Quality of Life, Exercise Capacity and Comorbidity in Old Patients with Permanent Atrial Fibrillation

Inger Ariansena, Knut Gjesdala, Michael Abdelnoorb, Elisabeth Edvardsenc, Steve Engerd, Arnljot Tveitd.

aDepartment of Cardiology, Ullevål University Hospital, Oslo, Norway, bCenter for Clinical Research, Ullevål University Hospital, Oslo, Norway, cDepartment of Pulmonary Medicine, Ullevål University Hospital, Oslo, Norway, dDepartment of Internal Medicine, Asker & Bærum Hospital, Rud, Norway.

Abstract

Background: The impact of atrial fibrillation (AF) on quality of life (QoL) differs with the AF population studied and is influenced by comorbidity. In hospital-based studies younger and highly symptomatic patients may be overrepresented. We performed an observational cross sectional study in two municipalities, comparing 75 year-old patients with and without permanent atrial fibrillation, with respect to health-related QoL and exercise capacity, with adjustment for the effects of confounders.

Methods: Maximal treadmill exercise testing provided peak oxygen uptake (VO2 peak). Health-related QoL was assessed by self-completed SF-36 questionnaires. The lowest quartile identified poor outcomes. Results: 27 subjects with permanent AF and 71 subjects in sinus rhythm participated. AF patients had higher prevalence of compensated chronic heart failure (p < 0.001), valvular heart disease (p < 0.001), lower mean VO2 peak (22.7 ± 5.5 vs. 28.6 ± 6.3 ml/kg/min; p < 0.001), and more often poor VO2 peak; crude OR 5.3 (95%CI 1.8, 15.3), adjusted OR 7.5 (2.0, 28.3). Median Physical Component Summary score (with 25th and 75th percentile) was 41 (31, 51) in AF vs. 52 (45, 55) in controls (p < 0.001). Furthermore, the AF group had higher odds for poor physical QoL scores; crude OR 5.0 (1.8, 13.7), adjusted OR 4.3 (1.5, 12.4). Median Mental Component Summary score was 56 (42, 61) in the AF group vs. 57 (51, 60) in controls (p=0.565). The AF group had non-significantly increased odds for poor mental QoL scores; crude OR 2.3 (0.8, 6.2), adjusted OR 2.8 (1.0, 8.4).

Conclusion: Also after adjustment for confounders, older patients with permanent AF had higher odds for poor exercise capacity and poor physical QoL compared to subjects in sinus rhythm.

Introduction

The prevalence of atrial fibrillation (AF) is high and increases exponentially with age, from 0.7% in the age group 55-60 years, to 17.8% in those aged 85 years and older.[1] The number of AF patients is estimated to increase 2.5 fold during the next 50 years.[2,3] The hospitalization rate for AF is increasing[4] and AF patients have an excess mortality.[5]

To plan health services for old people with AF, data are needed not only on the prevalence of AF,

Corresponding Address: Inger Ariansen, MD, Arrhythmia Center, Department of Cardiology, Ullevål University Hospital, 0407 Oslo, Norway.

but also on the impact of AF on their QoL. Neither hospital-based studies nor randomized studies, for instance on drug treatment or on rate versus rhythm control, are suitable for assessing the quantitative dimension of the health service programs for old patients with AF. In hospital-based studies younger and highly symptomatic patients may be overrepresented. Since cardiovascular and other diseases predispose to AF, epidemiologic data on AF should be adjusted for the confounding effects of comorbidity. The aim of the present study was to investigate the impact of AF on exercise capacity and QoL in a 75 year-old out-of-hospital population.

Material and Methods

The study was approved by the Regional Ethics Committee in Health Region East Norway. All patients provided written informed consent in accordance with the revised Declaration of Helsinki before enrolment.

Study Design

The design of the study was cross sectional with exposed (atrial fibrillation, AF+) and non-exposed (sinus rhythm, AF-) subjects. The endpoints were peak oxygen uptake (VO2 peak), and physical and mental QoL. Patients with AF+ and controls with AF- were recruited from the same source population. The lowest quartiles of the total study population identified poor outcomes. This report follows the epidemiologic guidelines for reporting observational studies.[6]

Participants

The source population comprised all citizens born in 1930 in two Norwegian municipalities, who were invited to ECG screening in the Asker and Bærum Atrial Fibrillation study, ABAF.[7] Subjects with permanent AF and a control group in sinus rhythm were invited to perform cardiopulmonary exercise testing (CPET), a 24h ECG, and to fill in self-assessed health-related QoL questionnaires. Exclusion criteria were paroxysmal AF, atrial flutter, AF in a patient with a pacemaker that stimulated >30% of the time, or mental inadequacy. The data were collected from June to October 2005 at Ullevål University Hospital.

Cardiopulmonary Exercise Testing

The participants performed a maximal treadmill exercise test, measuring peak oxygen uptake (VO2 peak). A warm-up phase was followed by a progressive one-minute step protocol with equal energy steps. The test aimed at achieving near maximum exhaustion corresponding to the Borg scale[8]18-19 (range 6-20).

The Medical Outcomes Study Short Form-36 (SF-36)

The standard (four weeks recall) Norwegian version of Medical Outcomes Study Short Form-36 (SF-36)[9]was mailed to the participants. The US general population means, standard deviations and factor score coefficients were used in the norm based aggregation of the eight scales into two components: The Physical Component Summary score (PCS) and the Mental Component Summary score (MCS).[10] The SF -36 Norwegian normative data[11] were similarly transformed into PCS and MCS scores. Quality control of the data was performed according to the SF 36 manual.[12]

Definition of Terms.

A clinical diagnosis was either reported by the participants or revealed by test results during the study. Hypertension was defined as a history of treated hypertension or BP ≥ 160/100. Coronary artery disease (CAD) was defined as a history of CAD or a positive coronary angiography. Valvular heart disease was defined as mitral and/or aortic valve pathology ≥ grade 2 on echocardiography. A history of chronic pulmonary disease or FEV1/FVC<65% defined chronic pulmonary disease.[13] Charlson Comorbidity Index was scored.[14]

Statistical Methods

Comparisons between groups were performed by the Students t-test, Mann-Whitney test or Chi square test where appropriate. We performed a stratification analysis using the Mantel-Haenszel method to pinpoint effect modification by the Breslow-Day test of homogeneity and to quantify confounders.[15;16] Adjustment for multi-confounders was performed by the logistic model; a back-

ward elimination procedure was used taking in consideration the concept validity and precision.[15] The data were analyzed using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois USA).

Results

Participants

The main features of the Asker and Bærum Atrial Fibrillation study have been reported elsewhere.[7] Briefly, 916 out of all subjects (n=1117) aged 75 in two municipalities in Eastern Norway partici-

pated in a prevalence study of AF. 55 patients had permanent AF, and 27 AF patients and 71 controls participated in the present study (Figure 1]).

Clinical Characteristics

Median AF duration was 5 years (range 0.6-25 years). AF patients had a higher prevalence of compensated chronic heart failure (p < 0.001) and valvular heart disease (p < 0.001) compared to controls without AF (Table 1). Furthermore, AF patients had a higher number of medications compared to controls (p < 0.001).

Figure 1: Flowchart of inclusion of study participants.
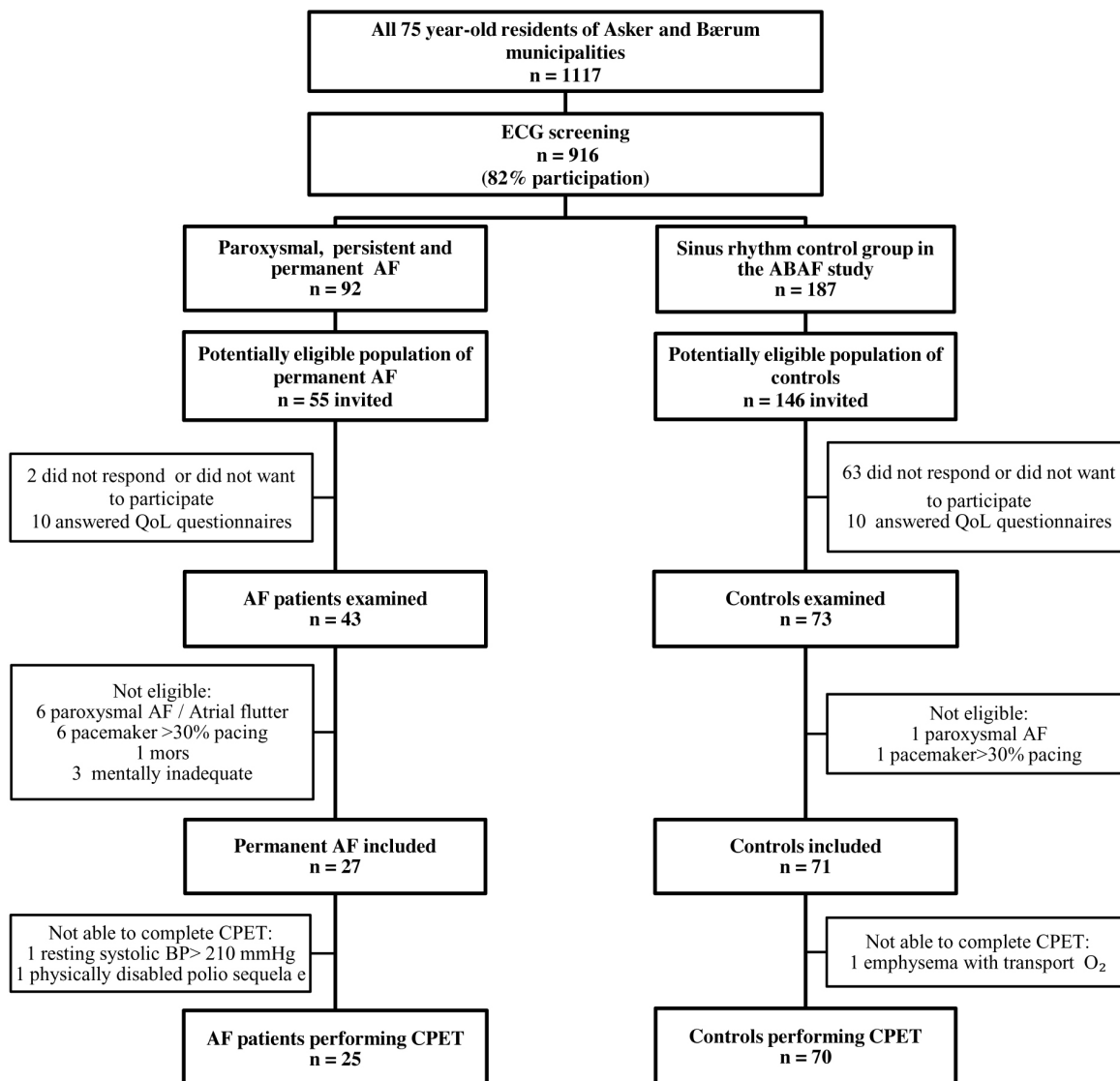
AF = atrial fibrillation, CPET = cardiopulmonary exercise testing, QoL = quality of life.

Definition of Poor Outcome

The lowest quartiles of the study population had VO2 peak less than 22 ml/kg/min, PCS less than 41 for physical QoL, and MCS less than 49 for mental QoL.

Exercise Capacity

No adverse events were seen during or after the exercise testing. AF patients had lower mean VO2 peak than the controls; 22.7±5.5 vs. 28.6 ± 6.3 ml/kg/min; p < 0.001 (Table 2). The VO2 results include maximal as well as submaximal tests, and reflect the average exercise capacity in this out-of-hospital population. A history of stroke was found to be an effect modifier, and for this reason two AF patients and two controls with a history of stroke were left out of the analysis for poor VO2 peak. AF

patients more often had poor VO2 peak; OR 7.5 (2.0, 28.3) after adjustment for the effects of CAD, diabetes and gender (Table 3).

Short Form -36

Median physical QoL score PCS (25th, 75th percentile) was 41 [31, 51] in the AF group vs. 52 [45, 55] in controls (p < 0.001) (Table 2). The AF group had higher odds for poor PCS; OR 4.3 (1.5, 12.4) after adjustment for CAD and diabetes (Table 3). Gender was found to be an effect modifier for the relation between AF and poor PCS. There were too few females to permit separate analysis for both genders. We therefore performed separate analyses for the males. However, the odds for poor PCS in AF males compared to male controls (adjusted OR 2.7 (0.7, 10.4)) was weaker than the odds for poor PCS in AF found for both genders combined.

Table 1	Clinical characteristics, n (%).		
	Atrial fibrillation		**p-values**
	Yes n 27	No n 71	
Female gender	7 (26)	20 (28)	0.824
Body mass index (kg/m²)*	25.3 ± 3.5	25.8 ± 3.1	0.495
Systolic blood pressure (mmHg)*	151 ± 26	158 ± 24	0.206
Resting heart rate (beats/min)**	68 (60, 84)	65 (60, 72)	0.052
Mean 24 hour heart rate**	73 (63, 77)	68 (64, 74)	0.099
Coronary artery disease	10 (37.0)	13 (18.3)	0.051
Chronic heart failure	7 (26)	0 (0)	<0.001
Valvular disease	7 (26)	1 (1)	<0.001
Hypertension grade II	17 (63)	30 (42)	0.067
Stroke	2 (7)	2 (3)	0.649
Pulmonary disease	7 (26)	14 (19.7)	0.503
Diabetes	3 (11)	4 (6)	0.616
Anxiety/depression	5 (19)	4 (6)	0.121
Number of medications**	5 (4, 8)	2 (1, 4)	<0.001
Charlson Comorbidity Index*	1.0 ± 1.1	0.6 ± 0.8	0.079
Education after primary school (years)*	6.2 ± 3.6	6.4 ± 3.5	0.803
Still employed	3 (11)	9 (13)	0.998
Physically very active (bicycling, swimming, running, skiing)	6 (22)	20 (28)	0.551
Receiving help from housekeeper funded from the municipality	1 (4)	2 (3)	1.000

*Mean ± SD. ** Median (25th, 75th percentile).

Table 2		Exercise capacity, mental QoL and physical QoL in patients with and without atrial fibrillation.		
		Atrial fibrillation	Control	p-value
VO_2*		22.7 ± 5.5	28.6 ± 6.3	<0.001
PCS**		41 (31,51)	52 (45, 55)	<0.001
MCS**		56 (42, 61)	57 (51, 60)	0.565

VO_2 peak = peak oxygen uptake, PCS = SF-36 Physical Component Summary score, MCS = SF-36 Mental Component Summary score. Higher score indicates better QoL (quality of life). *Mean ± SD. **Median (25th, 75th percentile).

There was little difference in median mental QoL score between the groups; MCS 56 [42, 61] in the AF group versus 57 [51, 60] in controls (p=0.565) (Table 2). However, the AF group had a trend towards higher odds for poor MCS; adjusted OR 2.8 (1.0, 8.4) adjusting for diabetes, pulmonary disease and gender (Table 3). The distribution of MCS in the AF patients was bimodal; a subgroup with low MCS probably accounting for the increased OR for poor MCS in AF patients. The larger AF subgroup with higher MCS explains the similar median MCS for AF patients vs. controls.

As for the normative Norwegian data for SF-36, the study females scored lower than the males. The controls scored equally or higher for MCS and PCS than their corresponding age group in the Norwegian normative population.[11] The AF patients scored equally or somewhat lower than their corresponding normative age group, except for the MCS score where the AF males scored higher than their corresponding normative data.

Confounding Factors

The confounders CAD and diabetes weakened

Table 3		Effect of atrial fibrillation on poor exercise capacity, poor physical QoL and poor mental QoL, n (%).				
		Atrial fibrillation		ORCrude (95% CI)	ORAdj (95% CI)	Confounders
		Yes	No			
Poor VO_2 peak*	Yes	11 (48)	10 (15)	5.3 (1.8, 15.3)	7.5 (2.0, 28.3)	Gender
	No	12 (52)	58 (85)	p=0.001	p=0.003	Coronary artery disease
						Diabetes
Poor PCS	Yes	12 (48)	11 (16)	5.0 (1.8, 13.7)	4.3 (1.5, 12.4)	Coronary artery disease
	No	13 (52)	59 (84)	p=0.001	p=0.007	Diabetes
Poor MCS	Yes	9 (36)	14 (20)	2.3 (0.8, 6.1)	2.8 (1.0, 8.3)	Gender
	No	16 (64)	56 (80)	p=0.109	p=0.059	Chronic pulmonary disease
						Diabetes

VO2 peak = peak oxygen uptake. MCS = SF-36 Mental Component Summary score. PCS = SF-36 Physical Component Summary score. Higher score indicates better QoL (quality of life). Poor outcome represents the lower quartile vs. the three higher quartiles of the total study population. ORCrude = the OR without adjustment for confounders. ORAdj = the OR adjusted for confounding effect.
*The patients with stroke are excluded from the analyses of poor VO2.

the relation between AF and poor PCS by 13%. The relation between AF and poor VO2 peak was strengthened by 41% after adjusting for gender, CAD and diabetes. Adjusting for gender, diabetes and chronic pulmonary disease strengthened the relation between AF and poor MCS by 26%. A history of compensated chronic heart failure and of valvular heart disease was not considered as potential confounders because of their close association to AF. Still, for validity reasons we forced the two diagnoses into the multivariate regression model, and found that whereas the odds estimates were strengthened, the confidence intervals widened (data not shown).

Discussion

In this population-based study on 75 year-old subjects, patients with permanent AF had lower exercise capacity as well as higher odds for poor physical QoL than subjects in sinus rhythm.Also after adjustment for confounders and consideration of effect modifiers, the AF patients had higher adjusted odds for poor exercise capacity and poor physical QoL compared to controls. Thus, AF itself, and not the associated comorbidity, seems to be responsible for the impaired physical QoL and exercise capacity in these old patients. To the best of our knowledge, the present study is the first controlled community-based study to investigate maximal CPET, QoL and comorbidity in old patients with permanent AF compared to controls in sinus rhythm. Albeit the small size of the study, the results appear consistent, presumably due to the homogenous out-of-hospital patient groups, the thorough examination and the use of a control group from the same source population.

Howes et al.[17]compared QoL and exercise tolerance in elderly men with permanent AF to a control group without AF. At variance from our observation, they found no significant differences in SF-36 scores or exercise tolerance between the AF and the non-AF groups after adjusting for comorbidity.[17] This study, however, differs from ours in several aspects. Females were almost not represented, recruitment was done at an outpatient clinic (hence it was a referred population), and third, the exercise tolerance test did not include VO2 measurement.

Community data are mandatory to assess the need for therapeutic measures. Highly symptomatic elderly patients with permanent AF are occasionally offered palliation through AV-node ablation and pacemaker implantation. Their exercise capacity and QoL then improve dramatically,[18] but this population is highly selected. Several studies compare the strategies of rate versus rhythm control.[19-22]and report little difference in QoL between the two strategies. These studies, however, suffer from several limitations with respect to exercise capacity and QoL. The groups are not compared to a control group without AF. The patients recruited to such studies are the ones who were willing to accept randomization to a rate-control group, and therefore the patients with more troublesome symptoms might not participate. Patients who were unable to achieve sinus rhythm before randomization, were excluded, selecting a more healthy study population. Furthermore, the rate-control group in AF was compared with AF patients kept in sinus rhythm by drugs that often are accompanied by side effects that reduce QoL. Some observational studies on QoL in outpatients with paroxysmal or newly diagnosed AF report impaired QoL in AF compared to controls without AF.[23-25] Paroxysmal or newly diagnosed AF is probably more symptomatic than permanent AF,[26] thus the results are not applicable for patients with permanent AF.

The populations in the municipalities of Asker and Bærum have a high socio-economic level. They rank among the top three municipalities as regards education for Norwegians born in 1930.[27] Nearly one fourth of these 75 year-olds were bicycling, running, swimming or skiing, reflecting a very active old population. Our results, however, must be interpreted as observations from a best-case population, both nationally and internationally.

CPET in older subjects

The AF patients had a significantly lower VO2 peak than the controls in sinus rhythm. The difference in VO2 peak is probably of clinical significance; the magnitude corresponds to the difference in mean VO2 peak between 55-59 year-olds and 75-79 year-olds in a Canadian normative population,[28] and another study comparing AF patients to a normal control group showed similar results.[29]

The recommended reference values for VO2 peak are based on studies including patients up to 74 years,[30] and only one study provides normative data for the older Canadian population based on an incremental maximal exercise test.[28] This illustrates that maximal exercise testing in older patients may be controversial. No adverse events occurred during the present exercise testing, and we have found no evidence documenting that age or AF are contraindications to maximal exercise testing.[31]

SF 36

The distribution of the mental QoL within the AF group was bimodal, identifying two different AF subgroups. This suggests also a psychological approach to the AF patients with most complaints. There were significantly increased odds for poor physical QoL in AF patients compared to the controls without AF. The median physical QoL score was 11.5 points lower in AF patients compared to controls, and this corresponds to the gender-matched difference in mean PCS between Norwegian 30-39 year olds and 70-80 year olds.[11] This illustrates the clinical relevance of the lower physical QoL score in AF patients, even though the comparison within normative age groups is confounded by the different expectations various age groups have to their physical QoL. When stratifying PCS into males versus both genders combined, the odds changed markedly, reflecting that female AF patients report much poorer physical QoL than their controls, compatible with previous reports of impaired QoL in women with AF[32;33].

Comorbidity

The AF patients used more medication than the controls, even when assuming that AF per se justified one anticoagulant and one rate-controlling drug. A history of compensated chronic heart failure and/or valvular heart disease was found almost exclusively in AF patients. The poorer physical QoL and VO2 peak in AF patients could be partly explained by their increased comorbidity. However, taking into consideration the substantial confounding effects, the adjusted odds for poor outcomes for the AF patients compared to non-AF controls were considerably increased. Even when adjusting for the diagnoses closely associated with AF; a history of

chronic heart failure and valvular heart disease, the adjusted odds estimates were strengthened, emphasizing that AF is responsible for impaired physical QoL and reduced exercise capacity.

Study Limitations

The main limitation of the present study is the low number of patients. This is in part compensated for by the fairly high participation rate from the eligible subjects and the homogeneity of the population addressed. We have no indication of non-responder bias, neither in the AF, nor in the control group. However, the conclusions may be valid only for well-situated 75 year-old citizens in a society offering good health care services. AF patients living under poorer conditions presumably fare worse.

Conclusions

In this out-of hospital-population patients with permanent AF had lower exercise capacity and higher odds for poor physical QoL compared to controls without AF, also after adjusting for confounders. The AF per se, and not comorbidity, seems to be responsible for this. The majority of the AF patients had a fair score for mental QoL. The bimodal distribution of mental QoL in AF patients, however, suggests that a minority of the AF population have considerably reduced mental QoL.

References

1 Heeringa J, van der Kuip DA, Hofman A, Kors JA, van HG, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006; 27: 949-953.CrossRef

2 Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.CrossRef Pubmed

3 Go AS. The epidemiology of atrial fibrillation in elderly persons: the tip of the iceberg. Am J Geriatr Cardiol 2005; 14: 56-61. CrossRef Pubmed

4 Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation 2003; 108: 711-716.CrossRef Pubmed

5 Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibril-

lation: population-based estimates. Am J Cardiol 1998; 82: 2N-9N. CrossRef Pubmed

6 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453-1457. Pubmed

7 Tveit A, Abdelnoor M, Enger S, Smith P. Atrial fibrillation and antithrombotic therapy in a 75-year-old population. Cardiology 2008; 109: 258-262.CrossRef Pubmed

8 Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970; 2: 92-98.

9 Loge JH, Kaasa S, Hjermstad MJ, Kvien TK. Translation and performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability, and construct validity. J Clin Epidemiol 1998; 51: 1069-1076.CrossRef Pubmed

10 Ware JE, Kosinski M. SF 36 Physical & Mental Health Summary scales: A manual for Users of Version 1. 2nd Ed., Lincoln, RI: QualityMetric Inc. 2001.

11 Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med 1998; 26: 250-258.

12 Ware JE, Kosinski M, Gandek B. SF-36 Health Survey: Manual & Interpretation Guide. Lincoln, RI, QualityMetric Incorporated. 2000.

13 Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J 2002; 20: 1117-1122.CrossRef Pubmed

14 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383. CrossRef Pubmed

15 Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research : principles and quantitative methods. New York, Van Nostrand Reinhold. 1982.

16 Hennekens CH, Buring JE. Epidemiology in medicine. Boston, Little, Brown. 1987.

17 Howes CJ, Reid MC, Brandt C, Ruo B, Yerkey MW, Prasad B, Lin C, Peduzzi P, Ezekowitz MD. Exercise tolerance and quality of life in elderly patients with chronic atrial fibrillation. J Cardiovasc Pharmacol Ther 2001; 6: 23-29.CrossRef Pubmed

18 Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. Circulation 2000; 101: 1138-1144.

19 Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T, Jr., Lader E, Constantine M, Sheppard R, Holmes D, Mateski D, Floden L, Prasun M, Greene HL, Shemanski L. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J 2005; 149: 112-120. CrossRef Pubmed

20 Hagens VE, Ranchor AV, Van SE, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ, Van G, I. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. J Am Coll Cardiol 2004; 43: 241-247.CrossRef Pubmed

21 Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol 2003; 41: 1690-1696.CrossRef Pubmed

22 Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J 2003; 24: 1430-1436.CrossRef Pubmed

23 Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 2000; 36: 1303-1309.CrossRef Pubmed

24 Van den Berg MP, Hassink RJ, Tuinenburg AE, van Sonderen EF, Lefrandt JD, de Kam PJ, Van G, I, Smit AJ, Sanderman R, Crijns HJ. Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. Eur Heart J 2001; 22: 247-253.CrossRef Pubmed

25 Kang Y, Bahler R. Health-related quality of life in patients newly diagnosed with atrial fibrillation. Eur J Cardiovasc Nurs 2004; 3: 71-76.CrossRef Pubmed

26 Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005; 26: 2422-2434.CrossRef Pubmed

27 Statistics Norway Division of Education Statistics.Table. Persons born in 1930 living in Norwegian municipalities in 2005, ranked after highest educational level. 2008.

28 Paterson DH, Cunningham DA, Koval JJ, St Croix CM. Aerobic fitness in a population of independently living men and women aged 55-86 years. Med Sci Sports Exerc 1999; 31: 1813-1820. Pubmed

29 Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. Chest 1997; 111: 934-940.CrossRef Pubmed

30 ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211-277.CrossRef Pubmed

31 Kallinen M, Era P, Heikkinen E. Cardiac adverse effects and acute exercise in elderly subjects. Aging (Milano) 2000; 12: 287-294.

32 Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, Van G, I. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol 2005; 46: 1298-1306.CrossRef Pubmed

33 Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C, Dorian P. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. Am J Cardiol 2000; 86: 764-768.CrossRef Pubmed