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N.B.: When citing this work, cite the original article.

Original Publication:

Urban Alehagen, Anne Ericsson and Ulf Dahlström, Are There Any Significant Differences Between Females and Males in the Management of Heart Failure? Gender Aspects of an Elderly Population With Symptoms Associated With Heart Failure, 2009, JOURNAL OF CARDIAC FAILURE, (15), 6, 501-507.

<http://dx.doi.org/10.1016/j.cardfail.2009.01.010>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-20001>

Are there any significant differences between females and males in the management of heart failure? Gender aspects of an elderly population with symptoms associated with heart failure.

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Abstract

An increasing interest has been shown in potential gender differences in treating patients with heart failure (HF), a serious condition for the individual.

Aim

To evaluate whether there are any differences in the prevalence of HF, cardiac function, biomarkers and the treatment of HF with respect to gender.

Methods

All persons age 70 to 80 in a rural municipality were invited to participate in the project; 876 persons accepted. Three cardiologists evaluated the patients including a new history, clinical examination, ECG, chest x-ray, blood samples, and Doppler echocardiography to assess both systolic and diastolic function. The patients were followed during a mean period of 8 years.

Results and Conclusion

Females had hypertension more frequently and included fewer smokers than their male counterparts. A female preponderance was seen in those with preserved systolic function, whereas males predominated among those with systolic dysfunction. During the follow-up period, 20% of the males and 14% of the females died of cardiovascular diseases. The results did not show any inferior treatment of females with HF, but it clearly was more difficult to correctly classify female patients presenting with symptoms of HF.

Introduction

Heart failure (HF) is a complex syndrome with high mortality and morbidity, and a poor prognosis [1-3]. However, over the past two decades there has been a substantial reduction in mortality, probably due to more widespread use of renin-angiotensin aldosterone (RAAS) and beta-receptor blocking agents [2, 4, 5]. Studies from Sweden and from Scotland have shown that the prognosis has improved [6-8]. With an ageing population, however, the impact of HF on individual health and health care systems is still profound.

Women with HF are older than men with the same diagnosis [8], but most HF studies have examined patients with a mean age of around 65 years or younger [9-11]. In these age groups HF is more common in men, and only about 20-30% of the patients in these studies were women [12, 13]. The guidelines for diagnosis and treatment of HF are also based on studies in which patients with HF have a mean age of 65 years or lower. Yet we know that the mean age of patients with HF is now 75 years or above and that at least half of the population suffering from HF consists of women [14].

The aim of the present study was to estimate the prevalence of HF in patients age 70 to 80 living in a small rural county community and to study aetiology, concomitant diseases, diagnosis, cardiac function, biomarkers, and treatment from a gender perspective.

Methods

A rural municipality with 10,300 inhabitants situated in south-eastern Sweden was chosen. All individuals age 70 to 80 residing in the municipality at the end of 1998 were invited to participate in the study. Of 1162 subjects, 876 (75%) agreed to participate in the study.

All participants (876 persons) were examined by one of three cardiologists, of which two were males, and one female. A new patient history was recorded, a clinical examination was performed, the New York Heart Association functional class (NYHA class) was assessed, and an ECG and chest x-ray were taken. Blood pressure was measured to the nearest 5mm Hg, with the patient resting in the supine position after fasting overnight. In addition, based on the patient history, the clinical examination and the ECG, the clinician also classified the participant according to clinical suspicion of having HF. At this phase, the clinician was blinded to all other information.

The symptoms regarded as associated with HF were dyspnoea, defined from patient history and/or by clinical examination, tiredness, or impaired subjective functional status. The signs that were regarded as potential signs of HF were peripheral oedema, rales, jugular distension and hepatic enlargement.

Blood samples

Blood samples were obtained from fasting subjects after a resting period of 30 minutes. The samples were collected in pre-chilled plastic tubes containing EDTA (Terumo EDTA K-3), placed on ice and centrifuged at 3000 g for 10 minutes at 4 °C. The samples were then immediately stored at -70 °C until further analysis. NT-proBNP was measured using an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany), first described by Karl[15]. The analytical range was 5-35.000 ng/L (0.6- 4130 pmol/L). Total CV was 4.8% at the level of 217 ng/L (26 pmol/L) (n=70) and 2.1% at the level of 4261 ng/L (503 pmol/L) at our laboratory. All blood samples were stored at -70 °C, and none had been thawed before analysis. All samples were analyzed within two weeks of inclusion in the study.

Doppler echocardiography

Doppler echocardiography was performed in all subjects (Accuson XP-128c) with the patient in the supine left position. Both M-mode and 2D methodology were used. Left ventricular systolic function was determined semi-quantitatively, with the global systolic function classified as follows: normal (ejection fraction (EF) $\geq 50\%$); mild impairment (EF 40-49%); moderately impaired function (EF 30-40%); and severely impaired function (EF $< 30\%$). The method has been validated against the modified Simpson algorithm [16, 17].

Diastolic function was evaluated by measuring the mitral flow ratio of peak early diastolic filling velocity to peak of atrial contraction (E/A ratio) and pulmonary venous flow to distinguish normal flow patterns from a pseudonormal or restrictive flow pattern.

Deceleration time (DT) was also evaluated.

Diastolic heart failure was defined as an E/A ratio < 0.6 and/or DT > 280 ms. Heart failure with preserved systolic function was defined as a combination of symptoms/signs of HF (dyspnoea, fatigue and peripheral oedema) and EF $\geq 50\%$.

Significant valvular disease was considered if a moderate or severe mitral or aortic regurgitation was detected. An aortic stenosis > 3.5 m/s was considered significant.

Concomitant diseases

Diabetes was defined as present in all patients previously diagnosed as having diabetes and on treatment, or who had a fasting glucose ≥ 6 mmol/L. Hypertension (HT) was present if a patient had a mean resting blood pressure of $> 140/90$ mm Hg, or had a previous diagnosis of HT and was on treatment for this. Ischemic heart disease (IHD) was defined as a history of angina pectoris, a verified myocardial infarction or if the subject had been through a CABG or a PCI.

Definition of heart failure

Heart failure was defined as the combination of signs/symptoms in combination with objective signs of impaired cardiac function. The objective evaluation of heart function was based on plasma concentration of NT-proBNP (>400pg/mL), or Doppler echocardiography in accordance with ESC guidelines [18] .

Follow-up of included patients

All patients included by the three cardiologists, were followed by use of the Swedish central population registry. From that registry information about mortality could be obtained. In all those cases reported as dead, death certificates and autopsy reports have been analysed. From the autopsy report, all-cause mortality and cardiovascular mortality were chosen as end points. No patient was lost during follow-up.

Statistics

The results were presented as percentage or mean and SD, or as median when values were not normally distributed. In the case of continuous variables, analysis was done using Student's unpaired t-test, whereas for discrete variables the chi-square test was used. Logistic regression analysis was used to obtain odds ratio and the 95% CI intervals. A multivariate model using backward stepwise logistic regression was used.

All data analysis was performed using a commercially available statistical analysis software package (Statistica v. 8.0, Statsoft Inc, Tulsa, OK, USA). The study protocol was approved by The Ethics Committee of the University Hospital of Linköping.

Results

Study population irrespective of cardiac function

Table 1 shows the baseline characteristics of the study population, which has been divided into females and males. The female population was 7 months older as measured from the mean age of the two groups. The difference was significant.

Table 1. Basic characteristics of patients in the study population

Variables	Females	Males	p value
n	443	433	
Mean age	73.3	72.6	t=3.3; p=.001
History			
HT n (%)	396 (89)	345 (80)	$\chi^2=15.3$; p=.0001
Smokers n (%)	70 (16)	223 (52)	$\chi^2=125$; p<.0001
Diabetes n (%)	69 (16)	72 (17)	ns
IHD n (%)	70 (16)	122 (28)	$\chi^2=19.6$; p<.0001
Clinical variables			
BMI mean (SD)	27.2 (4.8)	26.3 (3.4)	ns
BP syst mmHg mean (SD)	163 (19.2)	156 (17.8)	t=4.01; p<.0001
BP diast mmHg mean (SD)	86 (8.9)	85 (7.7)	ns
NYHA class I n (%)	258 (58)	273 (63)	ns
NYHA class II n (%)	148 (33)	128 (30)	ns
NYHA class III n (%)	37 (8)	32 (7)	ns
ECG AF n (%)	23 (5)	13 (3)	ns
Chest x-ray cong n (%)	16 (4)	8 (2)	ns
Treatment			
ACEI/ARB n (%)	96 (22)	87 (20)	ns
Beta blockers n (%)	121 (27)	122 (28)	ns
Diuretics n (%)	149 (34)	101 (23)	$\chi^2=11.4$; p=.0007
Lab			
Nt-proBNP g/L mean (SD)	284 (640)	336 (393)	ns

Note;ACEI: ACE inhibitors; ARB: Angiotensin receptor blockers; BMI: Body Mass Index; BP: Blood pressure; ECG AF: Atrial fibrillation on Electrocardiogram; HT: Hypertension; IHD: Ischaemic Heart Disease; NYHA: New York Heart Association Functional class; Smokers: present and previous smoker

HT was significantly more common (p=.0001) among females than among males, whereas a history of smoking and IHD were significantly more common among males (p<.0001 and p<.0001, respectively). If the analysis concerned only the population with HF

there was still a male predominance among the smokers (27/98 versus 8/98; $\chi^2= 17.3$; $p<0.0001$). There was also a male predominance of persons with IHD within the HF group (21/33 versus 12/33; $\chi^2= 4.91$; $p=0.027$). However, there was no difference in gender concerning those with HT among those with HF.

Analysis of the symptoms according to gender did not show any differences, except for peripheral oedema, which was more common among the females. Apart from the difference in the use of diuretics, which were more common among females ($p=.0007$), no difference was found between the genders with respect to functional class or choice of pharmacological treatment.

Functional status and gender

The patients included in the study were categorized according to NYHA functional class by means of self-assessment and assessment by the cardiologist. A significant difference was seen in a comparison of the female patient's own classifications of functional status and the classification done by the cardiologist of the same patient (Table 2). No such difference was found between the classification by the male patients and by the cardiologist.

Table 2. Distribution of scores of NYHA functional class as assessed by the patients themselves or by the cardiologist presented divided by gender

Score	Females			Males		
	s-NYHA	NYHA	p-value	s-NYHA	NYHA	p value
1 (%)	44 (29.5)	258 (58.2)	$\chi^2=36.8$; $p<.0001$	95 (61.3)	273 (63.0)	ns
2 (%)	71 (47.7)	148 (33.4)	$\chi^2=9.7$; $p=.002$	41 (26.5)	128 (29.6)	ns
3 (%)	30 (20.1)	37 (8.4)	$\chi^2=15.4$; $p=.0001$	17 (11.0)	32 (7.4)	ns
4 (%)	4 (2.7)	0	-	2 (1.3)	0	-
No answer	281 (63.4)			262 (60.5)		

Note: NYHA: New York Heart Association functional class; s-NYHA: self-assessed NYHA functional class

Ejection fraction >50%

In this analysis of those with a normal systolic function (EF >50%) and with symptoms of HF, there were certain differences between the two genders. More males were in NYHA functional class I, whereas more females were in NYHA functional class II. Moreover, a higher proportion of females was found to have congestion on chest x-ray. However, as the total amount is low, the result is uncertain.

Among the subpopulation with EF>50% and symptoms associated with HF, we also analyzed those with an E/A ratio of <0.6, or a deceleration time of >280ms according to Doppler echocardiography, using this as an indicator of diastolic dysfunction as measured in clinical routine (Table 3). Comparing the two genders in this subpopulation only revealed a difference concerning smoking habits, where more males than females smoked. Nevertheless, more male participants than females were in NYHA functional class I; no other differences between the two genders were found

A logistic regression of the total study population was performed using females as dependent variable. In this analysis the risk for females to be classified by the examining clinician as having symptoms associated with HF was almost 1.5 times the risk of so classifying males. In the female population there was almost 2.3 times increased risk of discovering congestion on the chest x-ray compared with the males in the same population. Analyzing the functional groups, the females had more than 1.6 times increased risk of being allocated to NYHA functional class III compared with their male counterparts. The female participants had to a greater extent a history of HT and a higher systolic blood pressure. Further, the females had a higher body mass index (BMI), whereas a higher proportion of males were smokers. In this subgroup, a greater percentage of the female population was on diuretics compared with the male population. No other differences in drug treatment were found between the genders.

Table 3. Study population with symptoms of heart failure based on EF>50%, or EF>50% and an E/A<0.6 or a deceleration time >280ms

Variables	EF>50% with symptoms			EF>50% or E/A<0.6, or DT>280ms		
	Females n	Males n	p value	Females n	Males n	p value
History	268	200		61	54	
HT n (%)	244 (91)	157 (79)	$\chi^2=14.7$;p= .0001	54 (89)	44 (81)	ns
Smokers n (%)	50 (19)	106 (53)	$\chi^2=61$;p< .0001	16 (26)	30 (56)	$\chi^2=10.3$;p=0.001
Diabetes n (%)	50 (19)	28 (14)	ns	13 (21)	11 (20)	ns
IHD n (%)	49 (18)	46 (23)	ns	8 (13)	12 (22)	ns
Clinical variables						
BMI mean (SD)	27.8 (4.9)	26.5 (3.8)	t=3.16; p= .002	27.3 (5.0)	26.9 (3.0)	n
BP syst mmHg (SD)	157 (19)	165 (20)	t= 4.45; p< .0001	165 (19)	161 (20)	ns
BP diast mmHg (SD)	85 (9)	86 (9)	ns	88 (10)	87 (11)	ns
NYHA class I n (%)	121 (45)	112 (56)	$\chi^2=5.4$; p= .02	20 (33)	28 (52)	$\chi^2=4.3$;p= .04
NYHA class II n (%)	123 (46)	72 (36)	$\chi^2=4.6$; p= .03	30 (49)	18 (33)	ns
NYHA class III n (%)	24 (9)	16 (8)	ns	11 (18)	8 (15)	ns
ECG AF n (%)	12 (4)	6 (3)	ns	12 (20)	6 (11)	ns
Chest x-ray cong n (%)	12 (4)	1 (0.5)	$\chi^2=6.7$; p= .01	5 (8)	0	
Treatment						
ACEI/ARB n (%)	58 (22)	37 (19)	ns	22 (36)	13 (24)	ns
Beta blockers n (%)	82 (31)	52 (26)	ns	19 (31)	15 (28)	ns
Diuretics n (%)	97 (36)	48 (24)	$\chi^2=8.0$; p= .005	27 (44)	15 (28)	ns
Lab						
NT-proBNP ng/L median (SD)	117 (498)	94 (283)	ns	140 (877)	138 (309)	ns

Note: AF: Atrial fibrillation; ACEI: ACE inhibitors; ARB: Angiotensin receptor blockade; BMI: Body mass index; BP: Blood pressure; ECG: Electrocardiogram; HT: Hypertension; IHD: Ischaemic heart disease; NYHA: New York Heart Association functional class; Smokers: Present and previous smokers

Heart failure in the study population

If the HF diagnosis was based on the combination of signs/symptoms + increased plasma concentration of NT-proBNP, 98/876 could be given the HF diagnosis. This gives a prevalence of 11% which is in accordance with the literature for the corresponding age classes [18] . However, if the diagnosis was based on signs/symptoms + EF<40% , 39 persons could be given the HF diagnosis, which gives a prevalence of 4.4%. From these figures the gender-specific prevalence of HF according to the two different definitions was calculated. Based on the definition of signs/symptoms + increased plasma concentration of NT-proBNP a prevalence of HF among males of 12.5% and females of 9.9% was found, which gave no statistical difference between the genders. However, if, instead, the definition of signs/symptoms and EF<40% was used, a prevalence of HF among the males of 6.5% and for females of 2.5% was found, which gave a statistically significant result that the HF diagnosis was more common among the males ($\chi^2=8.2$; $p=0.004$).

Ejection fraction <40%

Analyzing those with at least moderately impaired systolic function (EF<40%), and also with symptoms, three significant differences between the genders were found: a higher percentage of males were smokers; females had a significantly higher plasma concentration of NT-proBNP than had males; and a significantly higher proportion of the females were being treated with ACEI/ARB (Table 4). As the subpopulation was small, these findings must be interpreted with caution.

Table 4. Study population with symptoms of heart failure based on EF<50%, or EF<40%

Variables	EF<50% with symptoms			EF<40% with symptoms		
	Females n	Males	p value	Females	Males	p value
	27	73		11	28	
History						
HT n (%)	24 (89)	62 (85)	ns	9 (69)	23 (82)	ns
Smokers n (%)	2 (7)	45 (62)	$\chi^2=23;p< .0001$	2 (18)	17 (61)	$\chi^2=5.2;p= .02$
Diabetes n (%)	8 (30)	18 (25)	ns	3 (27)	8 (29)	ns
IHD n (%)	10 (37)	31 (42)	ns	5 (45)	14 (50)	ns
Clinical variables						
BMI mean (SD)	27.9 (6.4)	26.4 (3.5)	ns	26.6 (7.1)	27.2 (3.2)	n
BP syst mmHg (SD)	158 (19)	156 (18)	ns	147 (25)	151 (20)	ns
BP diast mmHg (SD)	86 (10)	86 (9)	ns	81 (12)	85 (9)	ns
NYHA class I n (%)	9 (33)	23 (32)		4 (36)	6 (21)	ns
NYHA class II n (%)	9 (33)	35 (48)	ns	2 (18)	14 (50)	ns
NYHA class III n (%)	9 (33)	15 (21)	ns	5 (45)	8 (29)	ns
ECG AF n (%)	5 (19)	4 (5)	ns	0	3 (11)	ns
Chest x-ray cong n (%)	4 (15)	6 (8)	ns	1	3	
Treatment						
ACEI/ARB n (%)	15 (56)	23 (32)	$\chi^2=4.8;p= .03$	8 (73)	10 (36)	$\chi^2=4.4;p= .04$
Beta blockers n (%)	9 (33)	32 (44)	ns	5 (45)	11 (39)	ns
Diuretics n (%)	18 (67)	34 (47)	ns	9 (82)	19 (68)	ns
Lab						
NT-proBNP ng/L median (SD)	386 (1857)	181 (670)	t=2.26; p= .03	600 (2661)	264(879)	t=2.2; p= .04

Note: AF: Atrial fibrillation; ACEI: ACE inhibitors; ARB: Angiotensin receptor blockade; BMI: Body mass index; BP: Blood pressure; ECG: Electrocardiogram; HT: Hypertension; IHD: Ischaemic heart disease; NYHA: New York Heart Association functional class; Smokers: Present and previous smokers

Follow-up

After the inclusion of the participants in the study, the population was followed through the Swedish central population registry during a period of more than 8 years; males during a mean period of 8.2 years (range 24-4482 days) and females during a mean period of 8.5 years (range 123-4491 days). During this period, 247 patients (28%) died of all-cause mortality. Of these 144 (33%) were males, and 103 (23%) were females, a significantly greater percentage of males (χ^2 :10.8; p =.001). Analyzing those that died from cardiovascular (CV) disease, 146 patients (17%) died (males: 86 of 433 (20%); females: 60 of 443 (14%); χ^2 :6.3; p =.01, Figs. I, II), whereas 41(5%) died because of malignancy (males: 19 of 433; females: 22 of 443; ns). Eleven (1%) died of infection (males: 9 of 433; females: 2 of 443; χ^2 :4.68; p =.03). Cardiovascular mortality was defined as deaths caused by heart failure and/or fatal arrhythmias, sudden deaths, IHD or cerebrovascular deaths. The cause of death was assessed by autopsy or on the basis of the information given in the death certificates issued by the physician(s) in charge of the patient. This information was based on knowledge of the patient's mortal disorder and/or on clinical observations made after death. During the follow-up period, no patient was lost.

Discussion

General remarks

In the past few years, potential differences in the management of female and male patients with symptoms of heart failure have been in focus [19-21]. To examine the consequences of such differences, we performed a population evaluation in a rural municipality. A significant problem in population studies is the sampling process. Therefore, everyone age 70 to 80 living in the municipality was invited to participate in the study. More than 75% agreed to

participate. Thus, we regard the study population as representative of the living elderly population in the municipality.

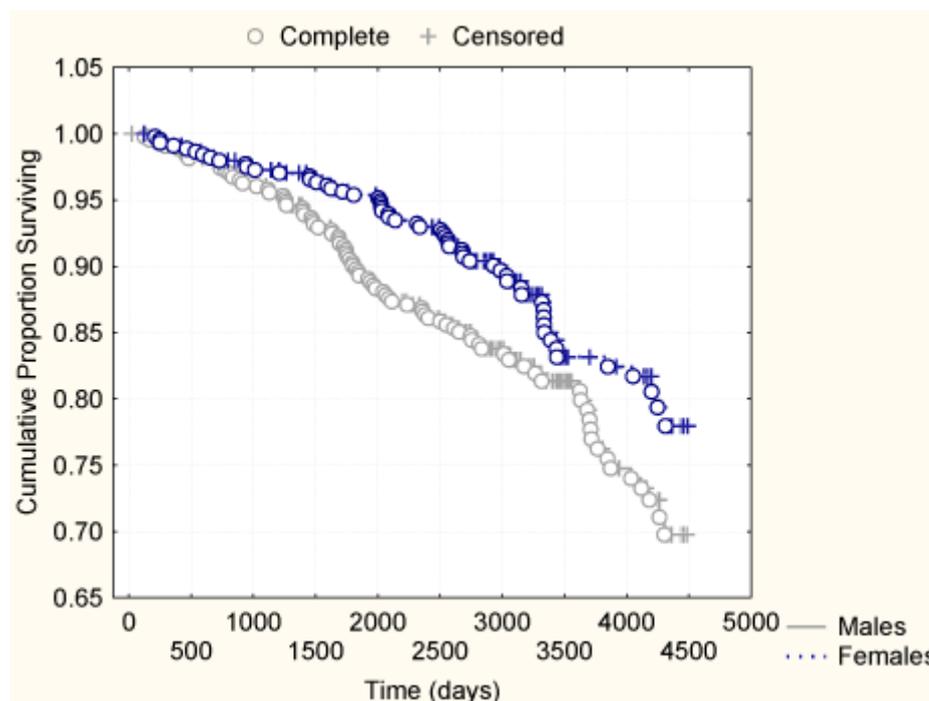


Figure I. Kaplan-Meier analysis of the study population divided into males and females concerning cardiovascular mortality during a follow-up period of up to 12 years

In order to demonstrate potential gender differences, the same study population was analyzed using the different criteria of objective and subjective symptoms/signs of HF.

Clinical differences between genders

The overall finding in the different subgroups were a consistently higher percentage of females with a history of HT and a significantly higher systolic blood pressure ($t=5.2$; $p<.0001$) compared with males. Moreover, when analyzing those with a diagnosis of HT, a significantly higher systolic blood pressure ($t=2.1$; $p=.004$) was found among the female group. Therefore it seems more complicated to successfully treat the female population with HT – at least concerning systolic blood pressure – than their male counterpart. This finding

agrees with the result from the CHARM study, which included 2,400 females and 5,199 males with HF [13].

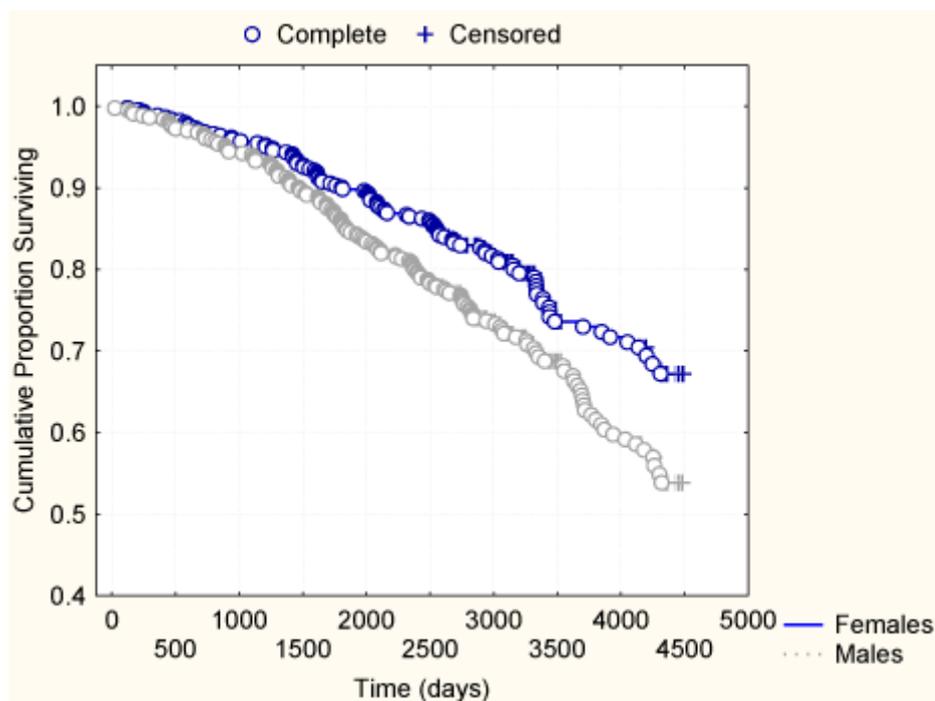


Figure II. Kaplan-Meier analysis of the study population divided into males and females concerning all-cause mortality during a follow-up period of up to 12 years

We also wanted to analyze whether pharmacological treatment varied according to gender in an elderly population. The majority of those in treatment with diuretics were females, as is reported in the literature [13]. The difference in treatment might be explained by the fact that the females in our study had a higher BMI, which in turn could result in peripheral oedema in the absence of HF in some people. In this category the use of diuretics would certainly be justified. However, in the group with impaired cardiac function, significantly more females than males were being treated with ACEI/ARB, which contradicts the belief that female patients with HF do not get optimal treatment compared with their male counterparts.

Cardiac function and gender

In general, the males in the study population had a significantly more impaired systolic cardiac function. This was found in both the EF<50% and EF<40% groups. This is in accordance with the literature, which shows that males more often suffer ischaemic heart disease, at least at a younger age, than their female counterparts [22].

More females than males were found in the group with normal systolic function (with or without diastolic dysfunction). However, analyzing those with an isolated diastolic dysfunction did not reveal any gender differences, which might be explained by the smallness of these subpopulations. Most of the literature reports a female predominance in these disease groups [23].

The interpretation of symptoms

One of the cornerstones of HF diagnostics is the presence of subjective symptoms, and this aspect has also been analyzed. Of the total study population the females presenting with symptoms were in the majority (276/443 versus 230/433; $\chi^2=7.5$; $p=.006$).

However, one of the important steps in making a correct diagnosis is interpreting the symptoms presented by the patient and acting on this information. Therefore, the clinicians that examined the patient also graded the suspicion of HF (none, slight, moderate, or strong suspicion) based on patient history, clinical examination and ECG. The clinician was blinded to all other information at this stage.

The interpretation process was significantly more difficult when performed in the female patient group ($\chi^2=9.3$; $p=.002$). This became apparent when analyzing the male group with strong or moderate clinical suspicion of HF and the female group with the same premises and comparing them with those who had at least moderately impaired systolic function

according to Doppler echocardiography (88/22 males versus 111/10 females). This could not be explained by a difference in age between the groups as none such existed. Ekman et al. reported that female patients gave a vaguer history compared with their male counterparts, which resulted in less accurate treatment of the females [24]. The gender difference in describing symptoms has also been reported in patients with acute coronary syndromes, which illustrates that the problem is more widespread than solely among elderly patients with symptoms of HF [25].

Follow-up

The patients were followed during a mean period of 8 years, during which all mortality was registered. During the follow-up, a greater proportion of males died of CV diseases (2482/100,000/year) than did the females (1693/100,000/year). Compared with the Swedish official mortality statistics of 2005 for cardiovascular deaths, (males: 3068/100,000/year; females 1829/100,000/year), the findings from the present study agree with the official statistics. In this respect, too, we maintain that the study population is representative of an elderly population.

Considerations

As the process of interpreting the symptoms of a patient is central to the interaction between the patient and the examining physician, some important considerations have to be made. The differences in perceived symptoms reported by females could be explained by the possibility that male physicians have difficulties interpreting the symptom panorama presented by female patients, as discussed above. On the other hand, it is also possible that female patients who might exhibit worse health-related quality of life express this in physical symptoms that are more difficult to interpret correctly [26]. The Kaplan-Meier analysis based on the total study

population also found that the female group, despite sometimes displaying more symptoms, has a lower mortality risk of cardiovascular death than their male counterparts. Therefore, the complex symptom interpretation of individual patients should be interpreted on a more individual basis to better classify those with symptoms of HF.

Limitations

One important limitation of this study is the size of the study population, which resulted in small subgroups of individuals with $EF < 40\%$ or less. The results of these evaluations should therefore be interpreted with caution. However, the strength of this study population is that it was recruited directly from the community, without sampling.

Another limitation is the limited age span of the individuals included in the study (70-80 years old), which makes it unwise to directly extrapolate the results to an elderly population outside the specified age span.

Conclusion

An elderly population of almost 900 individuals age 70 to 80 participated in this evaluation. The focus of the present paper was on symptoms associated with HF and a possible gender difference in prevalence and treatment given. We showed that females had more hypertension and smoked less than did their male counterparts. There was also a preponderance of females in the group with preserved systolic function but with symptoms of HF. However, in the different classes of systolic impairment, males dominated. The patients were followed during a mean time of 8 years, during which more cardiovascular mortality was found among the males than among females.

The female patients did not show signs of having received less modern HF treatment than did the male group, but it was clearly more difficult to correctly interpret the symptoms of heart failure in the female group. This requires further investigation.

Acknowledgments

The study was supported by grants from The County Council of Östergötland, The Swedish Heart and Lung Foundation, and The Linköping University Research Foundation CIRC.

We would like to thank Mrs. Kerstin Gustavsson, heart failure nurse, for her invaluable help.

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