg)	134±22	137±22	136±23	<0.001
DBP (mmHg)	82±14	81±13	77±13	<0.001
Electrocardiogram				
Heart rate (bpm)	94±32	91±29	89±29	<0.001
Atrial fibrillation (%)	70	78	81	<0.001
QRS duration (ms)	97±28	99±28	103±29	<0.001
QT interval (ms)	368±101	374±97	375±66	0.063
LV hypertrophy (%)	19	21	19	0.302
Left bundle branch block (%)	6	8	11	<0.001
Right bundle branch block (%)	6	8	12	<0.001
Transthoracic echocardiogram				
Left atrial diameter (mm)	45±9	46±9	47±9	<0.001
LV ejection fraction (%)	51±14	52±14	50±17	0.181
LV hypertrophy (%)	30	38	38	<0.001

Results are presented as mean ± standard deviation with the exception of Length of stay in hospital (median, 25th-75th percentile), or proportion within the column. Persistent AF: a sustained form of arrhythmia lasting beyond 7 days which can be interrupted by electrical or pharmacological cardioversion; Permanent AF: a sustained form of arrhythmia which cannot be steadily interrupted by means of cardioversion (8); LV: left ventricular.

A multivariable logistic regression analysis model was built to evaluate the independent effect of age on the prescription of recommended treatment and outcomes. Variables were removed from the model following a stepwise modality (p_{out} >0.10). Variables with a *p*-value <0.05 in the final model were considered to be predictors of the dependent variable. The net odds ratio (OR), with its 95% confidence interval (CI), and the related *p*-value are reported.

RESULTS

In the EHS on AF, 40% of patients were <65, 48% were 65 to 80, and 12% were >80 years old. The oldest subjects were more likely than younger ones to be enrolled by non-university hospitals or non-highly specialized cardiology centers (29 *vs* 43 *vs* 56%; *p*<0.001).

Patient characteristics

With advancing age the proportion of women and the presence of comorbid conditions increased (Table 1). The prevalence of hypertension, coronary artery disease, diabetes and thyroid diseases was higher in patients aged ≥65 years. The presence of relative contraindications for oral anticoagulation (OAC; i.e. a prior major bleeding, present or history of cancer and renal failure) displayed an age-related increasing trend. Because of age and higher prevalence of a prior stroke/TIA and associated diseases, patients >80 years had the highest $CHADS_2$ stroke risk score (Table 1).

AF was more often the only reason for visiting the clinic in the youngest patients (Table 2). While palpitations were the most common symptom in young patients, dyspnoea was most represented in the oldest, who had al-

so the worst NYHA functional class, and the highest in hospital length of stay. In almost half of patients >80 years AF was permanent (Table 2).

Management

Diagnostic procedures were employed less frequently in the oldest group (Table 3). Pacemaker implantation was more often performed in the oldest subjects while cardioversion and catheter ablation were more frequently used in the younger groups (Table 3).

The use of oral anticoagulation (OAC) had the lowest prevalence in patients >80 years (Table 3). However, given the more frequent use of antiplatelet agents in old subjects, the proportion of patients who received at least one anti-thrombotic drug was higher among patients >65 years (Table 3).

Class Ic antiarrhythmic drugs, amiodarone, sotalol and beta-blockers were less often prescribed in the oldest patients, who more often received prescription for diltiazem and digitalis (Table 3). However, the increased use of digitalis was observed only among elderly AF patients without signs or symptoms of HF (14 *vs* 21 *vs* 29%; $p<0.001$); when HF was present, no difference existed in the prescription rate of digitalis ($p=0.230$). The recommended combined use of beta-blockers and digitalis among patients with permanent AF and HF significantly decreased with age (34 *vs* 22 *vs* 11%; $p<0.001$).

When we combined interventions and drugs, the application of a rhythm control strategy decreased proportionally with age (72 *vs* 58 *vs* 38%; $p<0.001$). The same trend was observed for the prescription of at least one rate-control drug among subjects with permanent AF (91 *vs* 85 *vs* 75%; $p<0.001$).

Prognosis

One year follow-up data were available for 80% of the enrolled patients. The proportion of subjects lost to follow-up was highest in the oldest group (19 *vs* 20 *vs* 25%;

Table 3 - *Management.*

	Age <65 (n=2124)	Age 65-80 (n=2534)	Age >80 (n=671)	*p*-value
Diagnostics – ever performed (%)				
Chest X-ray	78	83	84	<0.001
Transthoracic echocardiogram	87	85	74	<0.001
Transesophageal echocardiogram	17	12	7	<0.001
Thyroid hormones levels	47	46	48	0.694
Holter monitoring	31	28	27	0.011
Exercise test	22	21	12	<0.001
Electrophysiological study	10	4	2	<0.001
Event recorder	2	2	2	0.742
Interventions – now or planned (%)				
Pharmacological cardioversion	28	24	13	<0.001
Electrical cardioversion	30	25	12	<0.001
Catheter ablation	10	2	2	<0.001
Pacemaker implantation	4	5	12	<0.001
ICD implantation	1	1	1	0.454
AF surgery	2	1	1	0.074
Antithrombotic drugs (%)				
OAC	57	60	50	<0.001
OAC + antiplatelet agent	7	8	6	0.381
Antiplatelet agent	23	25	33	<0.001
Heparin	2	2	3	0.256
No antithrombotic drug	12	6	9	<0.001
Rhythm and rate control drugs (%)				
Class I antiarrhythmic drug[a]	14	8	5	<0.001
Amiodarone	28	23	18	<0.001
Sotalol	7	7	4	0.008
Beta-blockers[b]	45	45	32	<0.001
Diltiazem	3	5	6	0.001
Verapamil	5	5	5	0.935
Digitalis	23	28	36	<0.001
Other cardiovascular drugs (%)				
Diuretics	42	56	70	<0.001
ACE inhibitors	45	54	47	<0.001
AT-II receptor blockers	11	14	16	<0.001
Statins	22	30	19	<0.001

Results are presented as proportion within the column. ICD: Implantable cardioverter-defibrillator; OAC: oral anticoagulation; ACE: angiotensin converting enzyme; AT: angiotensin. [a]According to Vaughan-Williams classification; [b]Excluding sotalol.

Table 4 - *Events at 1-year Follow-up.*

	Age <65 (n=1697)	Age 65-80 (n=1996)	Age >80 (n=486)	*p*-value
Mortality (%)				
All-cause mortality	2.2	5.6	14.8	<0.001
Cardiovascular mortality	1.5	2.0	6.7	<0.001
Thromboembolic and hemorrhagic events (%)				
Ischemic stroke	1.4	1.7	2.0	0.597
Myocardial infarction	0.8	1.0	2.7	0.002
Other thromboembolism	0.3	0.5	0.2	0.644
Hemorrhagic stroke	0.1	0.4	0.0	0.187
Other major bleeding	0.6	1.9	2.7	0.001
Heart failure (%)				
New onset heart failure	3.4	6.0	7.4	0.003
Heart failure worsening	25	23	29	0.274
Hospital admissions (%)				
Admission for AF	29	22	18	<0.001
Any cardiovascular disease	40	36	34	0.016
Non-cardiovascular disease	9	13	16	<0.001

Results are presented as proportion within the column.

$p<0.001$). An age-dependent increase in all-cause and cardiovascular mortality was observed, with morbidity following the same trend (Table 4). In particular, elderly patients more often experienced myocardial infarction, new onset heart failure and major bleedings, and were more often hospitalized for both cardiovascular and non-cardiovascular causes.

When patients aged >80 years were considered, multivariable analysis revealed that the 1-year risk of all-cause mortality was higher with renal failure (OR=3.25, 95% CI=1.62-6.53; $p=0.001$) and COPD (OR=2.62, 95% CI=1.44-4.75; $p=0.002$), and lower with hypertension (OR=0.45, 95% CI=0.23-0.91; $p=0.028$). The use of either an ACE-inhibitor or an angiotensin II receptor blocker was associated with lower mortality (OR=0.50, 95% CI=0.25-0.97; $p=0.041$). Although, in univariate analysis, OAC showed a protective effect on mortality in patients >80 years (OAC: 12% *vs* no OAC: 19%; $p=0.037$), this finding was not significant in the multivariable model.

DISCUSSION

AF is the most frequent arrhythmia in elderly people and has serious health-related and economic consequences. The EHS on AF provides a unique description of age-related differences in the characteristics, management and outcome of patients in European cardiology practice.

According to estimates of the European Union, people aged 65-80 years and >80 years represent 12.7 and 4.4% of the entire population, respectively (14). One of the main findings of our survey is that the absolute number of patients enrolled in the >80 years group is about four times less than expected (2), indicating a bias in the referral of the oldest subjects to specialized cardiology centers. In fact, recent data from the *Progetto Veneto Anziani* (Pro.V.A.) Study, aimed at describing the condition of elderly subjects living in community in the northern part of Italy, showed an AF prevalence of 7.4% and 17% in subjects aged >65 and >85 years, respectively (15). Moreover, the Pro.V.A. Study found a significant association between the arrhythmia and disability (15). Taking together, these data suggest that clinically complex elderly patients are less likely to be referred to cardiology centers. In addition, we found that the oldest old enrolled in the Survey less often underwent diagnostic tests as recommended by past and present AF guidelines (8, 16). In particular, standard transthoracic echocardiogram, ECG Holter monitoring and exercise stress test – necessary to define the origin and the quality of treatment of the arrhythmia – were under-prescribed in the oldest group of patients.

Several reasons can underlie exclusion of elderly subjects from specialized AF care. First of all, due to a worse general health condition, poor tolerance of drug treatment or physicians' fear of side effects, elderly patients are often underrepresented in clinical trials, which generates uncertainty on the efficacy and safety of evidence-based treatments in this age group (11, 17). Moreover, the high prevalence of comorbidities might cause physicians to primarily focus on other diseases, considered more urgent. The demonstration of effectiveness of guideline-based recommendations in the management of elderly AF patients could help physicians to be less hesitant to apply recommended care.

Oral anticoagulation for elderly AF patients

Patients >80 years of age – an evidence-based stroke risk factor (18) – had a lower likelihood of receiving an-

ticoagulants, despite the BAFTA trial has shown that, in the elderly, OAC is more effective than aspirin alone for stroke prevention (19). This behavior could be justified by the increased incidence of major bleedings observed during follow-up in our aged, under-treated subjects. However, hemorrhagic stroke – the most clinically severe bleeding – did not show any age-related increase in this Survey. In addition, a recent report on an outpatient population followed by an anticoagulation clinic demonstrated that the incidence of major bleedings is acceptably low also in the very old, equal to 1.87 events per 100 patient-years in subjects >80 years, provided a careful management of anticoagulation is obtained (20). The fear for bleeding seems to be overstated if we consider that the net clinical benefit of OAC (i.e. the adjusted annual rate of ischemic strokes and systemic emboli prevented by warfarin minus intracranial hemorrhages) is greatest for patients ≥85 years (21), particularly if not showing a history of bleeding, falls or active cancer (20).

Rhythm and rate control in elderly AF patients

In our survey, rate control was the preferred strategy in old patients. The lower application rate of a rhythm control strategy in the oldest old is probably due to the higher likelihood to accept AF as a permanent condition. This is, at least in part, supported by the results of a *post-hoc* analysis of the AFFIRM trial demonstrating the superiority of rate control over rhythm control in patients aged >65 years (22). In addition, a recent meta-analysis confirmed the high incidence of adverse events correlated with the use of rhythm control drugs (23), and a Markov decision model showed that a rate control strategy determines greater benefits in terms of mortality and quality-adjusted years of life in older patients (24). However, advanced age was not associated with an increased susceptibility to adverse events produced by electrical cardioversion or AF ablation (25, 26). Therefore, elderly should not be denied these interventions if needed. Moreover, safer anti-arrhythmic drugs to be used in elderly patients are warranted. Vernakalant may represent a novel therapeutic alternative, with greater impact on health related quality of life (27).

Digitalis is indicated for patients with AF and HF (8). However, despite safety concerns (1), the use of this drug is still high in elderly patients without HF. Although the AFFIRM study demonstrated that digitalis was less effective for rate control than beta-blockers (28), we report a scarce use of these agents in old patients.

Prognosis

The oldest AF patients had a higher rate of non-cardiovascular causes of hospitalization compared to younger subjects, and the worst prognosis. Indeed, AF may be considered as an indicator of a more compromised clinical status in the elderly, being associated with several comorbid conditions (e.g. pneumonia, COPD, urinary infections, dehydration) (3, 6).

The protective effect of renin-angiotensin system antagonists on all-cause mortality, as seen in the total cohort (13), was still maintained in the group aged >80 years. In addition, the application of either rhythm or rate control did not modify the prognosis of the oldest old (13). During follow-up, we observed a lower mortality in patients >80 years on OAC, in univariate analysis, which however did not persist in multivariate analysis, possibly due to the relatively small sample size of the oldest group.

Limitations

Enrolment was not equal among participating countries and there was an overrepresentation of highly specialized hospitals. Moreover, the vast majority of patients was of Caucasian origin. However, we must mention that some evidence seems to suggest that AF could be genetically linked to European Caucasian population, who shows a well-defined higher risk to develop the arrhythmia when compared to populations with African ancestry (29). Further, elderly were more often lost to follow-up than younger patients, which might have caused an underestimation of mortality and morbidity in this group.

CONCLUSION

To answer the question "are we ready to practice geriatric cardiology?" (30), our results indicate that we still have room for improvement. Older age itself should not be a reason to exclude patients from trials and to deny guidelines recommended treatment, especially since the very old are more likely to benefit from evidence based medicine.

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