Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry

Mitja Lainščak[1,2†], Ivan Milinković[3,4†], Marija Polovina[3,4], Marisa G. Crespo-Leiro[5], Lars H. Lund[6], Stefan D. Anker[7,8,9], Cécile Laroche[10], Roberto Ferrari[11,12], Andrew J.S. Coats[13], Theresa McDonagh[14], Gerasimos Filippatos[15,16], Aldo P. Maggioni[10,17], Massimo F. Piepoli[18], Giuseppe M.C. Rosano[19], Frank Ruschitzka[20], Dragan Simić[3,4], Milika Ašanin[3,4], Jean-Christophe Eicher[21], Mehmet B. Yilmaz[22] and Petar M. Seferović[4,23]*, on behalf of the European Society of Cardiology Heart Failure Long-Term Registry Investigators Group[‡]

[1]Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [3]Department of Cardiology, Clinical Centre of Serbia, Belgrade, Serbia; [4]Faculty of Medicine, Belgrade University, Belgrade, Serbia; [5]Unidad de Insuficiencia Cardiaca y Trasplante Cardiaco, Complexo Hospitalario Universitario A Coruna (CHUAC), INIBIC, UDC, CIBERCV, La Coruna, Spain; [6]Heart and Vascular Division, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden; [7]Division of Cardiology and Metabolism, Department of Cardiology, Berlin-Brandenburg Centre for Regenerative Therapies, Berlin, Germany; [8]German Centre for Cardiovascular Research (Berlin partner site), Charité Universitätsmedizin Berlin, Berlin, Germany; [9]Department of Cardiology and Pneumology, University of Medicine Göttingen, Göttingen, Germany; [10]EURObservational Research Programme, European Society of Cardiology, Sophia-Antipolis, France; [11]Centro Cardiologico Universitario di Ferrara, University of Ferrara, Ferrara, Italy; [12]GVM Care and Research, Maria Cecilia Hospital, Cotignola, RA, Italy; [13]Pharmacology Division, Centre of Clinical and Experimental Medicine, IRCCS San Raffaele Pisana, Rome, Italy; [14]Faculty of Life Sciences and Medicine, King's College Hospital, London, UK; [15]Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, Athens, Greece; [16]School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [17]ANMCO Research Centre, Florence, Italy; [18]Heart Failure Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy; [19]Cardiovascular and Cell Sciences Institute, King's College Hospital, London, UK; [20]Clinic of Cardiology, University Hospital, Zurich, Switzerland; [21]Department of Cardiology, Rhythmology and Heart Failure Unit, University Hospital François Mitterrand, Dijon, France; [22]Department of Cardiology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey; and [23]Serbian Academy of Sciences and Arts, Belgrade, Serbia

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Aims This study aimed to assess age- and sex-related differences in management and 1-year risk for all-cause mortality and hospitalization in chronic heart failure (HF) patients.

Methods and results Of 16 354 patients included in the European Society of Cardiology Heart Failure Long-Term Registry, 9428 chronic HF patients were analysed [median age: 66 years; 28.5% women; mean left ventricular ejection fraction (LVEF) 37%]. Rates of use of guideline-directed medical therapy (GDMT) were high (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists: 85.7%, 88.7% and 58.8%, respectively). Crude GDMT utilization rates were lower in women than in men (all differences: $P \leq 0.001$), and GDMT use became lower with ageing in both sexes, at baseline and at 1-year follow-up. Sex was not an independent predictor of GDMT prescription; however, age >75 years was a significant predictor of GDMT underutilization. Rates of all-cause mortality were lower in women than in men (7.1% vs. 8.7%; $P = 0.015$), as were rates of all-cause hospitalization (21.9% vs. 27.3%; $P < 0.001$) and there were no differences in causes of death. All-cause mortality and all-cause hospitalization increased with greater age in both sexes. Sex was not an independent predictor of 1-year all-cause mortality (restricted to patients with LVEF ≤45%). Mortality risk was significantly lower in patients of younger age, compared to patients aged >75 years.

*Corresponding author. Koste Todorovica 8, 11 000 Belgrade, Serbia. Tel: + 381 11 361 4738, Email: seferovic.petar@gmail.com
[†]These authors contributed equally to the manuscript.
[‡]Listed in *Appendix 1*.

Conclusions There was a decline in GDMT use with advanced age in both sexes. Sex was not an independent predictor of GDMT or adverse outcomes. However, age >75 years independently predicted lower GDMT use and higher all-cause mortality in patients with LVEF ≤45%.

Keywords Age • Sex • Mortality • Hospitalization • Registry

Introduction

Heart failure (HF) is a growing health concern affecting more than 26 million patients worldwide.[1,2] Despite advances in treatment, it accounts for significant proportions of hospitalization, disability and mortality.[3–6] Chronic HF predominantly affects elderly people; its incidence doubles in men and triples in women with each decade after the age of 65 years.[2] Clinical trials and registries of chronic HF have provided conflicting data on age- and sex-related characteristics in terms of their influence on patient management and prognosis.[7–12] Several studies have indicated a better prognosis in female than in male patients,[7–9] whereas other studies have shown no sex-specific differences in outcomes or a worse prognosis in women.[10–12]

With respect to HF treatment, a tendency for the underutilization or suboptimal dosing of guideline-directed medical therapy (GDMT) in women and elderly patients compared to men and younger patients has been shown. Women with HF receive beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) less frequently, and at lower than recommended dosages, than men.[13–15] One study has suggested a sex-specific bias in the choice of HF medication in relation to the health care provider's specialty (cardiologist vs. non-cardiologist).[16] In addition, suboptimal dosing of ACEIs and BBs has been reported in elderly HF patients.[17–19] These factors may contribute to the reported lesser improvements in functional status, quality of life and survival with GDMT in women and elderly patients with chronic HF.[20,21]

The reasons for such age- and sex-related discrepancies in the care of HF patients remain unresolved. They may reflect sex and age variability in HF pathophysiology, clinical phenotype, comorbidities and response to GDMT. Particularly, there is a paucity of data on medium- and long-term management and outcomes in relation to patient age and sex in chronic stable HF patients.

Therefore, the present study aimed to assess age- and sex-related differences in HF management, and 1-year risk for all-cause mortality and hospitalization, in 16 354 HF patients from the European Society of Cardiology Heart Failure Long-Term (ESC HF-LT) Registry.

Methods

Study design and participating centres

The ESC HF-LT Registry is a prospective, multicentre, multinational, observational database of patients with acute and chronic HF.[22] It involves a total of 133 participating centres across 21 European and Mediterranean countries, of which 47% are university centres, 49% are local/regional centres and 4% are based in private hospitals.

Inclusion and exclusion criteria

From the overall registry population ($n = 16\,354$) enrolled between 2011 and 2016, for the purpose of the present analyses, data on ambulatory patients with HF ($n = 9428$ patients) were selected. Ambulatory patients included all outpatients with chronic HF diagnosed according to the clinical judgement of the responsible cardiologist at the participating centre.[22] Further details on the registry protocol have been described elsewhere.[22] The only exclusion criterion was age <18 years.

At inclusion, demographic and clinical data were collected, and details on HF management before and after the ambulatory visit were recorded. Patients were followed up in accordance with the standard of care at each participating centre. A mandatory 1-year visit was set up to obtain data on morbidity, mortality and treatment (before and after the follow-up visit). Follow-up data were available for >95% of patients. The registry was approved by local institutional review boards or ethics committees and informed consent documents were signed by all participants. To ensure data quality and consistency, training meetings were organized for the investigators and data sources were verified by EURObservational Research Programme (EORP) monitors in a random sample of 5% of the enrolled patients.

Statistical analysis

Descriptive analyses were summarized and stratified by sex (male and female), age group (<55 years, 55–64 years, 65–75 years, and >75 years) and according to left ventricular ejection fraction (LVEF) (≤45% and >45%). Continuous variables are presented as the mean ± standard deviation (SD), median or interquartile range. For comparisons of continuous variables, the *t*-test or Mann–Whitney U-test was used. Categorical variables are presented as percentages and statistical analyses were performed using chi-squared or Fisher's exact tests for counts of less than 5. For group comparisons, the non-parametric Kruskal–Wallis test was applied.

At 1-year follow-up, the prescription of GDMT [ACEIs/angiotensin receptor blockers (ARBs), BBs, mineralocorticoid receptor antagonists (MRAs)], as well as all-cause mortality and all-cause hospitalization were assessed. For visual presentation, Kaplan–Meier curves for all-cause mortality and all-cause hospitalization stratified by sex, age and LVEF category (≤45% and >45%) were constructed. Log-rank tests were used to compare survival distributions. In patients with LVEF ≤45%, multivariable logistic regression models stratified by age and sex were used to assess the associations between predictor variables and GDMT prescription. For all-cause mortality at 1-year follow-up, a stratified Cox model was used. In both cases, a stepwise procedure was performed, using a *P*-value of <0.05 to allow entry to the model and a *P*-value <0.05 to remain in the updated model. No interaction was tested. A two-sided *P*-value <0.05 was used as a cut-off value to indicate differences of statistical significance. All analyses were performed in SAS Version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 16 354 patients enrolled in the ESC HF-LT Registry between 2011 and 2016, 9428 outpatients (median age: 66 years; 28.5% women) with chronic HF were included in the present analysis.

Baseline demographic and clinical characteristics

The baseline characteristics of all patients and comparisons between sexes are presented in *Table 1*. In comparison to male patients, women with chronic HF were older (median age of women and men: 69 years and 65 years, respectively), and had a lower body mass index (BMI), and higher mean systolic blood pressure (SBP) and heart rate (HR). Women also had higher mean LVEF compared to men (41.8 ± 15.0% and 35.3 ± 12.6%, respectively) and a higher prevalence of preserved LVEF >45%. Despite a higher mean LVEF, women more frequently presented with New York Heart Association (NYHA) class III or IV symptoms. Ischaemic heart disease (IHD), diabetes, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), sleep apnoea, renal dysfunction (all $P < 0.001$), a history of stroke ($P = 0.005$) and hepatic dysfunction ($P = 0.001$) were more frequent in men, in whom the prevalence of prior HF hospitalization was also higher than in women. Women suffered more often from aortic stenosis and depression. Both sexes had similar clinical signs of HF at presentation (*Table 1*).

Baseline characteristics stratified by age group in both sexes are presented in online supplementary *Tables S1* and *S2*. Female patients showed an age-related increase in the prevalences of lower BMI, higher SBP, lower HR and higher mean LVEF. Older female patients more often presented with NYHA class III or IV symptoms, and a higher burden of comorbidities [e.g. valvular disease, IHD, atrial fibrillation (AF), diabetes, hypertension, PAD, stroke and renal dysfunction]. Similar age-related characteristics were observed in men, but, in addition, pulmonary congestion and COPD became more prevalent in men with increasing age.

Baseline heart failure treatment

At baseline, high percentages of the total study population received ACEIs/ARBs or BBs (85.7% and 88.7%, respectively). Overall, MRAs were prescribed to 58.8% of patients. Fewer women than men were treated with ACEIs/ARBs, BBs and MRAs (*Table 1*). Rates of prescription of these medications also decreased with patient age in both sexes (online supplementary *Tables S1* and *S2*). In contrast, the proportions of patients prescribed diuretics, oral anticoagulants, nitrates and calcium channel blockers at baseline increased across the age categories (online supplementary *Tables S1* and *S2*).

Treatment for heart failure at 1-year follow-up

At 1-year follow-up, there was a high persistence of GDMT utilization in the overall study population and the proportions of patients receiving ACEIs/ARBs, BBs and MRAs remained comparable with those at baseline (86.5%, 88.8% and 58.7%, respectively). However, there was an evident gap in rates of prescription of ACEIs/ARBs, BBs and MRAs in female compared to male patients (*Table 2*). Similarly, age-related under-prescription of the key HF medications persisted at 1-year follow-up in both sexes (online supplementary *Tables S3* and *S4*).

Predictors of treatment at 1-year follow-up

The analysis of GDMT predictors was restricted to patients with LVEF ≤45%, in whom this treatment has a proven outcome benefit. In the multivariable analysis, sex was not confirmed as an independent predictor of the use of ACEIs/ARBs, BBs or MRAs. Advanced age (>75 years) was a significant predictor of a lower use of GDMT compared to younger age categories.

The odds of receiving ACEIs/ARBs increased with higher BMI and the absence of lower SBP (<110 mmHg). The odds of ACEI/ARB treatment were lower in patients with higher NYHA class (III or IV), prior HF hospitalization, and renal or hepatic dysfunction (*Table 3*).

Prior HF diagnosis (vs. *de novo* HF) was associated with higher odds for BB prescription (*Table 3*). Conversely, the likelihood of BB prescription was lower in patients with higher NYHA class (III or IV), COPD, depression and the presence of a pacemaker.

Mineralocorticoid receptor antagonists were more likely to be used in patients with lower SBP, higher NYHA class (III or IV), prior HF hospitalization, third heart sound and AF. Renal dysfunction was associated with a lower use of MRAs (*Table 3*).

All-cause mortality and all-cause hospitalization at 1 year

At follow-up, 8.2% of patients had died. Cardiovascular death was the most common cause of mortality (52.0%) in both sexes, whereas non-cardiovascular and unclassified deaths were recorded in 23.0% and 25.0% of patients, respectively. Hospitalization for any cause occurred in 25.7% of patients and hospitalization for HF in 12.0% (*Table 4*).

Compared to men, women had lower rates of all-cause mortality and all-cause hospitalization, as well as a lower rate of HF hospitalization. Although mortality was lower in women, there were no sex-related differences in causes of death (*Table 4*).

Rates of all-cause mortality, all-cause hospitalization and HF hospitalization demonstrated significant increases with greater age in both sexes (online supplementary *Table S5*).

Figures 1 and *2* present Kaplan–Meier survival curves for all-cause death and all-cause hospitalization stratified by sex and LVEF (≤45% and >45%). Online supplementary *Figures S1* and *S2* present similar data for the cohort stratified by age category and LVEF (≤45% and >45%).

Predictors of 1-year all-cause mortality

The analysis of the predictors of 1-year all-cause mortality was restricted to patients with LVEF ≤45%. In multivariable analysis, sex was not an independent predictor of mortality. The hazard

Table 1 Baseline demographic, clinical and treatment characteristics of female and male heart failure patients

Characteristic	All patients ($n = 9428$)	Female patients ($n = 2684$)	Male patients ($n = 6744$)	*P*-value
Age, years, median (IQR)	66.0 (57.0–75.0)	69.0 (59.0–78.0)	65.0 (56.0–74.0)	<0.001
BMI, kg/m^2, mean ± SD	28.1 ± 5.1	27.9 ± 5.7	28.2 ± 4.9	<0.001
SBP, mmHg, mean ± SD	124.4 ± 21.0	126.2 ± 22.2	123.7 ± 20.4	<0.001
SBP ≤ 110 mmHg, *n* (%)	2848/9427 (30.2%)	779/2683 (29.0%)	2069/6744 (30.7%)	0.117
HR, b.p.m., mean ± SD	73.1 ± 15.6	75.1 ± 16.6	72.3 ± 15.2	<0.001
HR ≥70 b.p.m., *n* (%)	5278/9427 (56.0%)	1619/2683 (60.3%)	3659/6744 (54.3%)	<0.001
EF, %, mean ± SD	37.1 ± 13.6	41.8 ± 15.0	35.3 ± 12.6	<0.001
EF >45%, *n* (%)	1938/8415 (23.0%)	850/2318 (36.7%)	1088/6097 (17.8%)	<0.001
NYHA class III or IV, *n* (%)	2454/9403 (26.1%)	778/2677 (29.1%)	1676/6726 (24.9%)	<0.001
Pulmonary or peripheral congestion, *n* (%)	2983/3982 (74.9%)	907/1194 (76.0%)	2076/2788 (74.5%)	0.317
Third heart sound, *n* (%)	548/9108 (6.0%)	137/2589 (5.3%)	411/6519 (6.3%)	0.067
Peripheral hypoperfusion/cold, *n* (%)	313/9123 (3.4%)	93/2594 (3.6%)	220/6529 (3.4%)	0.610
Mitral regurgitation, *n* (%)	2419/9127 (26.5%)	714/2594 (27.5%)	1705/6533 (26.1%)	0.164
Aortic stenosis, *n* (%)	373/9125 (4.1%)	140/2593 (5.4%)	233/6532 (3.6%)	<0.001
Prior HF hospitalization, *n* (%)	3963/9356 (42.4%)	1080/2670 (40.4%)	2883/6686 (43.1%)	0.018
HF diagnosis >12 months, *n* (%)	4837/7808 (61.9%)	1368/2178 (62.8%)	3469/5630 (61.6%)	0.330
Ischaemic aetiology, *n* (%)	4021/9372 (42.9%)	742/2668 (27.8%)	3279/6704 (48.9%)	<0.001
Atrial fibrillation, *n* (%)	3537/9427 (37.5%)	1028/2683 (38.3%)	2509/6744 (37.2%)	0.314
Diabetes mellitus, *n* (%)	2940/9428 (31.2%)	762/2684 (28.4%)	2178/6744 (32.3%)	<0.001
PAD, *n* (%)	1105/9129 (12.1%)	233/2594 (9.0%)	872/6535 (13.3%)	<0.001
Hypertension, *n* (%)	5534/9412 (58.8%)	1570/2675 (58.7%)	3964/6737 (58.8%)	0.896
COPD, *n* (%)	1322/9409 (14.1%)	232/2677 (8.7%)	1090/6732 (16.2%)	<0.001
Sleep apnoea, *n* (%)	459/8933 (5.1%)	61/2536 (2.4%)	398/6397 (6.2%)	<0.001
Prior stroke/TIA, *n* (%)	881/9419 (9.4%)	215/2679 (8.0%)	666/6740 (9.9%)	0.005
Renal dysfunction, *n* (%)	1772/9419 (18.8%)	443/2683 (16.5%)	1329/6736 (19.7%)	<0.001
Hepatic dysfunction, *n* (%)	320/9138 (3.5%)	65/2597 (2.5%)	255/6541 (3.9%)	0.001
Depression, *n* (%)	692/9387 (7.4%)	321/2675 (12.0%)	371/6712 (5.5%)	<0.001
Pacemaker, *n* (%)	545/9399 (5.8%)	203/2676 (7.6%)	342/6723 (5.1%)	<0.001
ACEIs/ARBs, *n* (%)	6285/7337 (85.7%)	1587/1968 (80.6%)	4698/5369 (87.5%)	<0.001
Beta-blockers, *n* (%)	8357/9424 (88.7%)	2274/2682 (84.8%)	6083/6742 (90.2%)	<0.001
MRAs, *n* (%)	5542/9425 (58.8%)	1508/2683 (56.2%)	4034/6742 (59.8%)	0.001
Diuretics, *n* (%)	7798/9424 (82.7%)	2255/2682 (84.1%)	5543/6742 (82.2%)	0.031
Digitalis, *n* (%)	2149/9422 (22.8%)	632/2683 (23.6%)	1517/6739 (22.5%)	0.275
Statins, *n* (%)	5690/9424 (60.4%)	1413/2683 (52.7%)	4277/6741 (63.4%)	<0.001
Antiplatelets, *n* (%)	4616/9424 (49.0%)	1094/2683 (40.8%)	3522/6741 (52.2%)	<0.001
Oral anticoagulants, *n* (%)	4004/9423 (42.5%)	1121/2683 (41.8%)	2883/6740 (42.8%)	0.379
Amiodarone, *n* (%)	1282/9203 (13.9%)	290/2612 (11.1%)	992/6591 (15.1%)	<0.001
Ivabradine, *n* (%)	768/9147 (8.4%)	224/2598 (8.6%)	544/6549 (8.3%)	0.624
Nitrates, *n* (%)	1770/9146 (19.4%)	472/2598 (18.2%)	1298/6548 (19.8%)	0.071
Calcium channel blockers, *n* (%)	1043/9146 (11.4%)	314/2597 (12.1%)	729/6549 (11.1%)	0.193

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; HR, heart rate; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack.

ratios for death were significantly lower in patients of younger age, compared to patients aged >75 years. The likelihood of death was also lower with increasing BMI. The risk for mortality increased with lower SBP, NYHA class III or IV status, presence of pulmonary or peripheral congestion, aortic stenosis, PAD and renal dysfunction (*Table 5*).

Discussion

The present study provides important information on age- and sex-related differences in the clinical presentation, management and outcomes of chronic HF in a large, multinational cohort of ambulatory patients included in the ESC HF-LT Registry.

Baseline demographic and clinical characteristics of patients

The median age, 66 years, of the overall study population in the present registry was lower than the mean ages (>70 years) reported in most earlier registries of chronic HF[23–26] and more closely corresponded to this patient characteristic in recent clinical trials in patients with HF with reduced ejection fraction (HFrEF).[27]

Table 2 Management at 1-year follow-up in female vs. male patients with heart failure

	All patients ($n = 9428$)	Female patients ($n = 2684$)	Male patients ($n = 6744$)	*P*-value
ACEIs/ARBs, *n* (%)	6493/7509 (86.5%)	1766/2107 (83.8%)	4727/5402 (87.5%)	<0.001
Beta-blockers, *n* (%)	6674/7515 (88.8%)	1800/2108 (85.4%)	4874/5407 (90.1%)	<0.001
MRAs, *n* (%)	4409/7516 (58.7%)	1183/2107 (56.1%)	3226/5409 (59.6%)	0.006
Diuretics, *n* (%)	6080/7518 (80.9%)	1722/2109 (81.7%)	4358/5409 (80.6%)	0.284
Digitalis, *n* (%)	1583/7517 (21.1%)	446/2108 (21.2%)	1137/5409 (21.0%)	0.896
Statins, *n* (%)	4715/7517 (62.7%)	1167/2108 (55.4%)	3548/5409 (65.6%)	<0.001
Antiplatelets, *n* (%)	3581/7515 (47.7%)	846/2107 (40.2%)	2735/5408 (50.6%)	<0.001
Oral anticoagulants, *n* (%)	3263/7517 (43.4%)	877/2108 (41.6%)	2386/5409 (44.1%)	0.049
Amiodarone, *n* (%)	1202/7517 (16.0%)	249/2108 (11.8%)	953/5409 (17.6%)	<0.001
Ivabradine, *n* (%)	751/7515 (10.0%)	211/2108 (10.0%)	540/5407 (10.0%)	0.977
Nitrates, *n* (%)	1346/7330 (18.4%)	351/2056 (17.1%)	995/5274 (18.9%)	0.075
Calcium channel blockers, *n* (%)	840/7517 (11.2%)	261/2108 (12.4%)	579/5409 (10.7%)	0.038

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

This provides important information on the clinical characteristics and management of a relatively younger HF patient population drawn from real-world cardiology practice across Europe. The lower median age probably reflects the inclusion of patients treated by cardiologists in accordance with the registry protocol, rather than the more general patient population included in most earlier registries of chronic HF.[23–26]

This registry included a significantly higher proportion of male (71.5%) than female patients. The reasons for this male predominance remain unresolved. It may relate to several factors, such as women's or doctors' underestimation of cardiovascular symptoms in female patients, the difficulties faced by women in participating in clinical trials or registries, and female under-representation caused by current study design, including the exclusion of outpatients with prevalent HFrEF. Other registries and clinical trials of HF patients have also documented a male predominance among the patients included.[23–30] This discrepancy may be relevant in the applicability of evidence-based therapies to both sexes.

Compared to men, female patients were on average 4 years older and more symptomatic, as indicated by a greater proportion of NYHA class III or IV symptoms, despite similar clinical presentations and better LVEF. These results comply with the MAGGIC meta-analysis of 31 studies including 41 949 patients (13 897 women), which demonstrated that women with HF were on average 5 years older than men with HF (mean ± SD age: 70.5 ± 12.1 years and 65.6 ± 11.6 years, respectively). Further, previous data indicate a greater burden of HF symptoms in women and differences between the sexes in aetiology, haemodynamic adaptations and disease perception.[31,32]

Similarly to the present registry, the MAGGIC database has also suggested a lower prevalence of IHD (46.3% vs. 58.7%) and a higher prevalence of hypertension (49.9% vs. 40.0%) in women than in men.[28] Likewise, in a Norwegian cohort of HF patients, women with LVEF <50% had less frequent ischaemic HF aetiology than did men (57% and 63%, respectively).[23] Type 2 diabetes mellitus (T2DM) in HF varies in prevalence from 20% to 40% and is less frequent in randomized trials than in registries, and sex-related differences in T2DM are inconsistent. In the Chronic Heart Failure Analysis and Registry in Tohoku District-2 (CHART-2), T2DM was less prevalent in female than in male patients (31.7% and 36.4%, respectively).[9] In contrast, the MAGGIC database reported a higher frequency of T2DM in female than in male patients (25.4% and 22.8%, respectively).[28] The Norwegian cohort showed no difference in T2DM prevalence between the sexes.[23] In the present registry, the prevalence of T2DM was ~30%, and it was less frequently observed in females than in males (28% and 32%, respectively).

Similarly to T2DM, higher prevalences of renal dysfunction have been reported in HF patients in registries than in clinical trials, in which severe renal dysfunction is generally an exclusion criterion. Sex-related heterogeneity in chronic kidney disease in HF has also been reported, with considerable discrepancies among studies. In the Olmsted cohort, the prevalence of chronic renal failure was lower in women than in men with HF, regardless of LVEF.[32] Conversely, in the National HF Registry under the Spanish Society of Internal Medicine (RICA), more women than men had chronic renal failure (59.1% and 53.0%, respectively), and it was not associated with impaired survival.[26] In the present registry, renal dysfunction was more often observed in men than in women (19.7% and 16.5%, respectively) and was associated with greater mortality.

In the current registry, COPD was more frequent in male than in female patients, probably as a consequence of a greater burden of smoking among men or of underdiagnosis of COPD in women.[26,33–35] In addition, and as expected, male patients more often suffered from sleep apnoea than did females.[36,37]

The frequency of depression in HF in female patients was more than double than that in male patients (12.0% and 5.5%, respectively). Previous data, including a meta-analysis of 27 studies of patients with HF, have shown similar findings.[38] The underlying reasons are currently unknown. Several clinical, cultural and societal factors have been implicated and deserve further specific investigation because depression in HF is associated with lower

Table 3 Multivariable analysis of independent predictors of treatment in patients with left ventricular ejection fraction of ≤45%

	Odds ratio (95% CI)[a]	*P*-value
ACEI/ARB treatment		
Female patients	0.96 (0.77–1.21)	0.7401
Age <55 years	1.93 (1.42–2.61)	<0.0001
Age 55–64 years	1.98 (1.50–2.61)	<0.0001
Age 65–75 years	1.36 (1.07–1.73)	0.0118
BMI	1.06 (1.04–1.08)	<0.0001
SBP ≤ 110 mmHg	0.63 (0.52–0.77)	<0.0001
NYHA class III or IV	0.58 (0.48–0.71)	<0.0001
Prior HF hospitalization	0.74 (0.62–0.90)	0.0019
Hypertension	1.35 (1.10–1.65)	0.0035
Renal dysfunction	0.32 (0.26–0.39)	<0.0001
Hepatic dysfunction	0.52 (0.36–0.75)	0.0006
BB treatment		
Female	0.81 (0.64–1.03)	0.0827
Age <55 years	1.60 (1.16–2.21)	0.0038
Age 55–64 years	1.93 (1.43–2.61)	<0.0001
Age 65–75 years	1.45 (1.11–1.90)	0.0062
NYHA class III or IV	0.64 (0.52–0.80)	<0.0001
Prior HF diagnosis	1.45 (1.18–1.79)	0.0004
COPD	0.51 (0.40–0.66)	<0.0001
Depression	0.60 (0.43–0.83)	0.0021
PM	0.55 (0.38–0.79)	0.0012
MRA treatment		
Female	1.09 (0.95–1.24)	0.2098
Age <55 years	2.03 (1.70–2.42)	<0.0001
Age 55–64 years	1.92 (1.64–2.25)	<0.0001
Age 65–75 years	1.57 (1.35–1.82)	<0.0001
SBP ≤ 110 mmHg	1.55 (1.37–1.74)	<0.0001
NYHA class III or IV	1.60 (1.41–1.83)	<0.0001
Third heart sound	1.78 (1.39–2.28)	<0.0001
Prior HF hospitalization	1.55 (1.39–1.73)	<0.0001
Atrial fibrillation	1.26 (1.12–1.42)	0.0001
Renal dysfunction	0.50 (0.43–0.57)	<0.0001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PM, pacemaker; SBP, systolic blood pressure.
[a]Reference values are male for sex and age >75 years for age.
Variables included in the Cox model: age classes, gender, BMI at baseline, SBP ≤110 mmHg, heart rate ≥70 b.p.m., NYHA class III or IV status, pulmonary or peripheral congestion, S3 gallop (third heart sound), peripheral hypoperfusion/cold, mitral regurgitation, aortic stenosis, prior HF hospitalization, HF diagnosis of >12 months, ischaemic aetiology, atrial fibrillation, diabetes mellitus, peripheral artery disease, hypertension treatment, COPD, sleep apnoea, prior stroke/transient ischaemic attack, renal dysfunction, hepatic dysfunction, depression, device therapy (PM).

levels of therapeutic adherence and greater risk for adverse outcomes.[39–41]

The majority of participants (77.0%) in the present registry had LVEF ≤45%. The predominance of reduced LVEF may suggest a selection bias that arises from the more severe clinical presentation of HF typically observed in the cardiology departments and specialized HF units that served as recruiting institutions for the ESC HF-LT Registry. Compared to men, women had higher mean ± SD LVEF (35 ± 13% and 42 ± 15%, respectively) and a higher rate of LVEF >45%. This is consistent with previous reports and confirms a lesser propensity for HFrEF in women than in men.[25,28,42,43]

Baseline and follow-up medical management

Despite high GDMT uptake in the overall population, crude prescription rates of ACEIs/ARBs, BBs and MRAs were lower in women than in men. This may be related to the higher prevalence of HF with preserved LVEF in women, which discourages treatment in view of no real survival benefit. However, even in HF patients with preserved ejection fraction, the use of ACEIs/ARBs, BBs and MRAs is currently recommended for the treatment of associated comorbidities (i.e. hypertension, AF etc.). The present study also observed a decline in GDMT prescription rates with ageing in both sexes, and an increase in the use of diuretics, oral

Table 4 **Outcomes in female and male heart failure patients at 1 year**

	All patients ($n = 9428$)	Female patients ($n = 2684$)	Male patients ($n = 6744$)	*P*-value
All-cause death, *n* (%)	757/9198 (8.2%)	186/2613 (7.1%)	571/6585 (8.7%)	0.015
Causes of death				
CV death, *n* (%)	394/757 (52.0%)	102/186 (54.8%)	292/571 (51.1%)	
Non-CV death, *n* (%)	175/757 (23.1%)	38/186 (20.4%)	137/571 (24.0%)	0.565
Unknown, *n* (%)	188/757 (24.8%)	46/186 (24.7%)	142/571 (24.9%)	
All-cause hospitalization, *n* (%)	2367/9198 (25.7%)	571/2613 (21.9%)	1796/6585 (27.3%)	<0.001
HF hospitalization, n (%)	1030/8357 (12.3%)	257/2364 (10.9%)	773/5993 (12.9%)	0.011

CV, cardiovascular; HF, heart failure.

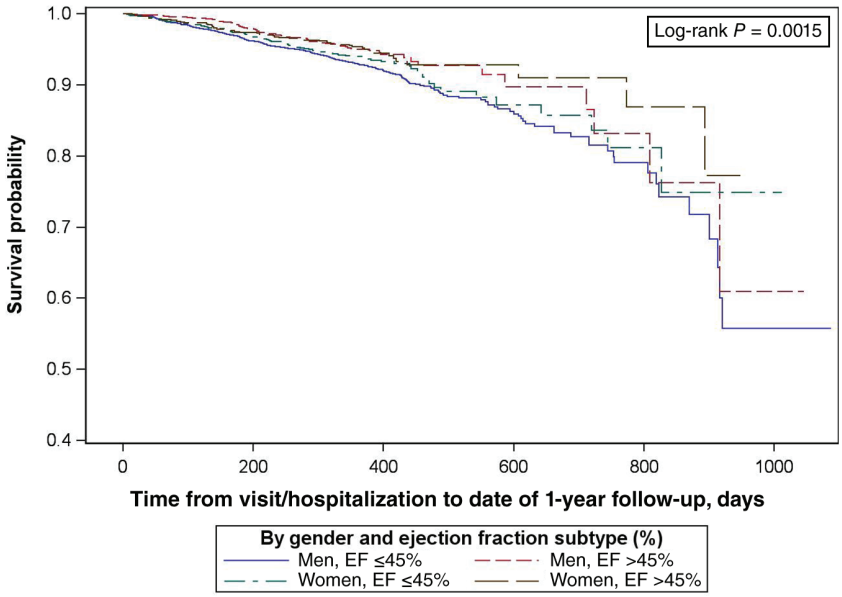

Figure 1 Kaplan–Meier product–limit survival estimates for all-cause death by gender and ejection fraction (EF) subtype (%).

anticoagulants, amiodarone and other ancillary therapies, indicative of an age-related greater burden of congestion and comorbidities. The proportion of patients receiving oral anticoagulants exceeded the proportion of patients with AF, suggesting that other indications or perhaps only significantly reduced LVEF influenced the decision to use anticoagulants. There was no improvement in sex- or age-related discrepancies in the prescription of GDMT at 1-year follow-up. Sex was not an independent predictor of the prescription of GDMT (in a subset of patients with LVEF ≤45%). Older age (>75 years) was an independent predictor of a lower utilization of GDMT at 1-year follow-up. This implies that advanced age is an important obstacle to the implementation of GDMT and this may adversely impact on prognosis.

These results are similar to those of the MAGGIC meta-analysis, CHART 2 study and CHARM Program,[9,27,28] although the overall proportion of patients receiving evidence-based therapies has increased compared to those in the earlier reports. In IMPROVE, there was a trend towards the lower prescription of evidence-based medications in the ageing population regardless of sex, and rates of use of ACEIs/ARBs, BBs and MRAs were similar in both men and women.[44]

Specifically, older age, higher NYHA class and impaired renal function have been repeatedly reported as predictors of MRA underuse. MRAs have been proven to be effective in elderly patients and in patients with moderate renal impairment (estimated glomerular filtration rate ≥30 mL/min/1.73 m^2).[45] More cautious MRA use is required in patients with high serum potassium levels, even when renal function is not significantly reduced, but this issue could be resolved with the use of potassium binders.[46] High serum potassium can also be the reason for a reluctance to up-titrate ACEIs/ARBs to optimal doses, but it does not adversely impact on the beneficial effects of ACEIs/ARBs.[47] In addition, frailty has been identified as an obstacle to the use of GDMT, in particular MRAs, although their beneficial effects on outcomes appears to be unaffected by frailty.[48,49]

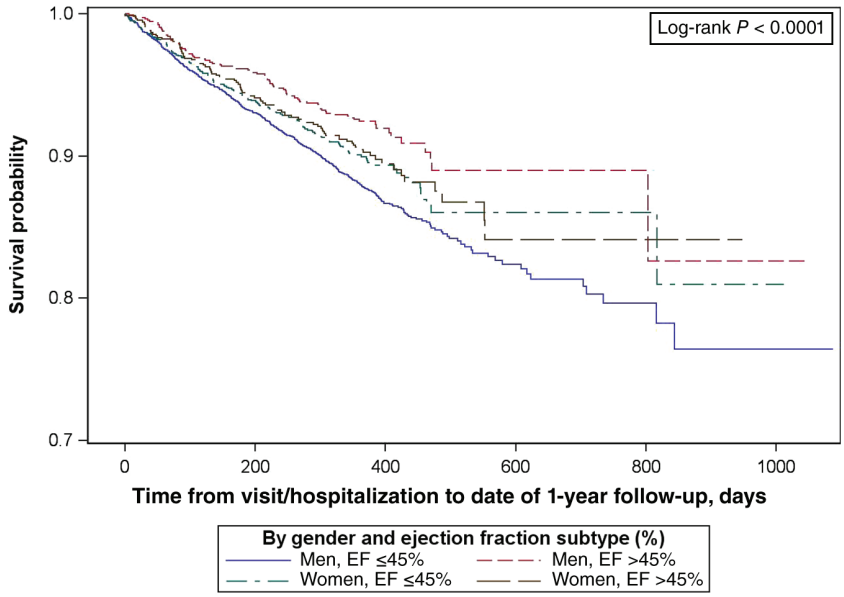

Figure 2 Kaplan–Meier product–limit survival estimates for all-cause hospitalization by gender and ejection fraction (EF) subtype (%).

Therefore, GDMT underuse cannot be justified by these clinical scenarios.

Sex- and age-related differences in outcomes

Compared to male patients, females had lower crude rates of all-cause mortality and all-cause hospitalization, as well as a lower crude rate of HF hospitalization. Although mortality was lower in women, there were no sex-related differences in causes of death. These results are in line with those of the CHARM trial and the MAGGIC meta-analysis.[27,28] A recent analysis of patients with dilated cardiomyopathy demonstrated better survival in women compared to men, which was explained by less severe left ventricular dysfunction and a smaller scar burden.[50] In addition, favourable outcomes were noticed in patients aged <60 years, whereas male patients aged >60 years demonstrated higher all-cause mortality and a greater propensity for non-sudden death compared to women.[50] These findings are likely to reflect differences in characteristics and associated comorbidities between patients with dilated cardiomyopathy and those with chronic HF of any aetiology included in the current study.

In the present study, rates of all-cause mortality, all-cause hospitalization and HF hospitalization significantly increased with advancing age in both sexes.[28,51,52] Sex, however, was not an independent predictor of all-cause mortality.

Limitations

There are several limitations to the present analysis. The study population consisted of outpatients managed mostly by cardiologists and hence does not completely reflect usual clinical practice. A further limitation refers to the lack of central validation and adjudication of diagnoses, LVEF measurements and causes of death. Some variables with prognostic importance, such as natriuretic peptide levels, were largely missing and therefore excluded from the analysis. The proportion of patients not using medications for reasons of contraindications or intolerance, and the proportion of patients deemed eligible for treatment but not receiving GDMT were not documented. At the time of analysis, the use of devices [cardiac resynchronization therapy (CRT), implantable cardioverter defibrillators, CRT defibrillators] was not widespread in several of the participating countries, and conclusions regarding these treatment modalities could not be adequately inferred. Finally, patients were stratified by LVEFs of ≤45% and >45% (according to an analysis plan defined at the time of registry commencement). These limitations can serve as valuable reminders of how to design future research projects to more closely represent the real-world population of HF patients.

Conclusions

The present study has demonstrated significant differences in the clinical characteristics and management of HF patients in relation to age and sex. There was a decline in GDMT prescription with advanced age in both sexes, suggestive of an underutilization of evidence-based therapies, which may have adversely impacted prognosis. Sex was not independently associated with either GDMT prescription or outcomes. However, older age (>75 years) independently predicted a lower use of GDMT and a higher rate of all-cause mortality. Although the reasons behind the disparities observed may be complex, it is important to raise

Table 5 Multivariable analysis of independent predictors of all-cause death in patients with left ventricular ejection fraction ≤45%

	Hazard ratio (95% CI)[a]	*P*-value
Female	0.90 (0.68–1.18)	0.4333
Age <55 years	0.48 (0.32–0.71)	0.0003
Age 55–64 years	0.70 (0.52–0.96)	0.0260
Age 65–75 years	0.65 (0.49–0.86)	0.0025
BMI	0.96 (0.94–0.99)	0.0025
SBP ≤110 mmHg	1.57 (1.25–1.98)	0.0001
NYHA class III or IV status	1.98 (1.56–2.51)	<0.0001
Pulmonary or peripheral congestion	2.15 (1.50–3.09)	<0.0001
Aortic stenosis	1.58 (1.04–2.41)	0.0323
PAD	1.40 (1.06–1.84)	0.0184
Renal dysfunction	1.70 (1.34–2.16)	<0.0001

BMI, body mass index; CI, confidence interval; HF, heart failure; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.

[a]Reference values are male for sex and age >75 years for age.

Variables included in the Cox model: age classes, gender, BMI at baseline, SBP ≤110 mmHg, heart rate ≥70 b.p.m., NYHA class III/IV, pulmonary or peripheral congestion, S3 gallop (third heart sound), peripheral hypoperfusion/cold, mitral regurgitation, aortic stenosis, prior HF hospitalization, HF diagnosis of >12 months, ischaemic aetiology, atrial fibrillation, diabetes mellitus, PAD, hypertension treatment, chronic obstructive pulmonary disease, sleep apnoea, prior stroke/transient ischaemic attack, renal dysfunction, hepatic dysfunction, depression, device therapy (pacemaker).

awareness among physicians of the fact that persistence in obtaining the optimal management of patients with HF is of crucial importance in improving outcomes.[53] Further research into the causes of undertreatment of HF in elderly patients may provide important insights that will facilitate the improvement of treatment options.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier curves for all-cause death by age and ejection fraction subtype (%).

Figure S2. Kaplan–Meier curves for all-cause hospitalization by age and ejection fraction subtype (%).

Table S1. Baseline demographic, clinical and treatment characteristics of female patients by age category.

Table S2. Baseline demographic, clinical and treatment characteristics of male patients by age category.

Table S3. Management at 1-year follow-up in female patients.

Table S4. Management at 1-year follow-up in male patients.

Table S5. Outcomes at 1 year in female and male patients.

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