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Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy

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Aims We conducted a population-based cross-sectional study to assess the prevalence of both preclinical and clinical heart failure (HF) in the elderly.

Methods and results A sample of 2001 subjects, 65- to 84-year-old residents in the Lazio Region (Italy), underwent physical examination, biochemistry/N-terminal pro brain natriuretic peptide (NT-proBNP) assessment, electrocardiography, and echocardiography. Systolic left ventricular dysfunction (LVD) was defined as left ventricular ejection fraction (LVEF) <50%. Diastolic LVD was defined by a Doppler-derived multiparametric algorithm. The overall prevalence of HF was 6.7% [95% confidence interval (CI) 5.6–7.9], mainly due to HF with preserved LVEF (HFpEF) (4.9%; 95% CI 4.0–5.9), and did not differ by gender. A systolic asymptomatic LVD (ALVD) was detected more frequently in men (1.8%; 95% CI 1.0–2.7) than in women (0.5%; 95% CI 0.1–1.0; $P = 0.005$), whereas the prevalence of diastolic ALVD was comparable between genders (men: 35.8%; 95% CI = 32.7–38.9; women: 35.0%; 95% CI = 31.9–38.2). The NT-proBNP levels and severity of LVD increased with age. Overall, 1623 subjects (81.1% of the entire studied population) had preclinical HF (Stage A: 22.2% and stage B: 59.1% respectively). A large number of subjects in stage B of HF showed risk factor levels not at target.

Conclusions In a population-based study, the prevalence of preclinical HF in the elderly is high. The prevalence of clinical HF is mainly due to HFpEF and is similar between genders.

Keywords Heart failure • Asymptomatic left ventricular dysfunction • Elderly • Prevention

Introduction

Heart failure (HF) is an important public health problem in the Western world, as it is associated with high morbidity, high mortality, and considerable healthcare costs.[1] In Italy, ~ 200 000 hospitalizations per year (88% among people aged >65 years) are registered with the main diagnosis of HF, and the trend is increasing.[2] In the general population, HF prevalence increases with age and is high in the elderly.[3–6] A preclinical phase of HF (stage B of HF), characterized by changes in cardiac geometry or asymptomatic left ventricular dysfunction (ALVD), has been identified as associated with a poor prognosis.[5,7,8] The available evidence indicates that early pharmacological strategies may prevent HF in the preclinical stage of HF,[9] and guidelines suggest a preventive approach.[7,8] The prevalence of ALVD varies widely in the general population, ranging from 1% to 34%,[4,5,10–13] depending on the characteristics of the study population, the definition of LVD and symptoms, and the method used to detect LVD.[13] In general,

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the elderly tend to show the highest prevalence of ALVD.[3,12,14] However, since there are scant data on the prevalence of ALVD and HF in elderly people, particularly in Southern Europe and in the Mediterranean area, there is a specific need for investigation of this issue.

We report the results of a large-scale epidemiological study (PREDICTOR; Valutazione della PREvalenza di DIsfunzione Cardiaca asinTOmatica e di scompenso caRdiaco) aimed at estimating the prevalence of HF and asymptomatic LVD in men and women aged 65–84 years randomly selected in the Lazio region in Central Italy.

Methods

Design, study population, and procedures

PREDICTOR is a cross-sectional, population-based study. Participating subjects were invited from the general population and were referred to eight cardiology centres for a clinical examination, blood test, electrocardiography, and echocardiography. Approval was obtained from the Local Ethics Committee. A random sample of 5940 residents, 65–84 years old, from four cities (Rome, Civitavecchia, Frosinone, and Viterbo) in the Lazio region ($\sim$ 5.5 million inhabitants) was identified based on the Regional Health Registry of 1 June 2007. In Rome (the largest Italian city with an elderly population of 550 000 inhabitants), we sampled the population from a list of 74 000 elderly residents living in the 21 neighbourhoods surrounding the participating cardiology centres. In Civitavecchia, Frosinone, and Viterbo, the entire elderly resident population was considered for sampling. The final sample size was determined on the basis of *a priori* criteria in order to estimate a prevalence of 3% [standard error (SE) $\pm$ 1.1] for HF and of 30% (SE $\pm$ 2.8) for ALVD with a significance level of $P < 0.05$ assuming a 30% participation rate.

All together, 5940 people were invited to participate by mail (up to three letters). They were informed of the aims and the methodology of the survey and were asked to send their telephone number for further contact. For those who refused to participate, the reasons for refusal were collected, and included major disability, severe co-morbidity status, and difficulty in reaching the participating centre. Information on previous hospitalizations [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coded diagnoses) for each invited person in the 9-year period before the survey was retrieved through a record-linkage procedure with the Hospital Information Systems (HIS) databases. In addition, for each resident in Rome, a socio-economic indicator was collected, based on the 2001 Census data.[15] Both clinical and socio-economic information were collected in order to better characterize the invited population and possible reasons for non-response. Between June 2007 and January 2010 a total of 2001 subjects (33.7%) provided written informed consent for the clinical examination.

Demographic variables, cardiovascular (CV) risk, clinical history, physical findings, and medications were recorded in a Case Report Form (CRF) by physicians or trained nurses in peripheral centres. Assessment of anthropometric measures, blood pressure, and heart rate was performed according to MONICA recommendations.[16] Overweight was defined as a body mass index (BMI) between 25 and 29.9 kg/m^2. Obesity was defined as BMI $\geq$ 30 kg/m^2. Metabolic syndrome (METs) was diagnosed according to the Adult Panel Treatment III (ATP-III) criteria.[17] Symptoms and signs of HF were evaluated and reported on the CRF by a dedicated expert physician in each peripheral centre at the time of the physical examination. Fasting blood samples were collected from each subject and analysed locally.

Echocardiography

Colour Doppler echocardiography was performed in peripheral centres using commercially available machines according to a predefined protocol.[18,19] Echocardiograms were recorded with standard DICOM format on digital supports and sent to the Core Lab at the European Imaging Laboratory in Rome for centralized reading. Linear measurements of cardiac chambers were obtained from the two-dimensional (2D) parasternal long axis view or, when available, from the M-mode parasternal short axis recording according to the recommendations of the American Society of Echocardiography.[19] Left ventricular volumes were determined from linear measurements of the left ventricle by using the Z-derived assumption that the ratio of LV epicardial long/short axes is constant throughout the cardiac cycle.[20] This formula avoids overestimation of LV volumes occurring with Teichholz's estimate and has been validated in both epidemiological and clinical settings.[21] Left ventricular systolic function was calculated either at the endocardial level (ejection fraction; EF) or at the midwall level (midwall fractional shortening; MFS) by using a modified ellipsoidal model as previously reported.[22] When linear measures of the LV were not available due to inadequate views or were not applicable due to wall motion abnormalities, LV volumes were obtained from the apical four-chamber view and the EF calculated by using the modified Simpson's rule method.[23] Doppler-derived indexes of transmitral flow and pulmonary vein flow, and tissue Doppler imaging of the lateral mitral annulus (E/e′) were used to define diastolic LVD. Peak early diastolic filling wave (E) velocity, peak atrial diastolic filling wave (A) velocity, and deceleration time of the E wave (DTE) were measured at the tips of the mitral leaflets. The DTE was calculated as the time from E to the time when the descent of E intercepted the zero line. The duration of the transmitral A wave velocity was also measured. The peak velocity of pulmonary venous (PV) systolic (S), and diastolic (D) flow, the peak velocity of PV backward flow at atrial contraction (PVa), and the PVa wave duration (PVa dur) were measured with the sample volume placed in the right upper pulmonary vein in the four-chamber axis view. The difference between the transmitral A wave duration (Adur) and PVa dur was derived as an indirect index of increased LV filling pressures, as previously reported.[24] All digital echocardiograms were centrally analysed off-line on a digital workstation (MediMatic 7.1; Genova, Italy) by two independent observers (V.R, G.D., or M.P.), blind to clinical data, and reviewed by the same experienced reader (G.F.M.).[25] Measurements were expressed as an average of three cycles in sinus rhythm and from three to five cycles in atrial fibrillation.

Electrocardiogram protocol

At each participating centre, 12-lead electrocardiograms (ECGs) were obtained from all subjects according to standard practices. The ECG tracings were centrally analysed. Left ventricular hypertrophy was defined as $S_{V3} + R_{AVL} > 2.8$ mV in men or > 2.0 mV in women (and based on the presence or absence of LV strain).[26]

Laboratory tests and N-terminal pro brain natriuretic peptide measurement

Fasting blood samples were collected and standard laboratory tests performed locally. N-terminal pro brain natriuretic peptide (NT-proBNP) was measured, blind, with an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics GmbH) in a central laboratory as previously reported.[27]

Quality control programme

Cardiologists and nurses were trained locally according to standardized methodologies. Before enrolment began, all participating centres were required to perform and send an echo-test to the Core Lab to verify the correctness of the acquisition procedure.

Case definitions of heart failure and left ventricular dysfunction

The diagnosis of HF was made on the basis of the clinical evaluation (clinical history, plus symptoms and signs of HF) done in peripheral centres according to the 2005 European Society of Cardiology (ESC) criteria.[8] Subjects with a clinical diagnosis (signs and symptoms) of HF and in New York Heart Association (NYHA) class >1 were checked centrally in order also to have objective evidence of systolic and/or diastolic LVD (confirmed at the echo central reading). Thus the diagnosis of HF was validated only when the three conditions (clinical diagnosis, NYHA class >1, and LVD confirmed by the central echo lab) occurred concomitantly. A panel of three cardiologists (A.B., G.C., and G.F.M.) was instituted to determine, on the basis of a majority decision, if the case definition had been met.[28] Systolic LVD was defined as EF <50%. Subjects with LVD, but without a history or clinical evidence of HF, were considered to have ALVD (systolic or diastolic). In addition, LV midwall dysfunction was defined as MFS <15%. This cut-off point has been used as a reference value in the setting of HF[29] and has demonstrated prognostic relevance in hypertensive subjects.[30]

Diastolic function was defined as normal if at least three of the following conditions were satisfied: E/A ratio >0.75 and <1.5; DTE >140 ms and <280 ms; PV peak S > PV peak D, PVa dur − Adur difference <0, and E/e′ <8, based on previously reported criteria.[5,18,24] When fewer than three diagnostic criteria were recognized in the case of discordant parameters, or when an equal number of criteria were recognized for more than one category of diastolic function, diastolic LVD was defined as indeterminate.

Stages of heart failure

Preclinical stages of HF were assessed by matching clinical history information obtained by the CRF and the echocardiographic data.[7] Stage A of HF was defined in the presence of risk factors such as arterial hypertension, type 2 diabetes, obesity, or the METs (ATP-III criteria), or of a documented clinical history of atherosclerotic disease or use of cardiotoxins without evidence of structural heart disease and signs or symptoms of HF (*Figure 1*). Stage B was defined in the presence of a structural heart disease detected at the echocardiographic examination,[7] or ALVD, or of a positive clinical history for cardiovascular or valvular disease in the absence of signs or symptoms of HF. Subjects with HF were classified in stage C. Levels of systolic blood pressure (<140 mmHg in stage A, <130 mmHg in stage B) and LDL-cholesterol (<130 mg/dL in stage A, <100 mg/dL in stage B) served as crude indicators of risk factor control. Furthermore, patients with clinical HF (stage C) and LV systolic dysfunction were considered undertreated if they did not assume any drug among angiotensin-converting enzyme (ACE) inhibitors/angiotensin-2 receptor blockers (ARBs), beta-blockers, or aldosterone antagonists (AAs).

Statistical analysis

The socio-demographic and health characteristics of the participants were tabulated by age and gender. We calculated the point estimates of prevalence and 95% confidence intervals (CIs) (by the exact binomial method) stratified by gender and age categories (65–74 and 75–84 years). χ^2 test was performed to evaluate statistical differences of proportions. Logistic regression models (odds ratio; OR) were used to evaluate differences between participants and non-participants, with participation status as the dependent variable in relation to demographic and clinical characteristics, taking into account gender and age (OR, 95% CI).

Results

A total of 2001 subjects participated in the study, while there were 3939 non-participants. *Table 1* shows the main socio-demographic characteristics and co-morbidities of participants and non-participants and the (age and sex adjusted) associations with 'non-participation'. Older age (OR = 3.38 for >80 years vs. 65–69 years), female gender (OR = 1.54), and disadvantaged socio-economic status (OR = 0.60 high vs. low socio-economic status) were the main determinants of non-response. Relevant additional factors limiting participation were: previous diagnosis of cancer (OR = 1.22), diabetes (OR = 1.26), and neurological diseases (OR = 1.88). The OR associated with previous hospitalization for HF (OR = 1.43) indicated that non-participants had a slightly higher probability of having clinical HF than responders. The main lifestyle characteristics and cardiovascular risk profile of the study population by gender and age group are reported in *Table 2*. As shown in *Table 3* there were no differences in blood pressure between age and gender groups. There was a high prevalence of overweight (50.7% in men, 35.4% in women) and overt obesity (13.8% in men, 19.5% in women) in the whole population. The prevalence of atrial fibrillation and ECG-detected LV hypertrophy increased with age both in men and in women (*Table 3*). NT-proBNP [median value = 92 pg/mL; interquartile range (IQR) = 47–186 pg/mL] levels were slightly lower in men (80 pg/mL; IQR = 41–181 pg/mL) than in women (103 pg/mL; IQR = 55–188 pg/mL, $P < 0.001$) and increased with age [73 pg/mL (IQR = 39–140) in 65- to 74-year-old subjects vs. 141 pg/mL (IQR = 68–284) in >75 year olds].

Among 2001 examined patients, 1858 (92.8%) had a central quantitative assessment of EF whereas 148 (7.1%) did not, due to poor imaging quality. The EF was obtained either from the 2D parasternal long axis or the parasternal short axis views (linear 2D or M-mode measurements) or from the four-chamber view (modified Simpson's rule method) depending on the better available echocardiographic window. The 2D parasternal long axis Z-derived EF showed a strong correlation with the four-chamber modified Simpson's rule EF ($r = 0.934$; $P < 0.0001$) and with the M-mode-derived EF ($r = 0.927$; $P < 0.0001$). The correlation between the M-mode-derived EF and the four-chamber modified Simpson's rule EF was $r = 0.879$ ($P < 0.001$).

The distribution of LV dysfunction phenotypes in the population with both systolic and diastolic measurements available (1720 subjects) is shown in *Figure 1*. Any LVD was found in 792 of 1720 subjects (46%) and it was mainly diastolic (42.8%) than systolic (0.6%) or combined (2.6%). It is noteworthy that an isolated systolic LVD was found only in five persons without symptoms of HF (systolic AVLD) and in six persons with clinical HF, whereas the prevalence of isolated diastolic dysfunction was high either in asymptomatic or in symptomatic groups.

Figure 2 shows the prevalence of HF in the study population according to age and gender. The overall prevalence of HF was

Table 1 Main characteristics of the population under study according to the response status and associations [odds ratios (ORs) 95% confidence interval (CI)] with non-participation

	Participants		Non-participants		Adjusted OR[a]	95% CI	
	n	%	*n*	%			
Total	2001	100.0	3,939	100.0	–	–	–
Age class (years)							
65–69	628	31.4	913	23.2	1.00	–	–
70–74	660	33.0	1009	25.6	1.22	1.06	1.42
75–79	476	23.8	1008	25.6	1.70	1.45	1.95
80 +	237	11.8	996	25.3	3.88	2.80	4.08
Gender							
Males	1034	51.7	1,598	40.6	1.00	–	–
Females	967	48.3	2,341	59.4	1.54	1.37	1.73
Area of residence							
Rome	1312	65.6	2505	63.6	1.00	–	–
Province of Rome	220	11.0	439	11.2	1.09	0.90	1.32
Frosinone	168	8.4	397	10.1	1.23	1.00	1.51
Viterbo	300	15.0	586	14.9	1.01	0.85	1.19
Area-based socio-economic status[b]							
Low	80	4.0	238	6.0	1.00	–	–
Medium-low	188	9.4	437	11.1	0.74	0.54	1.01
Medium	305	15.2	633	16.1	0.67	0.50	0.90
Medium-high	326	16.3	651	16.5	0.62	0.46	0.84
High	274	13.7	533	13.5	0.60	0.44	0.81
Co-morbidities[c]							
Tumours	195	9.7	507	12.9	1.22	1.01	1.46
Diabetes	128	6.4	358	9.1	1.26	1.01	1.56
Cardiovascular	662	33.1	1,456	37.0	0.95	0.84	1.07
Heart failure	44	2.2	153	3.9	1.43	1.01	2.04
Cerebrovascular	143	7.1	402	10.2	1.13	0.92	1.40
Neurological	46	3.0	212	5.4	1.88	1.35	2.63
Chronic pulmonary diseases[d]	116	5.8	335	8.5	1.25	0.99	1.57

[a]ORs non-respondents vs. respondents; ORs for age are adjusted only for gender, ORs for gender are adjusted only for age, all other ORs are adjusted for age and gender.
[b]Data are available only for residents in Rome. Missing data include both missing information and people who live outside Rome.
[c]Diagnoses reported in the 10-year previous hospital admissions (main or secondary diagnoses).
[d]Includes chronic obstructive clinical disase, respiratory failure, and other chronic respiratory disorders.

6.7% and did not differ between genders ($P = 0.214$). Among subjects with HF, more than half (63% of men and 62% of women) had normal EF (HFpEF). In contrast, HF with depressed EF was significantly more frequent in men than in women (3.3% vs. 1.4%, $P < 0.001$).

The prevalence of systolic LVD by gender and age groups is shown in *Figure 3*. The prevalence of EF <50% (either symptomatic or asymptomatic) was higher in men (5.1%) than in women (1.4%, $P < 0.001$). The prevalence of systolic ALVD was also significantly higher in men (1.8%) than in women (0.5%, $P < 0.01$). *Figure 4* shows the prevalence of diastolic LVD by gender and age groups. Diastolic LVD was found in 46.1% of participants (95% CI 43.8–48.4) and did not differ between sexes. The prevalence of asymptomatic diastolic LVD (35.4%) was similar in men and women and increased with age. The prevalence of depressed midwall shortening (MFS <15%) (234 subjects, 30.4% of the whole population) paralleled that of diastolic LVD, not being different between men (32.3%) and women (28.4%).

The NT-pro BNP values were elevated in subjects with HF compared with those without HF (251 pg/mL; IQR = 92–760 pg/mL vs. 88 pg/mL; IQR = 46–173 pg/mL; $P < 0.0001$), in those with EF <50% compared with those with EF ≥ 50% (595 pg/mL; IQR = 286–1297 pg/mL vs. 88 pg/mL; IQR = 46–174 pg/mL; $P < 0.001$), and in subjects with depressed MFS (<15%) compared with those with normal MFS (≥ 15%) (median value = 116 pg/mL; IQR = 56–306 pg/mL vs. 86 pg/mL; IQR = 44–165 pg/mL; $P < 0.001$). NT-proBNP levels also increased with severity of symptoms (NYHA class I vs. III) (73 pg/mL; IQR = 43–152 pg/mL vs. 806 pg/mL; IQR = 225–1394 pg/mL; $P < 0.001$) and with increasing severity of diastolic dysfunction (92 pg/mL; IQR = 50–173 pg/mL in mild diastolic dysfunction vs. 214 pg/mL; IQR = 98–664 pg/mL in moderate-to-severe diastolic dysfunction; $P < 0.001$).

Table 2 Risk factors and clinical characteristics of the study population by gender and age group

	Men			Women		
	65–74 years ($n = 669$)	75+ years ($n = 365$)	All ($n = 1034$)	65–74 years ($n = 619$)	75+ years ($n = 348$)	All ($n = 967$)
Cardiovascular risk factors (%)						
Smoking habit						
No	33.8	92.3	85.8	87.1	90.8	88.4
Yes	16.1	10.7	14.2	12.9	9.2	11.6
Alcohol consumption						
No	26.0	29.3	27.2	55.4	57.2	56.0
Yes	74.0	70.4	72.7	44.6	42.8	44.0
Physical activity (%)						
No	51.7	58.5	54.1	60.7	70.7	64.3
Yes	48.3	41.5	45.9	39.3	29.3	35.7
Family history of CVD (%)						
No	81.2	84.2	82.3	74.0	76.2	74.8
Yes	18.8	15.8	17.7	26.0	23.8	25.2
Dyslipidaemia (%)						
No	61.0	68.0	63.4	47.5	48.8	48.0
Yes	39.0	32.0	36.6	52.5	51.2	52.0
Hypertension (%)						
No	45.2	37.6	42.5	43.7	36.3	41.0
Yes	54.8	62.4	57.5	56.3	63.7	59.0
Diabetes (%)						
No	81.0	80.7	80.9	86.0	85.6	85.8
Yes	19.0	19.3	19.1	14.0	14.4	14.2
Previous CVD (%)						
No	74.2	60.5	69.4	75.9	69.3	73.5
Yes	25.8	39.5	30.6	24.1	30.7	26.5
Angina pectoris	6.5	9.3	7.5	4.5	5.5	4.9
Previous myocardial infarction	7.2	11.9	8.9	2.6	4.4	3.2
Revascularization procedures	10.0	16.4	12.3	3.6	4.9	4.0
Atrial fibrillation	4.8	12.9	7.7	6.3	10.1	7.7
Peripheral vascular disease	2.9	7.4	4.5	3.7	5.5	4.4
CVD	4.4	5.8	4.8	3.1	4.0	3.4
Valve disease	2.5	3.0	2.7	2.6	2.9	2.7
Other co-morbidities (%)						
No	55.3	51.0	53.7	46.2	40.5	44.2
Yes	44.7	49.0	46.3	53.8	59.5	55.8
Cancer	7.3	9.3	8.0	9.7	12.1	11.6
COPD	9.0	13.2	10.4	6.9	8.3	7.4
Renal disease	4.9	9.0	5.7	6.6	6.0	6.4

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Figure 5 shows the distribution of the study population into the stages of HF (percentage of subjects with preclinical and clinical HF). Overall, 444 subjects (22.2% of the whole population) were classified in stage A of HF, and 1183 subjects (59.1%) in stage B. At the time of clinical examination, 16% of subjects in stage A and 48% of those in stage B of HF showed risk factor levels not at target. Among patients with a validated diagnosis of HF (stage C), 14.7% (5 out of 34) of patients with systolic LVD function did not take any of the three evidence-based drug classes (ACE inhibitors/ARBs, beta-blockers, or AAs), whereas up to 24.4% (29 out of 119) of patients in stage C with evidence of diastolic dysfunction did not take any evidence-based drug (*Figure 5*).

Table 3 Characteristics of the study population at the clinical examination by gender and age group[a]

	Men			Women		
	65–74 years (*n* = 669)	**75+ years (*n* = 365)**	**All (*n* = 1034)**	**65–74 years (*n* = 619)**	**75+ years (*n* = 348)**	**All (*n* = 967)**
Demographic and clinical findings (mean ± SD)						
Age (years)	69.7 ± 2.5	78.6 ± 2.9	72.8 ± 5.0	69.7 ± 2.7	78.6 ± 2.8	72.9 ± 5.0
Weight (kg)	79.3 ± 12.4	77.0 ± 11.5	78.5 ± 12.1	67.7 ± 12.4	65.4 ± 11.6	66.9 ± 12.2
Height (cm)	171.8 ± 6.4	170.5 ± 6.2	171.4 ± 6.3	159.9 ± 6.1	159.2 ± 6.3	159.6 ± 6.1
Systolic blood pressure (mmHg)	138.1 ± 16.8	141.0 ± 16.8	139.1 ± 16.8	136.9 ± 17.7	140.4 ± 17.5	138.2 ± 17.7
Diastolic blood pressure (mmHg)	81.6 ± 9.3	80.3 ± 9.3	81.1 ± 9.3	80.5 ± 9.8	80.5 ± 9.0	80.5 ± 9.5
Heart rate (b.p.m.)	69.5 ± 11.7	69.6 ± 12.5	69.6 ± 12.0	71.6 ± 10.8	72.4 ± 11.2	71.9 ± 11.0
Electrocardiographic findings (no. of subjects)/%						
Left bundle branch block	(662)/2.1	(359)/5.0	(1021)/3.1	(613)/2.3	(344)/4.7	(957)/3.1
Atrial fibrillation	(648)/1.1	(343)/4.4	(991)/2.2	(601)/1.5	(328)/2.7	(929)/1.9
Left ventricular hypertrophy	(621)/4.5	(308)/7.8	(929)/5.6	(590)/8.3	(316)/9.8	(906)/8.8
Anterior Q waves	(648)/0.9	(343)/2.0	(991)/1.3	(601)/0.3	(328)/0.6	(929)/0.4
Biochemical values (no. of subjects) mean ± SD						
Creatinine (mg/dL)	(664) 1.03 ± 0.23	(360) 1.11 ± 0.31	(1024) 1.06 ± 0.26	(617) 0.82 ± 0.19	(344) 0.91 ± 0.27	(961) 0.85 ± 0.23
Uric acid (mg/dL)	(662) 5.54 ± 1.44	(360) 5.79 ± 2.28	(1022) 5.63 ± 1.78	(615) 4.56 ± 1.29	(343) 4.97 ± 1.43	(958) 4.71 ± 1.36
Potassium (mEq/L)	(664) 4.31 ± 0.45	(362) 4.35 ± 0.45	(1026) 4.33 ± 0.45	(616) 4.28 ± 0.47	(346) 4.40 ± 0.44	(962) 4.32 ± 4.61
Glucose (mg/dL)	(662) 109 ± 31	(361) 107 ± 33	(1023) 108 ± 32	(617) 100 ± 24	(345) 101 ± 27	(962) 101 ± 25
Haematrocrit (%)	(665) 43.5 ± 3.7	(358) 42.3 ± 4.4	(1023) 43.1 ± 4.0	(614) 40.4 ± 2.9	(342) 40.0 ± 3.2	(956) 40 ± 3.1
NT-proBNP (pg/mL) (no. of subjects)/median (25th–75th percentiles)	(668) 63 (32–118)	(364) 148 (68–324)	(1032) 80 (41–181)	(616) 88 (48–162)	(348) 130 (70–253)	(964) 103 (55–188)

NT-probBNP, N-terminal brain natriuretic peptide; SD, standard deviation.
[a]Values are given as mean and standard deviation for continuous variables; *n* and % for categorical variables.

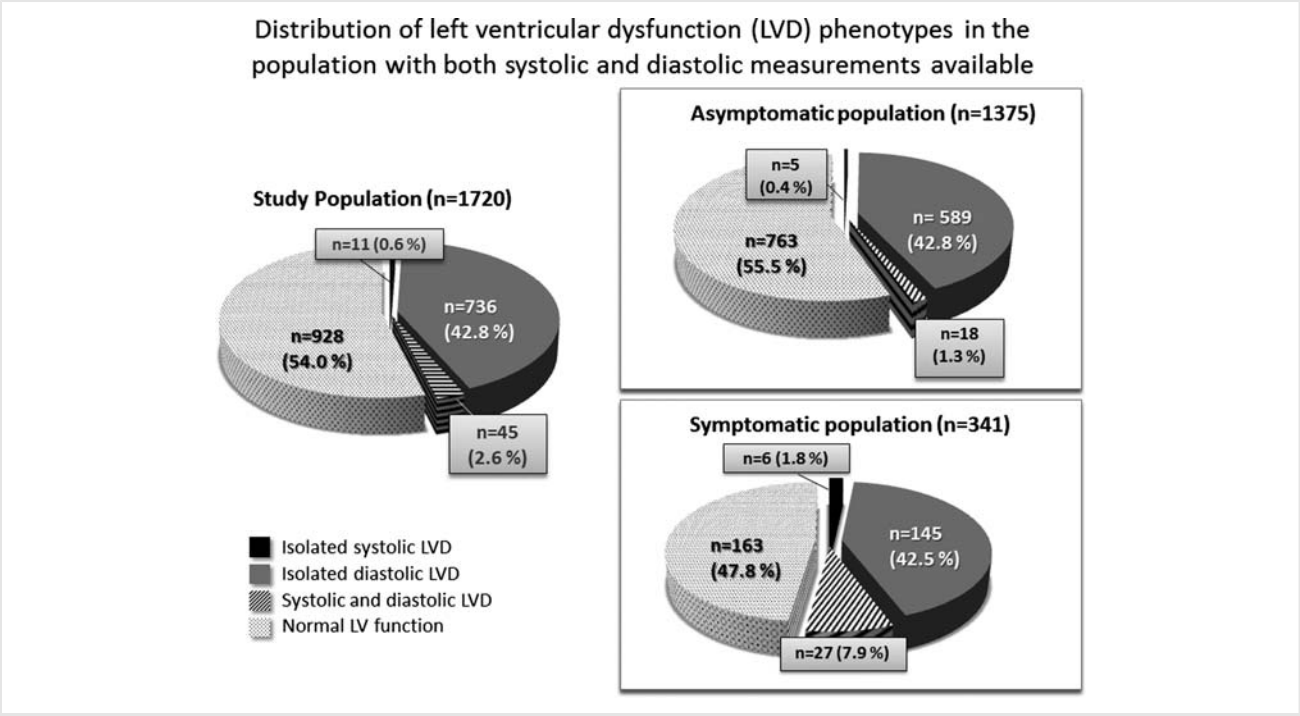

Figure 1 Distribution of left ventricular dysfunction (LVD) phenotypes in the entire population of the PREDICTOR study in whom both systolic and diastolic function could be detected. Pie charts show the percentages of isolated systolic LVD, isolated diastolic LVD, combined systolic + diastolic LVD, and normal LV function, respectively, in (*A*) the whole population, in (*B*) the subgroup with asymptomatic LV dysfunction, and in (*C*) the subgroup with symptomatic LV.

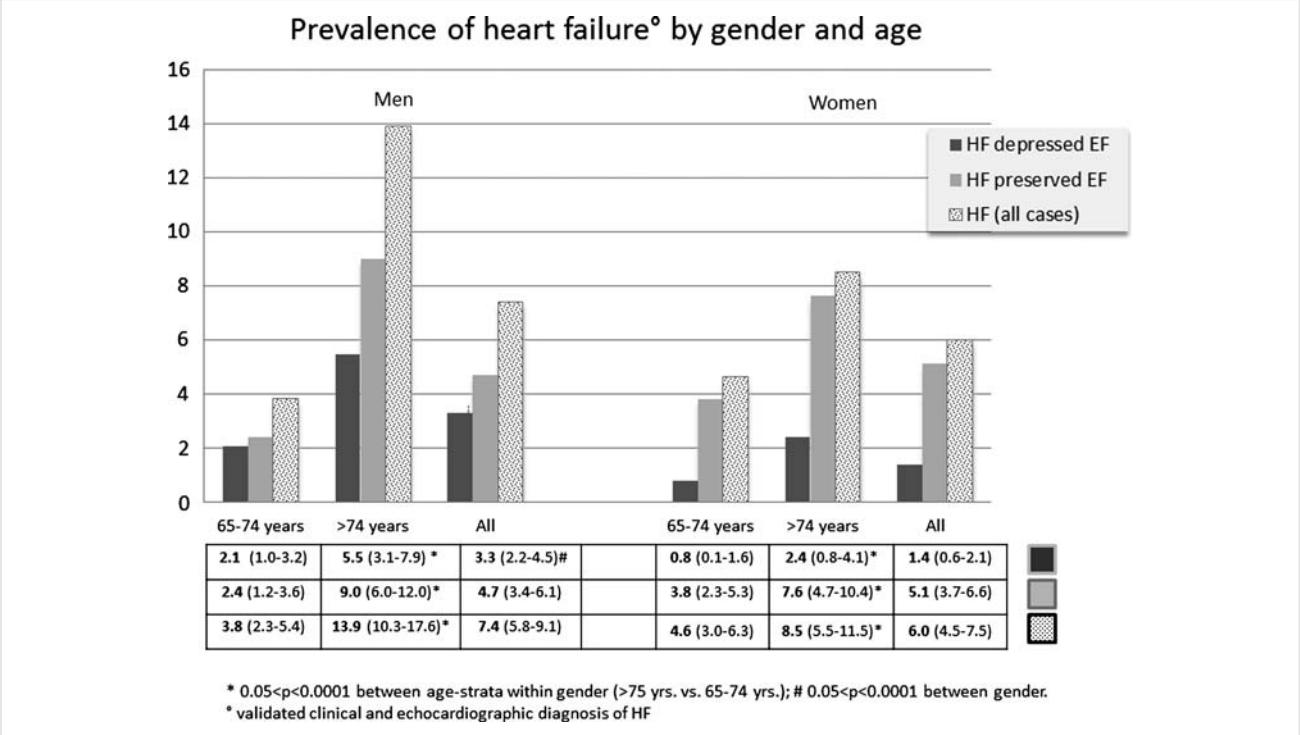

Figure 2 Prevalence of heart failure (HF) by gender and age. Prevalence of HF as a percentage (ordinate, %) is shown for age (65–74 years, >75 years, and all) and gender groups (abscissa). Dark grey bars, HF with depressed ejection fraction (EF); light grey bars, HF with preserved EF; dotted bars, all cases of HF. Mean percentage (in bold) and the 95% confidence interval (in parentheses) are shown for each condition (HF depressed EF, HF preserved EF, and all cases) at the bottom of the figure.

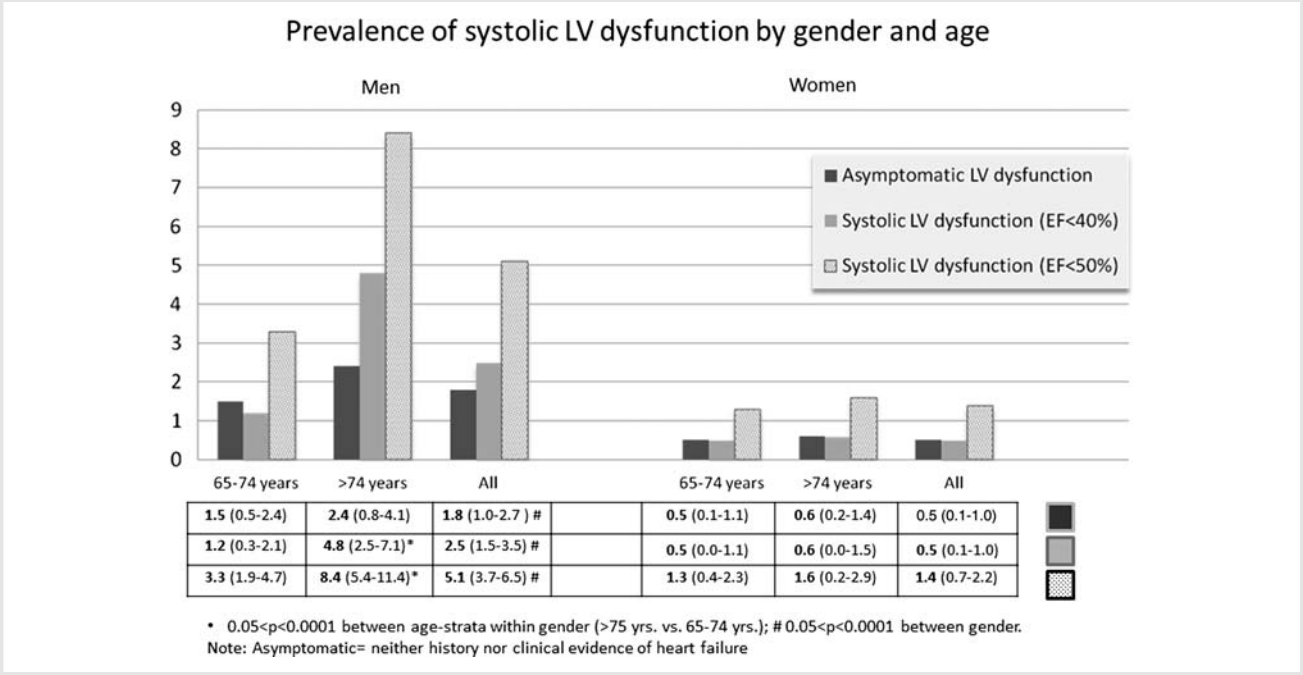

Figure 3 Prevalence of systolic left ventricular (LV) dysfunction by gender and age. Prevalence of systolic LV dysfunction as a percentage (ordinate, %) is shown for age (65–74 years, >75 years, and all) and gender groups (abscissa). Dark grey bars, asymptomatic systolic LV dyfunction; light grey bars, systolic LV dysfuntion (EF <40%); dotted bars, systolic LV dysfunction (EF <50%). Mean percentage (in bold) and the 95% confidence interval (in parentheses) are shown for each condition (asymptomatic systolic LV dysfuntion; systolic LV dysfunction as defined by EF <40%; systolic LVD as defined by EF <50%) at the bottom of the figure. EF, ejection fraction.

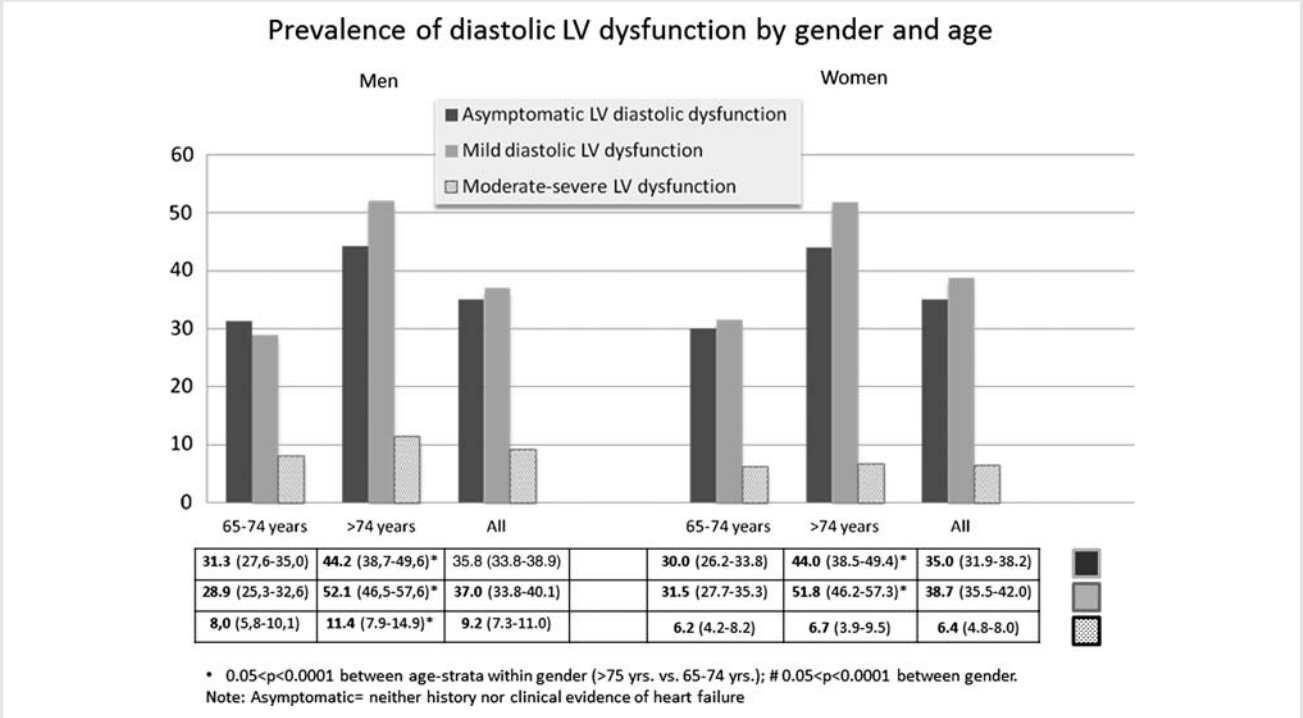

Figure 4 Prevalence of diastolic left ventricular (LV) dysfunction by gender and age. Prevalence of diastolic LV dysfunction in percentage (ordinate, %) is shown for age (65–74 years, >75 years, and all) and gender groups (abscissa). Dark grey bars, asymptomatic diastolic LV dysfuction; light grey bars, mild diastolic LV dysfuction; dotted bars, moderate-to-severe diastolic LV dysfuntion. Mean percentage (in bold) and the 95% confidence interval (in parentheses) are shown for each condition (asymptomatic diastolic LV dysfuntion; mild diastolic LVdysfuntion, and moderate-to-severe diastolic LV dysfunction) at the bottom of the figure.

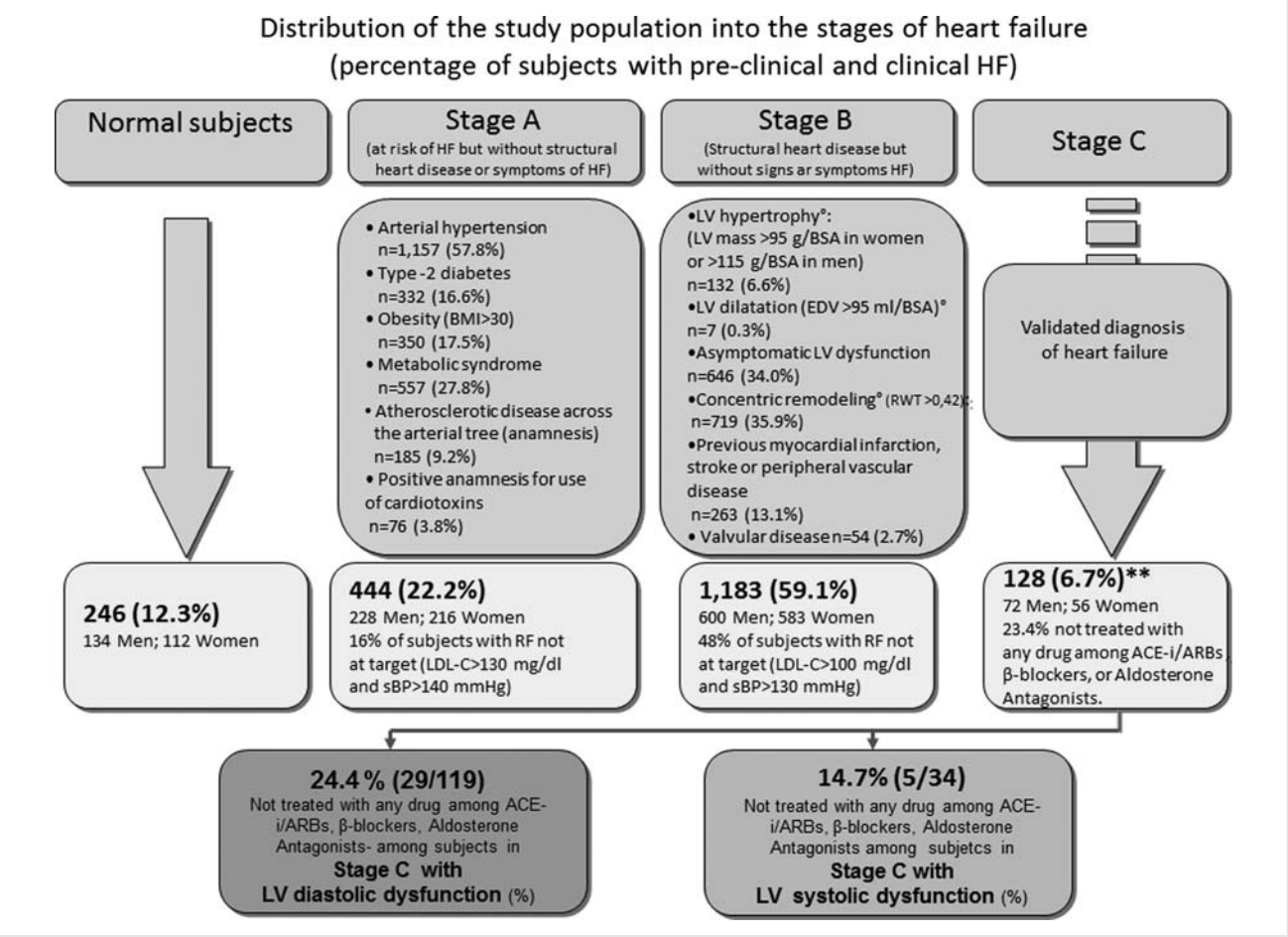

Figure 5 Distribution of the study population into the stages of heart failure (HF; percentage of subjects with preclinical and clinical HF). RWT, relative wall thickness; EDV, end-diastolic volume; BSA, body surface area; ATP-III, Adult Panel Treatment III criteria; at least three of the following: waist circumference >88 cm (women) or >102 cm (men), serum triglycerides ≥150 mg/dL, serum HDL-cholesterol <50 mg/dL (women) or <40 mg/dL (men), blood pressure ≥130/ ≥ 85 mmHg or treated hypertension, fasting glycaemia <100 mg/dL. Modified from [a]Hunt *et al. J Am Coll Cardiol* 2005;**46**:e1–e82; °Lang *et al. Eur J Echocardiogr* 2006;**7**:e79–e108. **Percentages of each HF stage refer to the whole population.

Discussion

The overall burden of HF is continuously increasing[31] due to the increasing availability of more sensitive diagnostic tools (echocardiography and biomarkers) and the continuous ageing of the population.[31] The prevalence of HF rises with age (from 2–3% to 10–20% at the age of 70–80 years), so that about half of the people with HF are >75 years old.[32] The high prevalence of pre-existing structural and functional abnormalities of the heart and that of co-morbidities could explain why the prognosis of HF is worse in older than in young patients.[33] HFpEF is the prevalent HF phenotype in elderly people, due to the predominance of female gender and the high prevalence of the above-mentioned age-related cardiac abnormalities. The pathophysiological mechanism underlying HFpEF is an impairment in diastolic function (namely abnormalities in left ventricle relaxation and/or of stiffness) that yields to an increase in end-diastolic pressure (LVEDP), first on exercise and then, as the disease progresses, even at rest. Patients with HFpEF show an increased morbidity and only slightly lower or even similar mortality to those with depressed EF.[34] HFpEF in the elderly may be underdiagnosed, because initial symptoms of HF such as exercise intolerance or decreased functional capacity may often be attributed simply to ageing. In contrast, it may be misdiagnosed, if an accurate evaluation of diastolic function is not carried out, because the co-existing co-morbidities (primarily lung disease) may act as confounders.[35]

Hence, recognizing the preclinical course of HF, encompassing LV dilatation, remodelling or hypertrophy, initial reduction of the contractile reserve, and signs of a slight increase of LVEDP at rest or on exercise,[35] is of great importance. Since it has been demonstrated that in this phase (stage B of HF) appropriate pharmacological treatment may slow or stop the natural course of the disease,[9,12,36] guidelines[7,8,32] recommend early identification of subjects at risk of HF and/or with ALVD in order to prevent the development of clinical HF. A good adherence to treatment is a

key factor to slow the progression of the cardiac abnormalities and the development of overt HF.[32]

The present study is the first to perform a comprehensive assessment of the prevalence of systolic and diastolic LV dysfunction and of HF in a large population-based sample of senior citizens. The overall prevalence of HF in this study was 6.7%. The prevalence of LVD was high and increased with age. More than half of the HF patients had normal systolic function; this proportion was even higher in women. The prevalence of diastolic dysfunction without clinical manifestations was > 40%, with no difference by gender.

Our data are very consistent with the results reported by Hedberg *et al.*,[3] that showed an overall prevalence of HF of 6.7% in a population-based sample of 75-year-old Swedish subjects, as well as with the Canberra study[14] in which the prevalence of HF was 6.3% in a population of 60–85 year olds. The Rotterdam study also reported a prevalence of HF that increased with age from 4.0% (95% CI 3.3–4.8) in subjects between 65 and 74 years, to 9.7% (95% CI 8.4–11.1) in those older than 75 years.[6] Both the Olmsted County survey and the ECHOES study showed a lower prevalence of HF (2.2% and 2.3%, respectively), mainly because these studies involved younger subjects.[5–11] However, even in the Olmsted County study the prevalence of HF increased from 1.5% in individuals between 65 and 74 years to 8.4% in those older than 75 years.[5] In the present study, we did not find different prevalences of HF between genders, and this is in line with the results of the Olmsted Study, the Rotterdam study, and in the EPICA.[4–6] This result is apparently in contrast to the Canberra study[14] in which the prevalence of HF was 8.2% in men and 4.4% in women. However, despite the large body of epidemiological data on HF all over the world, results are sometimes difficult to compare because of differences in the characteristics of the study populations, in the geographic areas, and in the time of data collection, as well as in the diagnostic criteria adopted.

Previous studies evaluated the prevalence of LVD in the community. In the Olmsted County survey,[5] the prevalence of systolic LVD in a population ≥ 45 years old was 6.0% (10.2% in men and 2.6% in women). The study by Raimond *et al.*,[37] carried out in a middle-aged and elderly urban population in Copenhagen (50–89 years), showed a prevalence of systolic LVD (EF ≤ 40%) of 4.7% (7.6% in men and 2.6% in women). The ECHOES study[11] showed an overall prevalence of LVD (EF ≤ 50%) of 5.3% that decreased to 1.8% (3.0% in men and 0.7% in women) with a cut-off value for EF ≤ 40%. Finally, in the Rotterdam study, the prevalence of systolic LVD (M-mode-derived linear fractional shortening ≤ 25%) was 5.5% in men and 2.2% in women.[6] In all these studies the prevalence of LVD increased with age, and the proportion of asymptomatic LVD was high, ~ 50% of all cases. In the present study, the prevalence of systolic LVD (5.1% in men and 1.4% in women) was similar to that reported in previous studies.[6,11] The assessment of midwall dysfunction allowed identification of systolic LVD in a higher proportion of subjects as compared with EF, without differences between genders (32.3% of men and 28.4% of women). Although MFS has not been extensively investigated in HF, it can identify LVD at an earlier stage compared with EF in patients with HFpEF[29] or in those with hypertensive HF,[38] probably paralleling the time of onset of diastolic dysfunction.[39]

Few studies have reported data on diastolic dysfunction in the elderly.[5,13,40] The study by Abhayaratna *et al.*,[13] designed to determine the prevalence of diastolic LV dysfunction in 1275 residents of Canberra aged 66–86 years, showed an overall prevalence of diastolic LVD of 34.7% (27.4% mild and 7.3% moderate to severe). The prevalence of mild diastolic LVD that we found was higher (35.6%) than in that study, whereas that of moderate-to severe diastolic LVD was similar (6.6%). In most cases, LVD was asymptomatic (78.7% of all cases of diastolic LVD in men and 76.9% in women). Since it has been demonstrated that diastolic LVD carries an independent worse prognostic value,[34] this finding highlights the need to assess diastolic function rigorously in elderly women. The current study confirmed previous observations in the general population that reported high concentrations of NT-proBNP in women and the elderly,[41] as well as its association with markers of impaired cardiac performance in an elderly population.[42]

Finally, in this study, the prevalence of preclinical HF was investigated by classifying subjects into stages A and B of HF, as suggested by guidelines. For the first time, in an epidemiological setting of elderly subjects, we showed a very high prevalence of individuals at risk of HF. Notably, almost 60% of the individuals examined showed some kind of structural heart disease. This could be easily underestimated if a complete, accurate echocardiographic examination had been not carried out. Of great importance was that a considerable number of individuals in stage B did not show an acceptable risk factor control, and, similarly, a considerable number of subjects in stage C (overt HF) were untreated or undertreated. Among patients with clinical HF, those with HFpEF were less treated than those with depressed EF. This may reflect a lack of evidence and of clear guideline recommendation, or even that the diastolic dysfunction was underdiagnosed.

Study limitations

The main limitation of the study is the low participation rate, a known problem in complex surveys such as the present one.[5–11] Furthermore, systematic differences between participants and non-participants may lead to biased estimates in prevalence studies, and methods to overcome this problem have been proposed.[43,44] Factors that influence participation may vary from study to study, but only a few studies provide details about both of these groups and give a measure of the bias in the estimates.[15] Based on clinical diagnoses reported in the hospital discharge registers in this study, we characterized the target population and examined differences between participants and non-participants. Old age, neurological disability and other selected medical conditions, and socio-demographic characteristics influenced participation in our survey. Given that we found a 43% higher probability to be a non-participant among those with a history of hospitalization with a diagnosis of HF in comparison with those people without it (*Table 1*), the potential underestimation of the true prevalence of HF in our study is in the order of 25%.

Conclusions

In a large population-based sample of senior citizens in Central Italy the prevalence of individuals at risk of HF is high. A large proportion of individuals with preclinical HF (stage B) do not have risk factors treated at target. The prevalence of diastolic dysfunction is also high, whereas the prevalence of systolic ALVD is low, particularly in women. In our population, the prevalence of clinical HF (stage C) is 6.7%, with HFpEF being by far the most prevalent phenotype of HF. Treatment of clinical HF is still suboptimal. The present study could be helpful in re-assessing the needs for HF prevention and detection in the elderly.

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Adjudication Committee: Alessandro Boccanelli; Giuseppe Cacciatore; Gian Francesco Mureddu.

Echo Core Lab: Gian Francesco Mureddu, Vittoria Rizzello.

Epidemiological design and analysis: Francesco Forastiere, Nera Agabiti, Giulia Cesaroni, Massimo Stafoggia.

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