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## Atrial fibrillation (AF) and comorbidity in elderly. A population based survey of 85 years old subjects

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#### Abstract

The occurrence of AF increases sharply with age. The aim of this study was to explore and compare prevalent co morbidity and self estimated health related quality of life in subjects with AF versus subjects with sinus rhythm or pacemaker in 85 years old subjects. We analyzed data from a population of 336 eighty five years old subjects participating in the Elderly in Linköping Screening Assessment (ELSA-85) study. Medical history was obtained from postal questionnaire, medical records and during medical examination that included a physical examination, cognitive tests, non fasting venous blood samples and electrocardiographic (ECG) examination. 19% had an ECG showing AF. There were very few significant differences regarding medical history, self-estimated quality of life (QoL), laboratory- and examination findings and use of public health care between the AF group and the non-AF group. The study showed that that the population of 85 years old subjects with AF was surprisingly healthy in terms of prevalent co-existing medical conditions, healthcare contacts and overall health related quality of life (HRQoL). We conclude that elderly patients with AF do not in general have increased co morbidity than subjects without AF.

**Keywords:** atrial fibrillation, co-morbidities of elderly, CHADS2 score, oral anticoagulation, health-related quality of life

#### 1. Introduction:

The occurrence of AF increases with age and the prevalence has previously been shown to be between 9 and 18% in subjects over 80 years old compared to about 0.5% in the ages 50-59 years old (Kannel et al., 1998; Heeringa et al., 2006). A risk factor for developing AF is presence of cardiovascular disease; high systolic blood pressure, prior myocardial infarction, valvular heart disease and left atrial enlargement (Mozaffarian et al., 2008). Also hyperthyroidism, overweight, excessive use of alcohol, and male sex (Friberg et al., 2003; Mukamal et al., 2005; Heeringa et al., 2006, 2008) are predictors of AF. Prior studies have suggested that patients with AF have an impaired quality of life depending on accurate rate and rhythm control (Thrall et al., 2006). Furthermore AF is also associated to diabetes (Ostgren et al., 2004; Du et al., 2009), decreased glomerular filtration rate (GFR) (Iguchi et al., 2008; Schmidt et al., 2010) and regular physical activity that has been shown to lower the risk of developing AF in older adults (Mozaffarian et al., 2008).

AF is associated with a five times greater risk of cardio embolic stroke (Lotze et al., 2010), which increases in old age (Wolf et al., 1991; Rojas et al., 2007). However prophylactic oral anticoagulation (OAC) treatment is not, by clinicians, always thought to be suitable in an older, frail patient with present and maybe dominating co morbidities such as cognitive impairment or giddiness and high risk of falling, where the fear of potential risk of OAC with intracranial hemorrhage is believed to exceed the benefits, following the reduced risk of cardio-embolic stroke (Vasishta et al., 2001). Recently it has been shown that the benefits of OAC are of great importance especially for an older patient with AF who has a greater risk of cardio-embolic stroke than a middle aged patient with AF. Risk of major bleeding is hard to estimate but is often overestimated. Furthermore, OAC appears to be protective in terms of stroke, myocardial infarction and death in patients with a high risk of falling and multiple stroke risk factors (Tulner et al., 2010).

Data on elderly patients with AF are limited in the vast majority of AF studies. The aim of this study was to explore and compare prevalent co morbidity and self estimated health related quality of life in subjects with AF versus subjects with sinus rhythm or pacemaker in 85 years old subjects in community based living or nursing homes in the municipality of Linköping, Sweden.

#### 2. Methods

The ELSA-85 study is a population-based survey where all residents born in 1922 (n = 650), living in the municipality of Linköping, Sweden, were identified through the local authorities' register and invited by letter to join the study at age 85. Data collection was performed between March 2007 and March 2008 as previously described (Nägga et al., submitted). The baseline data included a postal questionnaire, house call from occupational therapist and visit to the geriatric clinic for cognitive testing, blood samples, ECG and physical examination. The postal questionnaire contained questions about social network; need of assistance; use of assistive technology; presence of insomnia; feelings of loneliness; presence of prescribed drugs. It also included the **EQ-5D (1990)**, a generic instrument that assesses health related quality of life in terms of mobility, self care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels of severity graded from one to three; no problems, moderate problems or severe problems. The

EQ-5D also contains a visual analogue scale (VAS) that records the individual's selfrated evaluation of health, ranging from 0, worst imaginable health status, to 100, best imaginable health status. The scores of the five EQ-5D dimensions (VAS excluded) were converted to a single summary index value generated by means of the time trade off method (TTO) (Dolan, 1997; Rabin and De Charro, 2001).

Medical history was obtained from postal questionnaire, medical records and during medical examination by use of a specified protocol. A physical examination was performed with measurements of blood pressure in lying position after 5 minutes rest, height, waist circumference (to the nearest cm) and weight (to the nearest 0.1 kg) with the subjects wearing light indoor clothing. Non-fasting venous blood samples were drawn for measurement of plasma-glucose, serum-creatinine, TSH, C-reactive protein (CRP) and NT-proBNP. NT-proBNP was analyzed using the Elecsys 2010, Roche's method until September 2007 (total imprecision CV at level 180; 6.2% and at level 1900; 4.8%), and after that with the Modular E, modified Roche's method (total imprecision CV at level 90; 4.6% and at level 800; 4.5%). Estimated glomerular filtration rate (eGFR) as a parameter of renal function was calculated from serum creatinine level, age and weight according to the Cockroft-Gault formula (Cockcroft and Gault, 1976). An eGFR  $\geq$  60 ml/min was classified as normal or mildly impaired renal function, < 60 ml/min was classified as moderate renal impairment and < 30 ml/min as severe renal impairment (Schmidt et al., 2010).

A standard 12 lead ECG was recorded at 50 mm/s and 10 mm/mV standardization using a MAC 38 PC and interpreted according to American Heart Association (AHA) guidelines (Mason et al., 2007; Surawicz et al., 2009) manually and unidentified, by one physician (K.R). The review comprised rhythm and pace; sinus rhythm, pacemaker or AF/flutter, bradycardia (< 50 beats/min), tachycardia (> 100 beats/min), and presence of pathological Q-wave indicating past ischemic event. ECGs were also analyzed according to Cornell voltage-duration product; (RaVL + SV3) times duration of QRS complex, adjusted for female gender by adding 6 or 8 mm to the sum of (RaVL+SV3), with a partition value of 2440 mm x ms to recognize left ventricular hypertrophy (LVH) (Devereux et al., 2001; Pewsner et al., 2007), and complemented with Sokolw-Lyon voltage index (SV1+RV5 or V6) with > 35 mm as partition value (Sokolow and Lyon, 1949). Hypertension was defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 or ongoing antihypertensive medication in accordance with WHO guidelines (Whitworth, 2003).

Body mass index (BMI) was calculated using the formula weight x height<sup>-2</sup> and defined as underweight if; < 18.5 kg m<sup>-2</sup>, normal range; 18.5-24.9, overweight; 25.0-29.9 and obesity if  $\ge$  30.0, according to the criteria of WHO (1995).

Cardio-embolic stroke risk was estimated using CHADS2 score (congestive heart failure, hypertension, age > 75, diabetes, each 1 point. Prior stroke or transient ischemic attack (TIA), 2 points). CHADS2 score was calculated in the AF group and two or more points were considered as indication for OAC (Gage et al., 2001; Rietbrock et al., 2008). Data concerning diabetes, prior stroke or TIA were obtained from postal questionnaire, medical history provided by subjects during medical examination and in case of uncertainty by medical records. Fall risk was estimated with use of Downton fall risk index (DFRI) that consider earlier falls, medication, sensory loss, cognitive impairment and walking ability. Three or more points indicate high risk of falling (Downton, 1993). Cognitive impairment was evaluated with a minimental state examination (MMSE) where 26 points of 30 or less were considered as mild cognitive impairment and 20 points or less as moderate to severe cognitive impairment (Folstein et al., 2001).

#### 2.1. Statistical analysis

Analysis of binary variables was carried out using Fisher's exact test. Continuous variables with normal distribution were analyzed with an unpaired Student's t-test. Variables with skewed distribution were compared using the Mann-Whitney U-test. Statistical significance was set at p < 0.05. The PASW 18 software (IBM SPSS Statistics, Chicago, IL, USA) was used for analysis of data.

#### 2.2. Ethics

The study, which complied with the declaration of Helsinki, was approved by the Regional Ethical Review Board in Linköping, Sweden, 2006-12-12. (Clinical-Trials, gov. number 141-06)

#### 3. Results

Ninety percent (n = 586) of the 650 subjects responded to the invitation to participate in the study. Written informed consent was obtained from 496 individuals (78% of those alive) who also answered the postal questionnaire. During the course of the data collection, there was a drop-out of 158 subjects of which 13 died leaving

338 individuals (52%). However, two individuals were excluded because of poor quality or absent ECG registration due to technical problems. Hence, 143 men and 193 women remained for further analysis.

Out of the 336 participants, 25 females and 28 males had an ECG showing AF which comprised 13% of the female study population and 20% of the male study population, respectively.

Data presented in Table 1 show that history of CHF was more common in the AF group compared to the non-AF group but there were no significant differences in medical history apart from that. The AF group consumed more antihypertensive pharmaceuticals than the non-AF group, but there was no difference concerning history of hypertension between the groups. The AF group was also treated with warfarin to a higher extent than the non-AF group, but inversely the non-AF group was prescribed aspirin more often than the AF group. There was only one subject in the AF group that was treated with a low molecular weight heparin (LMWH) compared to none in the non-AF group.

There were no differences between the AF- and non-AF group concerning prior myocardial infarction (MI) identified as pathological q wave or history of previous MI, presence of LVH calculated from ECG, using both the Cornell duration product and Sokolw-Lyon index, history of diabetes, previous stroke or TIA. Adding 6 or 8 mm in the formula for Cornell duration product for women did not change the results (data not shown).

Both groups had a DRRI indicating high risk of falling but with no significant difference between the groups. Among AF subjects, the majority had a CHADS2 score of two or more points, which is the cut off for OAC treatment indication. In the AF group it was significantly more common with mild cognitive impairment than in the non AF group, but there was no difference between the groups concerning the presence of moderate or severe cognitive impairment.

There was a significant difference concerning obesity where the AF group had a prevalence of obesity of more than 2.5 times the prevalence in the non-AF group (Table 1). Accordingly, Table 2 shows that subjects in the AF group were more overweight both regarding waist circumference and BMI compared to the non-AF group. However, there was no difference regarding underweight between the groups.

Characteristics		Atrial Fibrillation n=53		Sinus rhythm or pacemaker n=283 <sup>a</sup>				
		n	(%)	)		n	(%)	р
Male/Female ratio		28/25(20/13)		20/13)	115/168(80/87)		0.130	
Medical history								
Pı	revious stroke	:	8	(15)		39	(14)	0.829
Pı	revious TIA	,	7	(13)		24	(8)	0.300
C	ongestive heart failure	2	24	(45)		35	(12)	< 0.001
Н	ypertension	3	32	(60)		151	(53)	0.371
Pı	revious myocardial infarction		9	(17)		44	(16)	0.837
D	iabetes	1	0	(19)		51	(18)	0.848
С	urrent smoker		1	(2)		8	(3)	1.000
Pı	revious smoker	1	3	(25)		56	(20)	0.460
Li	iving at nursing home	:	8	(15)		19	(7)	0.052
Medicati	ion							
T	reatment with warfarin	3	34	(64)		20	(7)	< 0.001
Ti	reatment with aspirin	1	3	(25)		117	(42)	0.021
N as	o current treatment with spirin or warfarin	:	8	(15)		149	(53)	< 0.001
Ti	reatment with betablocker	3	38	(72)		101	(36)	< 0.001
Ti	reatment with ACEI/ARB	2	22	(42)		65	(23)	0.010
Ti	reatment for hyperlipidemia	1	0	(19)		75	(27)	0.302
ECG								
Та	achycardia (> 100 beats min <sup>-1</sup> )		6	(11)		2	(1)	< 0.001
B	radycardia (< 50 beats min <sup>-1</sup> )	:	5	(9)		10	(4)	0.069
Ра	athological Q-wave		4	(8)		15	(5)	0.525
Le	eft ventricular hypertrophy (LVH)	b .	3	(6)		22	(8)	0.779
Le	eft ventricular hypertrophy (LVH)	<sup>c</sup> 1	4	(26)		54	(20)	0.357
MMSE <27 (mild cognitive impairment)		2	21	(40)		72	(25)	0.044

Table 1 Baseline characteristics of 336 subjects 85 years old in Linköping municipality 2007-2008

MMSE <21 (moderate-severe

cognitive impairment)	5	(9)	9	(3)	0.052
Estimated GFR < 30 ml min <sup>-1</sup>	1	(2)	27	(10)	0.098
BMI > 30 kg m <sup>-2</sup> (obesity)	19	(36)	39	(14)	< 0.001
BMI < 18.5 kg m <sup>-2</sup> (underweight)	0	(0)	5	(2)	1.000
Downton Fall Risk Index indicating high risk of falling ( $\geq$ 3 points)	47	(89)	229	(81)	0.240
CHADS2 score recommending warfarin treatment ( $\geq 2$ points)	47	(89)	n.a <sup>d</sup> .	n.a.	n.a.

Differences were analysed with Fisher's exact test <sup>a</sup> sinus rhythm n=272, pacemaker n=11 <sup>b</sup> LVH calculated from ECG using Sokolow-Lyon voltage <sup>c</sup> LVH calculated from ECG using Cornell duration product <sup>d</sup> n.a. = not applicable

Table 2 Baseline characteristics of 336 subjects 85 years old in Linköping municipality 2007-2008

Characteristics	Atrial Fibrillation n=53		Sinus rhy n	Sinus rhythm or pacemaker n=283 <sup>a</sup>				
	mean	(sd)	mean	(sd)	р	mean difference	(CI 95%)	
BMI, kg m <sup>-2</sup>	27.42	(4.57)	25.75	(4.09)	0.008	1.67	(0.43-2.91)	
Waist circumference, cm	97.33	(11.16)	93.85	(10.16)	0.027	3.48	(0.40-6.66)	
Systolic blood pressure, mm Hg	142.32	(20.47)	153.27	(21.57)	0.001	-10.94	(-17.264.63)	
Diastolic blood pressure, mm Hg	76.49	(12.03)	73.73	(12.01)	0.125	2.76	(-0.78-6.30)	
P-glucose, mmol $L^{-1}$	6.64	(1.74)	6.34	(1.95)	0.294	0.30	(-0.26-0.87)	
TSH, mU L <sup>-1</sup>	1.89	(1.32)	2.17	(4.43)	0.649	-0.28	(-1.49-0.93)	
S-Creatinine, µmol L <sup>-1</sup>	101.08	(32.40)	98.37	(32.52)	0.578	2.71	(-6.86-12.28)	
Estimated GFR ml min <sup>-1</sup>	50.12	(14.17)	45.94	(13.52)	0.043	4.18	(0.13-8.22)	
NT-proBNP, pg ml <sup>-1</sup> 1668.46)	1934.72	(1832.74)	659.17	(1218.85)	<0.001	1275.54	(882.62-	
CRP, mg $L^{-1}$	10.47	(2.91)	11.18	(5.68)	0.376	-0.71	(-2.28-0.87)	

Differences analysed with independent t-test <sup>a</sup> sinus rhythm n=272, pacemaker n=11

Concerning laboratory test results, we found significantly higher levels of NTproBNP and lower eGFR in the AF group than in the non-AF group. No other differences were found.

In Table 3 differences between the groups were analyzed using Mann Whitney U-test showing that there was no significant difference of median value between the groups regarding total sum of MMSE score, though a greater variance and interquartile range (IQR) in the AF group. The number of total yearly hospital contacts was low in both groups, somewhat higher in the AF group who was admitted to hospital in greater extent than the non-AF group. There were no differences of primary health care contacts or visits to primary health care physicians between the groups, which were overall low. Nor was there any difference of outpatient visits to hospital physicians between the groups. Regarding fall risk in means of DFRI sum and self estimated HRQoL using the EQ-5D index value and EQ-5D VAS scale no differences were found between the AF and the non-AF group. Concerning the different dimensions of EQ-5D, we found a significant difference in the usual activities dimension where subjects with AF estimated that they had greater difficulties than subjects in the non-AF group, with a median of 1 point in both groups, but a greater IQR in the AF group compared to the non-AF group (1 vs. 0, p < 0.001, data not shown). There were no differences between the groups regarding mobility, self care, pain/discomfort or anxiety/depression.

#### 4. Discussion

This study showed that the investigated population of 85 years old subjects with atrial fibrillation was surprisingly healthy in terms of healthcare contacts and overall health related quality of life. Health state scores decreases with age and the EQ-5D index value has been shown to be 0.74 in a general Swedish population aged 80-88 years old (Burstrom et al., 2001) which corresponds with our findings. Concerning the EQ-5D VAS-scale, the present data are also in concordance with the Euro heart survey where over 5000 adult patients with AF in all age groups assessed their health related quality of life using the EQ-5D VAS scale (Berg et al., 2010). Previously, it has been shown that there are several diseases that are co-morbid with AF such as hypertension, LVH, CHF, MI, diabetes and stroke (Benjamin et al., 1998). Apart from medical history of more frequent CHF, and elevated levels of NT-proBNP

### supporting this diagnosis, in the AF group compared to the non-AF group, we were not able to confirm any of these findings in our study population aged 85 years.

Characteristics	Atrial Fibrillation n=53		Sinus rh		
	median (interquartile range)		median (interquartile range)		р
Use of public healthcare					
Total number of admitted days/year	0.00	(0.00-3.00)	0.00	(0.00-0.00)	< 0.001
Total number of primary health care contacts/year	6.00	(2.00-16.00)	5.00	(2.00-9.00)	0.236
Visits to primary health care physician/year	2.00	(1.00-3.00)	2.00	(0.00-3.00)	0.408
Outpatient visits to hospital physician/year	2.00	(1.00-8.50)	2.00	(0.00-4.00)	0.098
Heart frequency (beats/min)	76.00	(63.00-86.00)	66.00	(59.00-75.00)	0.001
MMSE total score	28.00	(24.00-29.00)	28.00	(26.75-29.00)	0.483
Downton Fall Risk Index sum	3.00	(3.00-5.00)	4.00	(3.00-4.00)	0.795
EQ-5D (index value)	0.73	(0.62-0.81)	0.73	(0.66-0.85)	0.208
EQ-5D (VAS scale)	69.50	(50.00-77.25)	70.00	(53.75-80.00)	0.056

Table 3 Baseline characteristics of 336 subjects 85 years old in Linköping municipality 2007-2008

Differences were analysed with Mann Whitney U test <sup>a</sup> sinus rhythm n=272, pacemaker n=11

The prevalence of AF of 19% is high in comparison with some prior studies (Fitzmaurice, 2009), but corresponds with findings of the Rotterdam study (Heeringa et al., 2006). Our results showed that there were few major significant differences regarding subjects with AF in comparison with subjects without AF. There was a difference in NT-proBNP, where subjects with AF had significantly higher levels of NT-proBNP which probably reflects differences in medical history concerning CHF between the groups. CHF is an established risk factor for developing AF but we found no differences in LVH calculated from ECG between the groups. Cornell voltage-duration product needs to bee adjusted for female gender, but the opinion on whether 6 or 8 mm should be added to (RaVL+SV3) varies (Devereux et al., 2001;

Pewsner et al., 2007). We, therefore, used both values in comparison ((RaVL+SV3+6mm)\*QRSdur/ (RaVL+SV3+8mm)\*QRSdur) which did not change the results.

The lower blood pressure measurements in the AF group were considered as a result of multiple blood pressure lowering- and heart rate control medications. Subjects in the AF group qualified as suffering from mild cognitive impairment to a greater extent compared to the non-AF group which is in accordance with earlier results showing that cardiovascular disease, and also AF independently increases the risk of developing dementia (Kilander et al., 1998; Bunch et al., 2010). However there was no difference regarding the presence of moderate to severe cognitive impairment evaluated with MMSE. Obesity is a known risk factor for AF. Accordingly regular physical activity may serve as a protective factor, as it leads to a decrease in general overweight and waist circumference, which corresponds with our findings concerning BMI and waist circumference (Schoonderwoerd et al., 2008).

Type 2 diabetes is associated with AF and the combination of diabetes and AF constitutes a greater mortality risk than AF alone (Du et al., 2009). In our study we were not able to confirm a higher prevalence of diabetes or elevated p-glucose levels in the AF group compared to the non-AF group.

The findings concerning CHADS2 score, risk of falling and warfarin treatment are interesting. The subjects with AF in the present study were prescribed an OAC to a higher extent, 64% of our population vs. 7% and 22.5% that was reported in prior studies (Deplanque et al., 2004; Lotze et al., 2010). All subjects in the AF group had a CHADS2 score of at least 1 point due to age, and the absolute majority (47 out of 53 subjects) had a CHADS2 score of 2 or more points indicating a benefit of OAC treatment. The prevalence of high risk of falling, according to DFRI was overall high. The National Swedish Board of Health and Welfare (2009) recommends the use of DFRI for evaluation of risk of falling. However, the use of fall risk assessment tools, including DFRI, has not shown to be superior in estimating the risk of falling in nursing homes compared to the nurses' clinical judgment and conversely, the clinical use of such risk assessment tools is currently under debate (Meyer et al., 2009).

In a review of prior studies on antithrombotic treatment of AF in the elderly, it is stated that those with a high risk of falling also are more likely to experience a cardioembolic stroke and therefore should benefit even more from OAC therapy than those without a high fall risk. It is also suggested that an AF patient with a high risk of falling has to fall almost 300 times per year before the disadvantage of OAC treatment overshadows the cardio-embolic stroke protective benefits (Fang, 2009). There are no validated tools available to predict the risk for OAC caused intracranial hemorrhage, which is a complication with high mortality in the frail, elderly patient. However, the elderly patient with AF has a 16-times higher risk of developing a cardio-embolic stroke than a middle aged patient with AF (Ferro, 2003) which must also be taken in to account when deciding up on prophylactic OAC treatment.

In the BAFTA study it was shown that the bleeding risk associated with OAC treatment in AF patients over 75 years old was not higher than in those treated with aspirin 75 mg daily and OAC treatment was as effective in people aged 85 years or over as it was in younger people in preventing cardio-embolic strokes (Mant et al., 2007). Permanent AF is associated with an increased stroke incidence (Schoonderwoerd et al., 2008) which could not be observed in our study population where there was no difference regarding prior stroke or TIA.

Our study was not able to confirm previous results indicating raised inflammatory parameters, such as CRP, in patients with AF compared to the non-AF population (Schoonderwoerd et al., 2008; Patel et al., 2010).

A limitation of the present study is the relatively low number of AF subjects. Furthermore, the cross sectional design of our study precludes conclusions about causality and the categorization of groups was based on one single ECG examination. Finally, LVH is nowadays not diagnosed from ECG but from ECG (Dickstein et al., 2008) which precludes conclusions on the prevalence of LVH in the two groups. However, this does not undermine the fact that the subjects with AF were found not to differ in major respects compared to the subjects without AF.

In conclusion, this study shows that elderly patients with AF, in general, do not have increased co-morbidity than those without AF. Elderly with AF should not be excluded from OAC treatment simply because of old age. Furthermore, elderly subjects with AF do not report poorer QoL nor do they have an overall higher healthcare consumption compared to subjects without AF.

12

#### Conflict of interest statement: None.

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