

## CARDIOVASCULAR MEDICINE

# Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen

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**Objective:** To assess the prevalence of impaired left ventricular systolic function and manifest heart failure in a general population aged 50–89 years.

**Design:** In this cross sectional survey, participants filled in a heart failure questionnaire. ECG, blood tests, and echocardiography were performed.

**Setting:** The study population was recruited from general practitioners situated in the same urban area and examined in a university hospital in Copenhagen, Denmark.

**Participants:** 764 participants (432 women and 332 men, median (SD) age 66 (11) years) participated. The study population was stratified to include a minimum of 150 persons in each age decade.

**Main outcome measures:** Prevalence of impaired systolic function and manifest heart failure.

**Results:** The prevalence of systolic dysfunction (left ventricular ejection fraction  $\leq$  40%) was more than twice as high among men (7.6%) as among women (2.6%). In the male population systolic heart failure (left ventricular ejection fraction  $\leq$  40% and symptoms) was found in 1.8% of the 50–59 years age group and approximately doubled for each age decade to reach 13.9% in octogenarians. Among women systolic dysfunction increased from 0.8% to 4.3% in the same age groups. Asymptomatic cases accounted for 44.0% of all cases of systolic dysfunction in the male population and only 9.1% in the female population.

**Conclusions:** In this age controlled population study impaired left ventricular systolic function and heart failure increased substantially with age and was more than twice as frequent among men as among women. Asymptomatic left ventricular dysfunction occurred more frequently in men than in women and was less prevalent with increasing age.

Heart failure (HF) is a major and growing public health concern in terms of incidence, prevalence, morbidity, mortality, and economic burden. Despite significant progress in the prevention and treatment of cardiovascular disease during the past two decades, health care statistics indicate that the incidence and prevalence of HF have steadily increased in recent years.<sup>1–3</sup> HF is associated with substantial morbidity, accounting for approximately four hospitalisations per year per 1000 inhabitants in western countries.<sup>4</sup> Moreover, the number of hospitalisations of patients with the principal diagnosis of HF has increased for the past two decades. The number of cases is expected to double as a result of progressive aging of the population during the next 40 years.<sup>2 5 6</sup> Since septuagenarians and octogenarians are the fastest growing segment of the population in western countries, the seriousness of the HF epidemic is being mirrored by some of the highest health care costs for a single disorder.<sup>7</sup> The disease is associated with poor quality of life and a poor prognosis, comparable with many malignant diseases.<sup>8</sup>

While a multitude of large intervention studies have shown that pharmacological treatment of HF convincingly reduces morbidity and mortality,<sup>9–11</sup> HF is adequately diagnosed in only about half of the patients suffering from it. Hence, it is mandatory to identify all HF patients to be able to apply current, proven treatments.

A variety of definitions of HF and methods have been applied in previous epidemiological studies, from clinical criteria based on HF score systems<sup>12 13</sup> to studies based on

drug prescriptions, or hospital or general practitioner records.<sup>14 15</sup> In more recent studies echocardiographic examination has been applied to objectify evidence of cardiac dysfunction.<sup>16–19</sup> The definition of HF in the two latest investigations was based on the European Society of Cardiology criteria from 1995 and updated in 2001<sup>20</sup>: symptoms of HF at rest or during exercise, and objective evidence of cardiac dysfunction at rest. In this context it is noteworthy that objective evidence of cardiac dysfunction can be determined by using different and in some cases even a combination of examinations. There is a general consensus that impaired left ventricular (LV) systolic function is a cornerstone of the disease. LV systolic function is most often measured by echocardiography. Although it is not the most precise method, it is the most accepted one in daily clinical practice and in large studies, simply for its practicality.<sup>21 22</sup> Aortic and mitral valve defects, LV dilatation, LV hypertrophy (LVH), increased right ventricular pressure, and atrial fibrillation are often contributors to cardiac dysfunction.<sup>20</sup>

Several attempts to describe the prevalence and prognosis of HF with preserved systolic function have been carried out,

**Abbreviations:** ACE, angiotensin converting enzyme; CI, confidence interval; ECHOES, echocardiographic heart of England screening; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MONICA, monitoring of trends and determinants in cardiovascular disease; OR, odds ratio; WMI, wall motion index

but considerable variations in the results have been reported, probably because of disagreement on definition and terminology. Hence, the present cross sectional survey in a large age adjusted sample of the general population aged 50 to 89 years was set up to investigate the prevalence of HF, systolic and non-systolic HF, asymptomatic LV systolic dysfunction, and the risk factors for these.

## METHODS

### STUDY DESIGN

The design of the study has been described in detail elsewhere.<sup>23</sup> Every Danish citizen and resident is signed up to one general practitioner. The number of patients assigned to each practice is fairly equally distributed. The study population, aged 50–89 years old, was recruited from randomly selected general practitioners situated in the same local area. To optimise statistical power the sampling was stratified by 10 year age groups, and we attempted to invite at least 150 patients in each age decade. The only inclusion criterion was age between 50 and 89 years. Exclusion criteria were an inability to cooperate in the examinations (for example, because of dementia), permanent residency in a nursing home, or lack of response to two written invitations. An invitation to participate in the study was sent to 1088 people between 50 and 89 years of age (3.5% of the background population in the age group) and 764 people participated, giving an overall response rate of 70.2%. The study was conducted from September 1997 to February 2000. The study was performed according to Helsinki II declarations and approved by the local ethics committee. All participants signed a written informed consent form.

### QUESTIONNAIRE

The questionnaire provided information on, firstly, known heart diseases and other major diseases known to be associated with cardiac complications (such as hypertension, diabetes, pulmonary diseases); secondly, hospital admissions for major cardiovascular diseases; thirdly, symptoms of HF, including the degree of shortness of breath according to a modified World Health Organization classification<sup>24</sup> and ankle swelling, angina, and cough; fourthly, medication; and lastly, alcohol and tobacco consumption. During evaluation six grades of dyspnoea were used (defined in appendix 1).

### BLOOD PRESSURE AND HEART RATE

Blood pressure and heart rate were measured twice after 15 minutes of rest in the sitting position with an automatic oscillometric device with an appropriate cuff applied on the upper arm.

### LABORATORY ANALYSES

Blood and urine samples were collected for routine biochemical and haematological analyses including red and white cell counts, sodium, potassium, creatinine, random blood glucose, and plasma glycosylated haemoglobin A<sub>1c</sub>.

### ELECTROCARDIOGRAM

A 12 lead standard ECG was obtained according to standard procedures and evaluated according to the Minnesota code.<sup>25</sup> The following abnormal findings were recorded during evaluation: presence of pathological Q waves, left bundle branch block, significant ST segment abnormalities (ST elevation or depression > 1 mm) in two or more contiguous leads, T wave abnormalities (T wave inversion ≥ 3 mm in two or more contiguous leads or flattening of T waves in two or more contiguous leads), LVH (SV1 + RV5–6 > 35 mm or RaVL + SV3 > 20 mm), atrial fibrillation or flutter, heart rate < 50 or > 100 beats/min, and the appearance of three or more ventricular extrasystoles in 10 seconds. Normal ECG

was characterised by sinus rhythm with no pathological signs.

### ECHOCARDIOGRAPHY

Each participant underwent a transthoracic echocardiographic examination with state of the art equipment (either HP Sonos 5500 (Hewlett-Packard, Andover, Massachusetts, USA), Acuson 128/10c (Acuson Corp, Mountain View, California, USA), or Vingmed 750 (Vingmed, Horten, Norway)) according to standard protocols. Two dimensional apical four and two chamber and apical long axis views were used for all participants, supplemented by parasternal long and short axis views. Systolic function was evaluated off line in a blinded fashion by two experienced cardiologists (FSH, PH) by means of both the ninth and 16th segment wall motion index (WMI) score. LV ejection fraction (LVEF) was calculated by multiplying the ninth segment WMI score by 30.<sup>26–27</sup> LVEF was expressed as the average values between observers. Normal investigations were set to a value of 2.0. LV systolic dysfunction was graded as mild (LVEF 41–45%), moderate (LVEF 36–40%), or severe (LVEF ≤ 35%). LV end diastolic diameter was measured perpendicularly from the interventricular septum to the lateral wall through the plane of the tip of the mitral valve leaflets.<sup>28</sup> In case of visual signs of LVH, the interventricular septum and posterior wall thickness was measured with a parasternal M mode scan according to standard procedures,<sup>29</sup> with LVH defined as wall thickness exceeding 11 mm. The transvalvar flow was evaluated by standard colour Doppler technique and possible valvar dysfunction was further assessed by grading the valvar incompetence on a four grade scale as negligible, mild, moderate, or severe. All echocardiograms were recorded on videotapes. The inter-observer variation for systolic dysfunction was 2.9% (expressed as a median percentage error) and the inter-observer coefficient of variation was 4.9%. In a random sample of 198 echocardiograms, 22 (11.1%) were characterised as low quality echocardiograms. In these 22 examinations the inter-observer coefficient of variation was 6.8%.

### STATISTICAL ANALYSIS

Normal or log normal distribution of continuous data was verified with the use of histograms and normal plots. Measures of plasma creatinine showed a log normal distribution. Two sample *t* tests were performed for mean or geometric mean values of variables in men and women in case of normal or log normal distribution of data; otherwise non-parametric statistics were used (Mann-Whitney tests). Pearson  $\chi^2$  test was used to compare independent groups with categorical data. Mantel-Haenszel common odds ratio (OR) estimates were used for both sexes on each variable. Logistic regression analysis with backward stepwise elimination was used for the multivariate model to analyse independent variables in relation to systolic dysfunction and HF. Variables were arranged in a sequence based on their theoretical probability of being predictors of systolic dysfunction and HF. The analysis was repeated several times by pulling out variables to decline the equation until the number of variables was appropriate to the number of cases. All variables in the equations were tested for interaction, comparing models with and without interaction parameters. Probability values of *p* < 0.05 were considered significant. All tests were computed with SPSS software (SPSS 9.0 for Windows, SPSS Inc, Chicago, Illinois, USA).

Appendix 2 provides the definitions of HF used.

### RESULTS

Table 1 shows basic demographics of the study population. Interestingly, symptoms (adjusted for age) of HF were

**Table 1** Basic demographic data of the study population

	Women (n = 432)	Men (n = 332)	p Value	Total
Medical history				
Hypertension	22.2%	25.0%	NS	179 (23.4%)
Diabetes mellitus	4.9%	8.1%	NS (0.07)	48 (6.3%)
HF	3.5%	6.6%	0.04	37 (4.8%)
CAD	4.2%	5.1%	NS	35 (4.6%)
COPD	10.9%	9.0%	NS	77 (10.1%)
Hospital admissions				
Pulmonary congestion	3.7%	5.4%	NS	34 (4.5%)
Ankle swelling	3.5%	5.4%	NS	33 (4.3%)
MI	3.5%	5.1%	NS	32 (4.2%)
Symptoms				
Dyspnoea	33.6%	28.3%	NS	239 (31.3%)
Grade 2				99 (13.0%)
Grade 3				56 (7.3%)
Grade 4				48 (6.3%)
Grade 5				16 (2.1%)
Grade 6				20 (2.6%)
Ankle swelling	27.5%	16.3%	0.0001	173 (22.6%)
Chest pain	13.9%	14.2%	NS	107 (14.0%)
Medication				
Diuretics				130 (17.0%)
ACE inhibitor and ATIIb				46 (6.0%)
Digitalis				30 (3.9%)
β Blockers				31 (4.1%)
Other CV drugs				65 (8.5%)
Current daily smoker				284 (37.2%)
Measurements (mean)				
Systolic BP (mm Hg)	144.5	143.4	NS	
Diastolic BP (mm Hg)	85.4	87.5	0.03	
Heart rate (beats/min)	76.2	74.8	NS	
LVEF (%)	58.5*	55.9*	<0.001	
LVEDD (mm)	44.2	48.4	<0.001	
Echocardiography and ECG				
LVH—echocardiographic	3.2%	4.8%	NS	30 (3.9%)
VHD (moderate and severe)	2.3%	1.2%	NS	14 (1.8%)
Abnormal ECG†	28.3%	33.8%	NS	208 (30.7%)

\*Geometric mean value; †Total 678 usable ECGs. ACE, angiotensin converting enzyme; ATIIb, angiotensin II blocker; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NS, not significant; VHD, valvar heart disease.

reported more frequently in women than in men ( $p = 0.014$ ). Dyspnoea was reported in 239 (31%) participants, 33.6% of the women and 28.3% of the men, with about 40% ( $n = 99$ ) of those reporting dyspnoea grade 2 (appendix 1). Ankle swelling was reported in 22.6% ( $n = 173$ ) patients, more commonly in women (27.5%) than in men (16.3%,  $p = 0.0001$ ).

Echocardiograms were evaluated with WMI scores computed for 99.7% of patients. The distribution of LVEF in patients with wall motion abnormalities depicts a pattern similar to the lower half of a normal distribution curve with the 5th centile at 42% and the 2.5th centile at 35%.

Systolic dysfunction increased significantly and almost exponentially with age and was especially more pronounced in the male population ( $p = 0.26$  for men,  $p = 0.39$  for women; table 2). Moderate to severe systolic dysfunction ( $LVEF \leq 40\%$ ) was found in 7.6% of the men and 2.6% of the women ( $p = 0.001$ ) (table 2). No HF symptoms were reported by 44.0% of the men with  $LVEF \leq 40\%$ , and only in 9.1% of the women had asymptomatic LV systolic dysfunction (table 2). The prevalence of asymptomatic participants with  $LVEF \leq 40\%$  decreased with age. Among men, the prevalence of systolic HF was 4.2% versus 2.3% among women.

**Table 2** Prevalence of systolic dysfunction and systolic heart failure by sex and age ( $LVEF \leq 40$ )

	Age (years)	No.	Non-treated	Treated*	Symptomatic* (treated and non-treated)†	Total
Women	50–59	124	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)
	60–69	102	0 (0%)	0 (0%)	1 (1.0%)	1 (1.0%)
	70–79	112	1 (0.9%)	0 (0%)	4 (3.6%)	5 (4.5%)
	80–89	93	0 (0%)	0 (0%)	4 (4.3%)	4 (4.3%)
Total	50–89	431	1 (0.2%)	0 (0%)	10 (2.3%)	11 (2.6%)
Men	50–59	114	3 (2.6%)	0 (0%)	2 (1.8%)	5 (4.4%)
	60–69	102	3 (2.9%)	0 (0%)	2 (2.0%)	6 (5.9%)
	70–79	79	1 (1.3%)	2 (2.5%)	5 (6.3%)	8 (10.1%)
	80–89	36	0 (0%)	1 (2.8%)	5 (13.9%)	6 (16.7%)
Total	50–89	331	7 (2.1%)	4 (1.2%)	14 (4.2%)	25 (7.6%)
Total men and women	50–89	762	8 (1.0%)	4 (0.5%)	24 (3.1%)	36 (4.7%)

\*ACE inhibitors, β blockers, diuretics, or digitalis; †dyspnoea, ankle oedema, or both.

The age and sex specific prevalence proportions obtained in the study sample were applied to the entire background population aged 50–89 years, with its current age and sex structure. The estimated overall prevalence proportions of LV systolic dysfunction and systolic HF were 4.4% (95% confidence interval (CI) 3.0% to 5.9%) and 3.0% (95% CI 1.8% to 4.2%). The prevalence of mild (LVEF  $\leq$  45%) and severe (LVEF  $\leq$  35% systolic dysfunction) was 7.0% (10.8% in men, 3.9% in women) and 3.1% (4.8% in men, 1.9% in women), respectively.

Table 3 shows the frequencies of medical conditions and cardiovascular medications within the cohort, stratified according to LVEF below or above 40%. “Definite” ischaemic heart disease (IHD) (defined in appendix 1) existed in 9.1% of the women with systolic dysfunction and in 1.2% of those with normal ventricular function. “Definite” IHD was very frequent (32%) in the group of men with systolic dysfunction and rather infrequent (1.6%) in the group of men with LVEF  $>$  40%. Other important co-morbidities were “definite” hypertension, occurring in 45.5% versus 32.3% of women (decreased versus normal LVEF, respectively) and in 55% versus 33.6% of all men. Furthermore, definite diabetes

mellitus occurred in 9.1% versus 4.8% of the women (decreased versus normal LVEF, respectively) and in 8.7% versus 8.2% of men.

Univariate analysis showed that patients with systolic dysfunction more often had a history of myocardial infarction than did normal participants (OR 14.7,  $p < 0.00001$ ), a history of pulmonary congestion (OR 10.3,  $p < 0.00001$ ), a history of coronary artery disease (OR 4.8,  $p = 0.002$ ), a history of HF (OR 4.3,  $p = 0.006$ ), and hypertension (OR 2.8,  $p = 0.004$ ). Dyspnoea was reported in 81.8% versus 32.4% of all women (LVEF  $\leq$  40%  $v >$  40%, respectively) and in 56.8% versus 25.8% of all men. Ankle swelling—as a symptom or as a cause for admission—was not more frequent in any of the groups except as a symptom among men with systolic dysfunction. Both men and women with systolic dysfunction had higher plasma creatinine concentrations than those without (table 3).

In patients with LVEF  $\leq$  40%, angiotensin converting enzyme (ACE) inhibitors were given to only 18.2% of participating women and to 32.0% of the men, and 27.3% (women) and 26.5% (men) used loop diuretics. In those with a history of HF, 50.1% of the women were taking ACE

**Table 3** Predictors of impaired left ventricular ejection fraction—univariate analysis

	Women		Men		OR†	95% CI for OR
	LVEF $>$ 40% (n = 420)	LVEF $\leq$ 40% (n = 11)	LVEF $>$ 40% (n = 306)	LVEF $\leq$ 40% (n = 25)		
<b>Medical history, symptoms and cardiovascular medication</b>						
Medical history						
Hypertension	22.1%	18.2%‡	22.2%	56.0%***	2.8	1.39 to 5.47
Diabetes mellitus	4.8%	9.1%‡	7.5%	16.0%‡	2.3	0.83 to 6.19
CAD	4.0%	9.1%‡	3.9%	20.0%**	4.8	1.81 to 12.75
HF	3.1%	18.2%*	5.9%	16.0%*	3.3	1.50 to 9.89
COPD	10.7%	18.2%‡	8.2%	16.0%‡	2.0	0.81 to 5.12
Admissions for						
Pulmonary congestion	2.9%	36.4%***	3.9%	24.0%***	10.3	4.40 to 24.20
Ankle swelling	3.6%	0.0%‡	5.2%	8.0%‡	1.2	0.26 to 5.23
MI	2.9%	27.3%***	2.9%	32.0%***	14.7	6.18 to 34.63
Symptoms						
Dyspnoea	32.4%	81.8%**	25.8%	56.8%**	4.8	2.33 to 9.77
Ankle swelling	27.4%	27.3%‡	15.0%	28.0%‡	1.6	0.77 to 3.52
Chest pains	13.8%	18.2%‡	13.1%	28.0%*	2.3	0.98 to 4.77
CV medication						
Diuretics	20.7%	36.4%‡	8.8%	40.0%***		
ACE inhibitor and ATIIb	4.0%	18.2%*	5.9%	36.0%***		
Digitalis	3.3%	9.1%‡	3.3%	20.0%***		
$\beta$ Receptor blocker	4.5%	0.0%‡	3.3%	8.0%‡		
Other CV drugs	7.9%	18.2%‡	7.2%	32.0%***		
Current daily smoker	32.4%	36.4%‡	45.1%	24.0%*	0.56	0.27 to 1.18
Echocardiography and ECG						
LVIH (echocardiography)	3.3%	0.0%‡	4.6%	4.0%‡	0.6	0.08 to 4.98
VHD (moderate and severe)	1.9%	18.2%**	0.3%	12.0%***	20.0	5.56 to 72.17
Abnormal ECG	26.5%	90.9%***	29.3%	94.7%***	35.8	8.41 to 152.43
Atrial fibrillation	3.2%	9.1%‡	3.6%	0.0%‡	0.98	0.13 to 7.39
Diagnosed disease						
Definite IHD§	1.2%	9.1%*	1.6%	32.0%***	22.1	7.92 to 61.67
Definite hypertension¶	32.3%	45.5%‡	33.6%	55.0%‡	2.2	1.04 to 4.45
Definite DM††	4.8%	9.1%‡	8.2%	8.7%‡	1.3	0.37 to 4.35
Definite COPD‡‡	8.3%	18.2%‡	7.2%	12.0%‡	2.0	0.74 to 5.37
<b>Assessment of objective variables (data are means)</b>						
	LVEF $>$ 40%	LVEF $\leq$ 40%	p Value	LVEF $>$ 40%	LVEF $\leq$ 40%	p Value
Systolic BP (mm Hg)	145	142	NS	144	136	NS
Diastolic BP (mm Hg)	86	82	NS	88	82	NS
Heart rate (beats/min)	76	78	NS	75	69	NS
LVEDD (mm)	44	55	0.001	48	55	$<$ 0.0001
Plasma creatinine ( $\mu$ mol/l) (geometric mean)	78.9	105.4	$<$ 0.001	91.4	100.4	0.03

\* $p < 0.05$ ; \*\* $p < 0.005$ ; \*\*\* $p < 0.0001$ .

†Common odds ratio for men and women; ‡not significant.

Co-morbidities as assessed based on the following definitions: §(1) MI discharge diagnosis, (2) self reported MI and Q waves or left bundle branch block (LBBB) or T wave inversion, (3) CAD discharge diagnosis or self reported chest pains on exertion and significant ST segment depression or elevation; ¶(1) self reported hypertension and BP  $>$  140 mm Hg systolic or 90 mm Hg diastolic, antihypertensive drugs, or both or (2) blood pressure  $>$  140/90 mm Hg and current treatment or (3) blood pressure  $>$  161 mm Hg systolic or 112 mm Hg diastolic; ††self reported diabetes and antidiabetic treatment or random blood glucose  $>$  11.1 mmol/l or haemoglobin A1c  $>$  7.5%; ‡‡self reported COPD and cough or treatment for asthma (ATC code r03-).

CI, confidence interval; DM, diabetes mellitus; HF, heart failure; IHD, ischaemic heart disease; OR, odds ratio.

inhibitors and 50.0% received loop diuretics, while 62.1% of the male participants with diagnosed HF received ACE inhibitors and 100% diuretics.

An abnormal ECG was found in 90.9% of women and 94.7% of men with LVEF  $\leq$  40%. Significantly more participants with LVEF  $\leq$  40% had moderate to severe valvular heart disease and ECG signs of LVH.

Participants with LV systolic dysfunction had a larger LV end diastolic diameter (mean 55 mm *v* 44 mm,  $p = 0.001$  for women, 55 mm *v* 48 mm,  $p < 0.0001$  for men, LVEF  $\leq$  40% *v*  $>$  40%, respectively). No difference was found in blood pressure and heart rate in the two groups (table 3).

In 762 participants (variables were missing for two), independent factors associated with LV systolic dysfunction, which included medical history as presented to the doctor (model 1), were analysed in a logistic regression analysis (table 4). The multivariate analysis showed that a history of myocardial infarction (OR 11.4,  $p < 0.00001$ ), pulmonary congestion (OR 6.9,  $p < 0.0005$ ), male sex (OR 3.9,  $p = 0.001$ ), and dyspnoea (OR 3.1,  $p = 0.007$ ) were independent factors associated with LV systolic dysfunction (table 5).

A subanalysis (model 2) applied to 635 participants (129 with missing variables) included variables of cardiovascular and related diseases (as diagnosed by the doctor (appendix 2)), ECG, and blood tests (table 4). The multivariate analysis showed that abnormal ECG (OR 33.6,  $p < 0.00001$ ), definite IHD (OR 10.7,  $p < 0.0001$ ), plasma creatinine (OR 1.04 per unit,  $p = 0.0001$ ), and a low systolic blood pressure (OR 1.02 per mm Hg,  $p = 0.002$ ) were independent factors associated with LV systolic dysfunction (table 4). No interaction between variables in the two models was found.

Table 5 shows the prevalence of HF with preserved systolic function-symptomatic (dyspnoea) cardiac dysfunction (defined in appendix 1).

## DISCUSSION

The main goal of the present study was to obtain valid estimates of the prevalence of cardiac dysfunction and manifest HF. In our sample of 764 patients aged 50–90 years recruited randomly from an urban population, 8% of the men and 3% of the women had LV systolic dysfunction defined by LVEF  $\leq$  40% as estimated by echocardiography. Interestingly, 44% of the men and 9% of the women with LV dysfunction were asymptomatic.

Two types of selection bias may flaw our population sample. The first possible bias stems from the trend, although not significant, of a higher proportion of men among the elderly than in the background population, which would tend to increase the apparent prevalence of HF. The other potential

bias originates from the possible differences between those volunteering to participate and those who did not respond. If the non-responders were more ill than the participants, this potential bias would tend to underestimate the true prevalence. In supplementary analyses, we found that the study population was comparable with the background population with respect to cardiac morbidity in the year preceding inclusion into the study and with respect to mortality one year after examination. However, the non-responders had a higher mortality rate than both the participants and the background population in the first year after invitation to participate.<sup>23</sup>

Previous studies have tended to find a lower prevalence of LV systolic dysfunction when LVEF  $<$  40% was chosen as the cut off value. In the Rotterdam study,<sup>17</sup> the prevalence of systolic dysfunction was found to be 6% in men and 2% in women when LV fractional shortening of  $<$  25% was used as the cut point (corresponding to LVEF  $<$  42.5%). In the ECHOES (echocardiographic heart of England screening) study<sup>18</sup> the prevalence was 3% in men and 1% in women when a cut off of  $<$  40% was used for LVEF, which was evaluated primarily according to Simpson's rule. Morgan *et al*<sup>19</sup> used similar echocardiographic criteria and found a prevalence of 8% in men and 2% in women. Finally, the Glasgow MONICA (monitoring of trends and determinants in cardiovascular disease) study found a prevalence of 4% in men and 2% in women<sup>16</sup> with LVEF  $\leq$  30% as the cut off. In the first two of the cited studies, the age of the study population was comparable with our sample. The participants in the study by Morgan *et al*<sup>19</sup> were older (70–84 years), and those in the Glasgow MONICA study were younger.<sup>16</sup>

The variation in prevalence of LV systolic dysfunction may be explained by three factors: the echocardiographic method, the choice of cut off values, and the selection of the study population. With regard to the echocardiographic method, we used WMI evaluated by experienced observers, which is a well established method for the determination of LV systolic function<sup>30–31</sup> and which has been used in some of the large HF treatment trials. To obtain a more direct comparison with previous studies, we chose to transform WMI into LVEF, although the precision of this method has been reported with mixed results.<sup>27–32</sup> In the present study interobserver variation as assessed on both high quality and poor quality echocardiograms was acceptable and in line with other HF epidemiological studies.<sup>16–33</sup> The more objective measurements obtained by Simpson's rule or M mode measurements of fractional shortening do have several drawbacks, which make these methods difficult to apply in a population based study. They tend more often to exclude older and obese patients and patients with pulmonary disease, often reaching a discard rate of 10–15%.<sup>16–17</sup> Both methods are flawed by the

**Table 4** Independent factors associated with systolic dysfunction (LVEF  $\leq$  40%) in a logistic regression model

	OR	95% CI for OR	p Value
Model 1 factors: medical history			
Male sex	3.87	1.72 to 8.73	0.001
Admission for pulmonary congestion	6.92	2.34 to 20.42	0.0005
Admission for MI	11.41	4.57 to 28.46	$<$ 0.0001
Breathlessness	3.08	1.35 to 7.01	0.007
Model 2 factors: CV and related diseases, ECG, and blood tests			
Systolic BP (low, decrease per mm Hg)	1.02	1.01 to 1.04	0.02
Definite IHD	10.71	3.08 to 37.23	$<$ 0.0001
Abnormal ECG	33.59	7.49 to 150.65	$<$ 0.0001
Plasma creatinine (increase per $\mu$ mol/l)	1.05	1.02 to 1.07	$<$ 0.0001

Model 1 variables are age, sex, hypertension, DM, COPD, CAD, congestive HF, admission for pulmonary congestion, admission for ankle swelling, ankle swelling, admission for MI, chest pains on exertion, shortness of breath. Model 2 variables are age, sex, systolic BP, diastolic BP, heart rate, definite IHD, definite hypertension, definite DM, definite COPD, abnormal ECG, atrial fibrillation, plasma creatinine.

**Table 5** Heart failure with preserved left ventricular systolic function in the study population

	Women	Men	p Value	Total
VHD	5 (1.2%)	0 (0%)	0.05	5 (0.7%)
LVEDD >50 mm(women) or 56 mm (men)	10 (2.3%)	2 (0.6%)	0.06	12 (1.6%)
LVH (echocardiography)	4 (0.9%)	2 (0.6%)	NS	6 (0.8%)
Total*	16 (3.7%)	4 (1.2%)	0.04	20 (2.6%)
Symptomatic atrial fibrillation	5 (1.2%)	7 (2.2%)	NS	12 (1.6%)†

\*Number of patients with one or more signs of cardiac dysfunction; †total population of 740 patients, 24 excluded.

fact that they may overestimate LV systolic function in patients with regional wall motion abnormality. Both the exclusion of a certain category of patients and the possible overestimation of LV systolic function would tend towards an underestimation of the prevalence of systolic dysfunction.

Based on the results of many of the large HF pharmacological intervention studies in which LVEF  $\leq$  40% was arbitrarily chosen as the cut off point for treatment, it appeared reasonable to use the same upper limit. In addition we chose to present the prevalence of three cut off values characterised as mild (LVEF 41–45%), moderate (LVEF 36–40%), and severe (LVEF  $\leq$  35%), since patients with HF symptoms and mild systolic dysfunction should be treated for HF as recommended, which makes it compelling for the clinician to know how frequent the condition is. We found that every fourth man aged 80–90 years had an ejection fraction equal or below 45%. McDonagh *et al*<sup>16</sup> and Davies *et al*<sup>18</sup> used LVEF  $\leq$  30% and  $<$  40% as their limits, respectively. Nevertheless, Davies and associates reported a lower prevalence than McDonagh and colleagues, despite their older study population. This difference underscores the importance of selection of the study population and the variation of echocardiographic methods used. In the study from Glasgow the prevalence of systolic dysfunction was similar to ours in comparable age groups (45–74 years): 5.4–6.4% in men and 2.4–4.8% in women.

It seems that defining severe systolic dysfunction in the present study was more similar to the approach in the ECHOES study. McDonagh *et al*<sup>16</sup> defined the prevalence of mild (possible) systolic dysfunction as LVEF  $\leq$  35% with an overall prevalence of 7.7%, in which 77% were asymptomatic; Davies *et al*<sup>18</sup> (LVEF 40–50%) found an overall prevalence of 5.3% for LVEF  $<$  50%, and 21.7% of the men older than 85 years had this condition. McDonagh *et al*<sup>16</sup> stated that patients with LVEF 31–35% may be cardiologically healthy. In contrast it has been shown that patients with LVEF 41–45% and even 46–50% have a poorer outcome than patients with higher ejection fractions.<sup>34 35</sup>

Finally, an important aspect in the context of population studies is the response rate and the sex distribution. In our study, we had a response rate of about 70%, which compared favourably with other studies. We found no sex related difference between the cohort investigated and the background population, and consequently no distortion in sex distribution between non-responders and the background population. Previous studies have had response rates varying from 61–78%, and not all studies have reported the age distribution among non-responders. It is noteworthy in this context that both the Glasgow MONICA study and the Rotterdam study had to exclude predominantly older participants because of unreadable echocardiograms, which would tend to underestimate the true prevalence.

Asymptomatic LV systolic dysfunction was found with a prevalence of 3.3% in men and 0.23% in women of the total population sample. This is very much in accordance with previous studies, reporting prevalence between 2.4% and 2.9% for men and between 0.2% and 0.7% for women.<sup>16 18</sup>

These small variations in prevalence can probably be ascribed to differences in the interpretation of reported symptoms. One important possible source of error is that shortness of breath in elderly people may in some cases not be a symptom but rather reflects a natural age related decline in physical capacity. In other cases shortness of breath is a result of obesity.<sup>36</sup>

The major co-morbidity in LV systolic dysfunction was IHD, which, given the high prevalence of IHD and its direct impact on myocardial function, is not surprising. Definite or possible IHD was found in about every third woman and every other man with LVEF  $\leq$  40%. The same high level of co-morbidity holds true for hypertension, occurring in 45% of men and 55% of women with LV dysfunction. Moreover, 18% of the women and 28% of the men with LV dysfunction had a history of both IHD and hypertension. Valvar heart disease was found in 18% of the women and 12% of the men with LVEF  $\leq$  40%, and dilated cardiomyopathy was found in 64% of women and 40% of men with systolic dysfunction (7% of the total population). Taken together, these conditions reflect the known most common causes of HF.<sup>12 37 38</sup> Intriguingly, diabetes was almost twice as frequent in women with systolic dysfunction as in those with normal function, in accordance with a previous report.<sup>12</sup>

A decrease in renal function may either result from or cause failure of cardiac function. Underlying diseases such as hypertension and diabetes cause both of these conditions. Reduced cardiac output decreases perfusion of the kidneys. On the other hand, volume overload as a consequence of renal dysfunction may induce a reduction in cardiac function.<sup>20</sup>

HF with preserved LV systolic function (HF symptoms combined with cardiac dysfunction) presents a special problem and was found in 3.7% of women and 1.2% of men (4.5% and 3.4%, respectively, when atrial fibrillation was included). Our findings on symptomatic valvar heart disease and atrial fibrillation are in accordance with those of Davies *et al*,<sup>18</sup> who reported a prevalence of symptomatic valvar heart disease of 0.4% and atrial fibrillation of 0.6%. Cowie *et al*<sup>38</sup> reported that in patients with preserved systolic function, six of 220 patients with a new diagnosis had LVH. Fox *et al*<sup>37</sup> found that patients with LV dilatation had extensive coronary artery disease with no evidence of prior infarction. Taken together, the reported findings indicate that hypertension and chronic IHD without prior infarction are important contributors to non-systolic HF. Importantly, in the Framingham heart study, Vasan and colleagues<sup>39</sup> showed that patients with clinical HF and preserved LV function had a slightly higher mortality than healthy controls.

In an attempt to deduce diagnostic recommendations from our data, the multivariate analysis clearly indicates that patients who report a history of HF or prior hospital admissions for pulmonary congestion or myocardial infarction, or who have IHD combined with an abnormal ECG, are at high risk of having LV systolic dysfunction. These patients, along with the ones who complain of shortness of breath, should be referred for an echocardiographic examination.

These findings concur with the findings in prior studies.<sup>16 17 19</sup> Since LV systolic dysfunction is associated with poor prognosis and since more than half of the patients are not sufficiently treated, it is essential that patients be referred for further investigations and treatment.

## CONCLUSIONS

The present study suggests that the prevalence of LV systolic dysfunction and clinical HF have been underestimated in previous epidemiological studies, which is actually suspected by many of the authors of other studies. This is primarily due to bias in the stratification of the study population and to differences in cut off values used to define the disease. The disturbingly large number of patients with asymptomatic LV systolic dysfunction, viewed by many as an early stage of HF, and of patients with undetected and untreated HF clearly advocates an increased effort to trace these patients.

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## APPENDIX 1

1. Dyspnoea: grade 0-1 is no dyspnoea or dyspnoea with considerable physical activity; grade 2 is dyspnoea caused by vacuum cleaning or climbing stairs to the second floor; grade 3 is when walking on an even road; grade 4 is with minimum exertion or when dressing; grade 5 is orthopnoea; grade 6 is at rest).

2. IHD: "definite IHD" was a (1) discharge diagnosis of myocardial infarction (MI) or (2) self reported MI and the following ECG changes: Q waves in two or more contiguous leads or T wave inversion  $\geq 3$  mm in two or more contiguous leads or left bundle branch block or (3) angina pectoris (AP) discharge diagnosis/coronary artery disease (CAD) discharge diagnosis/self reported exertional chest pains and ST depressions  $\geq 1$  mm in two or more contiguous leads.

3. Hypertension: "definite hypertension" was (1) self reported hypertension and blood pressure more than 140 mm Hg systolic or 90 mm Hg diastolic or antihypertensive medication or (2) blood pressure exceeding 140/90 mm Hg and current treatment or (3) blood pressure exceeding 161 mmHg systolic or 112 mm Hg diastolic.

4. Diabetes: "definite diabetes" was (1) self reported diabetes and antidiabetic treatment or (2) random blood glucose  $> 11.1$  mmol/l or (3) haemoglobin A1c  $> 7.5\%$ .

5. Chronic obstructive pulmonary disease (COPD): "definite COPD" was self reported COPD and (1) cough or (2) treatment for asthma (ATC code r03-).

## APPENDIX 2

Definitions of heart failure used:

- "Systolic heart failure" was defined according to the European Society of Cardiology criteria: symptoms of heart failure (dyspnoea or ankle swelling) and objective evidence of LV systolic dysfunction (LVEF  $\leq 40\%$ ).
- "Heart failure with preserved systolic function" was defined by (1) dyspnoea and (a) LVH or (b) aortic/mitral dysfunction or (c) dilated left ventricle and LVEF  $> 50\%$  and no definite COPD.
- "Dilated left ventricle" was defined as  $> 97.5$ th percentile of the healthy population (no history of cardiovascular disease, no diabetes mellitus, no COPD, blood pressure  $< 140/90$  mm Hg, and normal ECG) in each sex.
- "History of heart failure" was self reported diagnosed HF or admission for HF or pulmonary congestion or HF discharge diagnosis.

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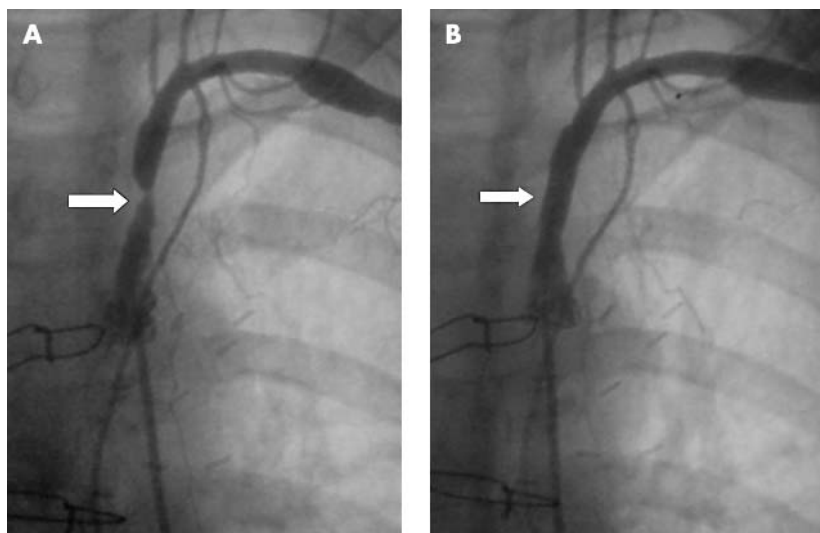
## IMAGES IN CARDIOLOGY .....

### Subclavian artery stenosis as a cause for recurrent angina after LIMA graft stenting

**A** 53 year old woman with multiple risk factors for ischaemic heart disease (hypercholesterolaemia, ex-smoker, family history, severe peripheral vascular disease) presented with an acute coronary syndrome in April 2001. Coronary angiography showed mild left main stem disease and a severe left anterior descending (LAD) stenosis. Urgent off-pump bypass grafting was performed, placing the left internal mammary artery (LIMA) to the LAD. Two months later she was admitted with recurrence of angina and found to have occlusion of the graft at the insertion site. This was successfully stented and the patient's symptoms resolved. At review the following year she reported increasing limitation caused by angina (Canadian Cardiovascular Society grade 3). Myocardial perfusion imaging revealed reversible ischaemia in the anterior wall, raising the possibility of in-stent restenosis.

Femoral and left radial access was attempted unsuccessfully and therefore repeat coronary angiography was performed via the right radial artery. An aortic injection revealed a left subclavian artery stenosis and demonstrated feasibility of access from the left femoral artery.

The left subclavian artery was tackled by direct stenting using a 13.0 mm × 5.0 mm Tetra stent (Guidant) (panels A and B). Angiography showed the LIMA to be patent,



without significant in-stent restenosis. The patient remained free of angina at six months follow up.

In patients with recurrence of angina following LIMA grafting, left subclavian artery stenosis should be considered as a possible cause for myocardial ischaemia, especially in patients with peripheral vascular disease.

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