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CLINICAL RESEARCH
Heart failure/cardiomyopathy

The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions

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Aims Recent data from national registries suggest that acute heart failure (AHF) outcomes might vary in men and women, however, it is not known whether this observation is universal. The aim of this study was to evaluate the association of biological sex and 1-year all-cause mortality in patients with AHF in various regions of the world.

Methods and results We analysed several AHF cohorts including GREAT registry (22 523 patients, mostly from Europe and Asia) and OPTIMIZE-HF (26 376 patients from the USA). Clinical characteristics and medication use at discharge were collected. Hazard ratios (HRs) for 1-year mortality according to biological sex were calculated using a Cox proportional hazards regression model with adjustment for baseline characteristics (e.g. age, comorbidities, clinical and laboratory parameters at admission, left ventricular ejection fraction). In the GREAT registry, women had a lower risk of death in the year following AHF [HR 0.86 (0.79–0.94), $P < 0.001$ after adjustment]. This was mostly driven by northeast Asia [$n = 9135$, HR 0.76 (0.67–0.87), $P < 0.001$], while no significant differences were seen in other countries. In the OPTIMIZE-HF registry, women also had a lower risk of 1-year death [HR 0.93 (0.89–0.97),

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$P < 0.001$]. In the GREAT registry, women were less often prescribed with a combination of angiotensin-converting enzyme inhibitors and beta-blockers at discharge (50% vs. 57%, $P = 0.001$).

Conclusion Globally women with AHF have a lower 1-year mortality and less evidenced-based treatment than men. Differences among countries need further investigation. Our findings merit consideration when designing future global clinical trials in AHF.

Keywords Acute heart failure • Gender • Biological sex • Mortality • Prognosis

Introduction

Acute heart failure (AHF) is a modern-day epidemic. Its rising incidence is the result of the relative success in the management of historically fatal pathologies (e.g. hypertension, coronary artery disease, diabetes) that now leave a large and growing population with impaired prognosis and a resultant huge economic burden. The prevalence of heart failure (HF) increases with age. With each 10-year age increase from 65 to 85 years, the HF incidence rates double in men and triple in women.[1] Approximately 50% of all HF patients are women.[1] Female AHF patients show marked differences in clinical presentation, precipitating factors for decompensation, comorbidities, and short-term outcomes compared to men.[2–5] Nevertheless, women are currently still underrepresented in cardiology research.[6,7] Current guidelines for HF therapy[8,9] are based on trials conducted predominantly in middle-aged men, though most studies have not demonstrated heterogeneity in clinical response by biological sex. Furthermore, some studies have suggested lower quality of care in women with HF and worse outcomes in comparison with men. However, the association of biological sex and long-term outcomes in patients with AHF is not fully recognized. Recent data from national registries[10,11] suggest that outcomes might vary in men and women. As major clinical trials are mostly performed in the northern hemisphere, it is not known whether this observation is universal around the world.

The primary objective of our analysis was to assess the effect of biological sex on 1-year all-cause mortality in patients presenting with AHF to the emergency department in different geographic regions using data from the international GREAT (Global Research on Acute Conditions Team) registry. Our secondary objective was to describe clinical characteristics and management of AHF patients according to biological sex.

Methods

Data collection

The discovery cohort was derived from the international GREAT registry, a prospective observational cohort of adult patients presenting with AHF to the emergency department. Methodologic details of the GREAT registry have been previously described.[12,13] For the current analysis, we included 22 523 AHF patients from five countries in Western Europe (Finland, France, Italy, Spain, and Switzerland), two countries in Central Europe (Czech Republic and Lithuania), two countries in North America (USA and Canada), and three countries in Northeast Asia (China, Japan, and South Korea). The patient population of the GREAT registry was then compared to a large validation cohort from the OPTIMIZE-HF study, which included a total of 26 376 patients from the USA. We also performed identical analyses in REALITY-AHF and ASIAN-HF study populations. Results of these registries as well as patient characteristics have been previously published.[14,15] Both patients with new-onset and acute decompensated HF were included, as defined by the European Society of Cardiology.[8] For the ASIAN-HF study (which recruited both in- and outpatients with HF), only the subset of patients recruited in the hospitalized setting were included in the current combined analysis. Clinical characteristics (demographic data, clinical status, comorbidities, and chronic medication use), as well as echocardiographic and laboratory data on admission, were recorded prospectively. Sex status was self-reported. For patients who survived the initial hospitalization, medication use at discharge was also recorded. Follow-up at 1 year was performed via personal contact or national data registries. The primary outcome of the study was 1-year all-cause mortality.

The study was performed in accordance with the Declaration of Helsinki. Ethics committee approvals were obtained for all sites according to local requirements. If requested by the local ethics committee, patient consent for data collection was obtained.

Statistical analysis

Continuous variables are expressed as the median (interquartile range, IQR). Categorical variables are presented as number (percentage). No missing data imputation was performed. All variables were tested for normality using the Shapiro–Wilk test. Group characteristics were compared with the *t*-test or Mann–Whitney test for continuous variables and χ^2 test for categorical variables. One-year all-cause mortality was plotted with the Kaplan–Meier curve. Hazard ratios (HRs) for 1-year mortality were calculated using a Cox proportional hazards regression model with and without adjustment for the baseline covariates. Baseline covariates included sex, age, body mass index, systolic blood pressure, heart rate at admission, creatinine, sodium, haemoglobin, history of diabetes, hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease, atrial fibrillation, hospital length of stay, and left ventricular ejection fraction (LVEF) ≤40%.

The analyses were performed with R software (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered statistically significant.

Results

Risk of death according to biological sex in the international GREAT registry

Characteristics of the patients included in the GREAT database are summarized in *Table 1*. Female AHF patients were older [median (IQR) age 78 (69–84) vs. 71 (61–79) years, $P < 0.001$], more often had a history of hypertension (70% vs. 64%, $P < 0.001$), and a higher

Table 1 Comparison of baseline characteristics and outcomes in acute heart failure patients according to biological sex

	Available data	Total cohort	Men	Women	*P*-value
Age (years)	22 498 (99)	74 (64–82)	71 (61–79)	78 (69–84)	<0.001
Gender[a]	22 523 (100)	22 523 (100)	12 589 (56)	9933 (44)	<0.001
Clinical parameters on admission					
Systolic blood pressure (mmHg)	22 189 (99)	135 (115–158)	132 (112–155)	139 (119–160)	<0.001
Heart rate (b.p.m.)	22 164 (98)	89 (73–108)	89 (73–108)	89 (73–108)	0.867
LVEF ≤ 40% (%)	20 312 (90)	12 096 (60)	7942 (69)	4440 (51)	<0.001
BMI (kg/m^2)	17 528 (78)	25.0 (22–28.7)	25.3 (22.5–28.7)	24.5 (21.3–28.8)	<0.001
Laboratory tests on admission					
Estimated GFR (mL/min/1.73 m^2)	21 683 (96)	53 (37–70)	55 (40–73)	49 (35–66)	<0.001
Sodium (mmol/L)	21 842 (97)	139 (136–141)	139 (136–141)	139 (136–141)	0.064
Haemoglobin (g/dL)	21 446 (95)	12.6 (11.0–14.1)	13.2 (11.5–14.7)	12.0 (10.6–13.3)	<0.001
BNP (pg/mL)	9305 (41)	820 (403–1510)	837 (417–1525)	795 (392–1494)	<0.001
NT-proBNP (pg/mL)	4614 (21)	4098 (1700–9447)	3726 (1585–8518)	4515 (1797–10 530)	<0.001
Medical history					
Diabetes mellitus	22 367 (99)	8280 (37)	4621 (37)	3659 (37)	0.917
COPD	21 011 (93)	3639 (17)	2317 (20)	1322 (14)	<0.001
Hypertension	21 492 (95)	14 368 (67)	7737 (64)	6631 (70)	<0.001
Coronary artery disease	22 272 (99)	10 004 (45)	5626 (45)	4378 (45)	0.434
Previous history of heart failure	21 088 (94)	9339 (44)	5347 (45)	3992 (43)	0.001
Atrial fibrillation/atrial flutter	20 921 (93)	6455 (31)	3626 (31)	2829 (31)	0.787
Causes of decompensation					
Acute coronary syndrome	10 798 (48)	3062 (28)	1817 (30)	1245 (26)	<0.001
Atrial fibrillation/flutter	11 806 (52)	1258 (11)	639 (10)	619 (12)	0.004
Infection	6161 (27)	785 (11)	386 (12)	399 (14)	0.066
Compliance	5739 (25)	245 (4)	142 (5)	103 (4)	0.047
Hypertension	11 552 (51)	676 (6)	306 (5)	370 (7)	<0.001
Hospital length of stay (days)	21 199 (94)	10 (5–17)	10 (6–18)	9 (5–17)	<0.001
Medication at discharge (n = 19 648)					
Beta-blockers	21 045 (93)	12 288 (58)	7230 (61)	5058 (54)	<0.001
ACEIs or ARBs	20 031 (89)	13 572 (68)	7744 (69)	5828 (68)	0.007
Both BBs and ACEIs/ARBs	20 022 (89)	9672 (48)	5767 (51)	3905 (45)	<0.001
Aldosterone receptor antagonists	16 931 (75)	7098 (42)	4194 (44)	2904 (40)	<0.001
Outcome					
In-hospital mortality	22 376 (99)	1675 (7)	919 (7)	756 (7)	0.393
30-Day mortality	21 937 (97)	1869 (9)	1025 (9)	844 (9)	0.517
1-Year mortality[b]	21 082 (94)	5210 (24)	2934 (24)	2276 (24)	0.636

Data are presented as median (1st and 3rd quartile) or *n* (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BBs, beta-blockers; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal-proBNP.
[a]The proportion of female patients was similar to previous studies: ALARM-HF[3] (37%), EHFS II[2] (39%), EFICA[16] (41%).
[b]Unadjusted 1-year mortality was comparable to previous findings: 20.5% in EHFS II[2], 17% ATTEND, 30% EAHFE[10].

systolic blood pressure at admission [139 (118–160) vs. 132 (112–155) mmHg, $P < 0.001$] compared to men. Women more often presented with *de novo* HF (previous history of HF was present in 43% of female vs. 45% of male patients, $P = 0.001$). Female AHF patients less often had a reduced LVEF ≤40% (52% vs. 69%, $P < 0.001$). Women also had a lower estimated glomerular filtration rate [49 (35–66) vs. 55 (40–73) mL/min/1.73 m^2, $P < 0.001$].

Concerning comorbidities, hypertension was more prevalent in women, whereas men more often presented with a history of COPD and previous HF ($P < 0.001$).

Among precipitating factors, acute coronary syndromes (ACS) emerged as the most common in both sexes. Nevertheless, ACS was less frequent in women than men (26% vs. 30%, $P < 0.001$). In addition, hypertensive crisis (10% vs. 7%, $P < 0.001$) and acute arrhythmia (12% vs. 10%, $P < 0.001$) were also more frequent in women, whereas men more often decompensated due to issues related to compliance (4% vs. 5%, $P = 0.047$).

Median hospital length of stay was longer in men than in women [10 (6–18) vs. 9 (5–17) days, respectively, $P < 0.001$]. In-hospital mortality was 8% in both sexes ($P = 0.539$). Women were less often

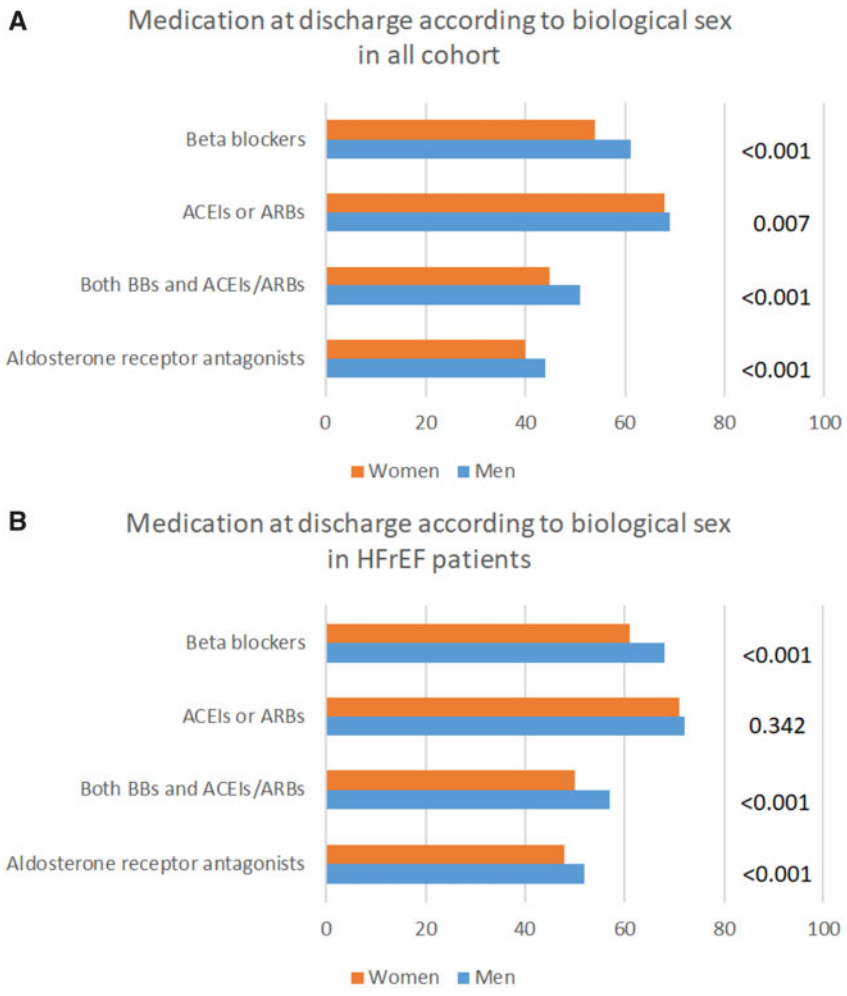

Figure 1 Treatment prescribed to acute heart failure patients at discharge according to biological sex and left ventricle ejection fraction. (*A*) Medications at discharge according to sex in all patients from GREAT. (*B*) Medications at discharge according to sex in heart failure with reduced ejection fraction patients from GREAT. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BBs, beta-blockers; HFrEF, heart failure with reduced ejection fraction.

prescribed with optimal HF therapy at discharge: a combination of beta-blocker and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) as well as aldosterone receptor antagonist (MRA) was less often prescribed to women than men (45% vs. 51% and 42% vs. 46%, respectively, $P < 0.001$) (see *Figure 1A*). The subgroup analysis of patients with HF with reduced ejection fraction (HFrEF) confirmed these findings. Women with HFrEF were less often prescribed with a combination of beta-blocker and ACE/ARB as well as an MRA (50% vs. 57% and 48% vs. 52% respectively, $P < 0.001$) (see *Figure 1B* and Supplementary material online, *Table S1*). Treatment rates in HFrEF patients according to the country of origin are described in the Supplementary material online, *Figure S2*.

Despite differences in treatment at discharge, unadjusted 1-year mortality in the whole cohort was 24% without a significant difference between men and women.

Unadjusted HR of 1-year mortality for women vs. men was similar [HR 1.02 (95% confidence interval 0.96–1.07), $P = 0.526$], but demonstrated a lower female mortality when adjusted for age [HR 0.82 (0.78–0.87), $P < 0.001$], which persisted after adjustment for both age and LVEF [HR 0.86 (0.81–0.91), $P < 0.001$]. Differences in mortality were also apparent after adjusting for other baseline covariates (age, body mass index, systolic blood pressure, heart rate at admission, creatinine, sodium, haemoglobin, history of diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, atrial fibrillation, hospital length of stay, and LVEF ≤40%): HR 0.86 (0.79–0.94), $P < 0.001$.

Additional sensitivity analyses were performed: after multiple imputation for missing data the survival benefit in women persisted with an HR of 0.87 (0.80–0.95). Consistent results were also found after adjustment for cluster effect [HR 0.87 (0.80–0.95)] as well as after stratification by age groups [HR 0.86 (0.79–0.94)]. After stratifying age by quartiles, the results remained harmonious, however, a statistical significance was found only in the 2nd quartile [patients aged from 65 to 74 years old; HR 0.82

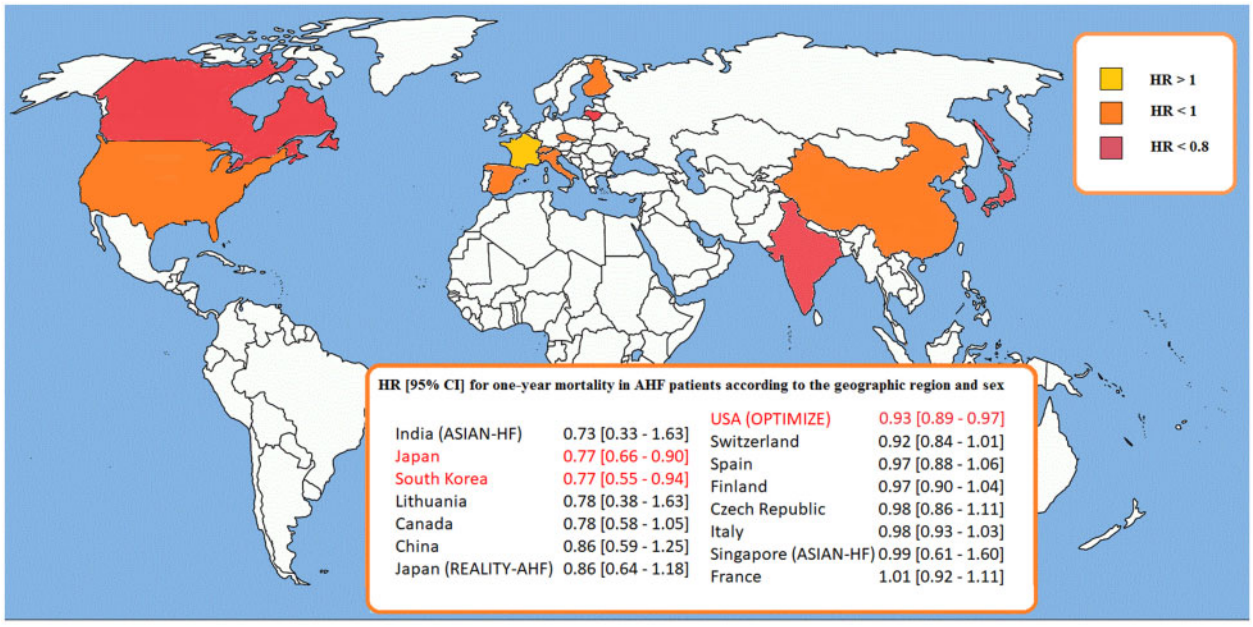

Figure 2 Risk of 1-year all-cause death in acute heart failure patients according to biological sex and geographic region. Adjusted Kaplan–Meier analysis for all-cause mortality and the hazard ratios and 95% confidence intervals for 1-year in the international GREAT registry and the American OPTIMIZE-HF registry. CI, confidence interval.

(0.68–0.99)]. The sensitivity analysis is presented as Supplementary material online, *Figure S3*.

Interestingly, despite being prescribed less optimal medical therapy at discharge women with HFrEF had lower mortality rates than men: HR 0.87 (0.79–0.97), $P = 0.016$ (see Supplementary material online, *Table S2*). These differences persisted in the mid-range and preserved ejection fraction subgroup: HR 0.86 (0.78–0.96), $P = 0.007$ after adjustment (see Supplementary material online, *Table S3*).

Sex-related outcomes among regions

Acute heart failure patient characteristics throughout geographic regions are presented in Supplementary material online, *Table S4*. We observed that the differences between men and women persisted in all of the studied regions. However, long-term outcomes according to sex were distinctive according to the geographic zones. After adjustment for covariates in each geographic region, women had significantly lower 1-year mortality rates in Northeast Asia [HR 0.76 (0.67–0.87), $P < 0.001$], but not in Western [HR 0.83 (0.68–1.03), $P = 0.087$] and Central Europe [HR 0.95 (0.84–1.08), $P = 0.435$] or North America [HR 0.88 (0.65–1.19), $P = 0.417$]. HRs for each country are presented in *Figure 2* and Supplementary material online, *Figure S1*).

To further explore the Asian population, we performed identical survival analysis using the Japanese REALITY-AHF registry ($n = 1682$) and ASIAN-HF study from Singapore ($n = 812$). Baseline characteristics for each are presented in Supplementary material online, *Tables S5 and S6*. We observed a trend towards a survival benefit of Asian women over men in both cohorts, however, it did not reach statistical significance [adjusted HR 0.86 (0.64–1.18), $P = 0.369$ and 0.99 (0.61–1.60), $P = 0.958$ for REALITY-AHF and ASIAN-HF, respectively].

Risk of death according to biological sex in the USA OPTIMIZE-HF registry

To confirm our findings, we analysed a large cohort OPTIMIZE-HF study ($n = 26\,376$) from the USA. Patient characteristics are described in Supplementary material online, *Table S7*. Unadjusted 1-year mortality in this registry was 35%. Results of OPTIMIZE-HF also demonstrated a 1-year survival benefit for women compared to men, with an adjusted HR of 0.93 (0.89–0.97), $P < 0.001$ (see *Figure 3*).

Discussion

This study describes clinical characteristics, treatment, and outcomes of AHF patients according to biological sex. Our results show that men and women differ in clinical presentation and receive different treatment at discharge. More importantly, our study highlights sex-related favourable long-term outcome in women compared to men.

The proportion of female patients in our study (44%) was similar to that reported in previous studies: ALARM-HF[3] (37%), EHFS II[2] (39%), and EFICA[10] (41%). The present data confirm the reports on sex differences in clinical presentation of AHF. Compared to men, women develop AHF at an older age, present with a higher admission blood pressure and a higher rate of preserved left ventricular ejection fraction (HFpEF).[18] This is in line with previous studies showing that female HF patients more often present with HFpEF due to increased concentric left ventricular remodelling in response to chronic arterial

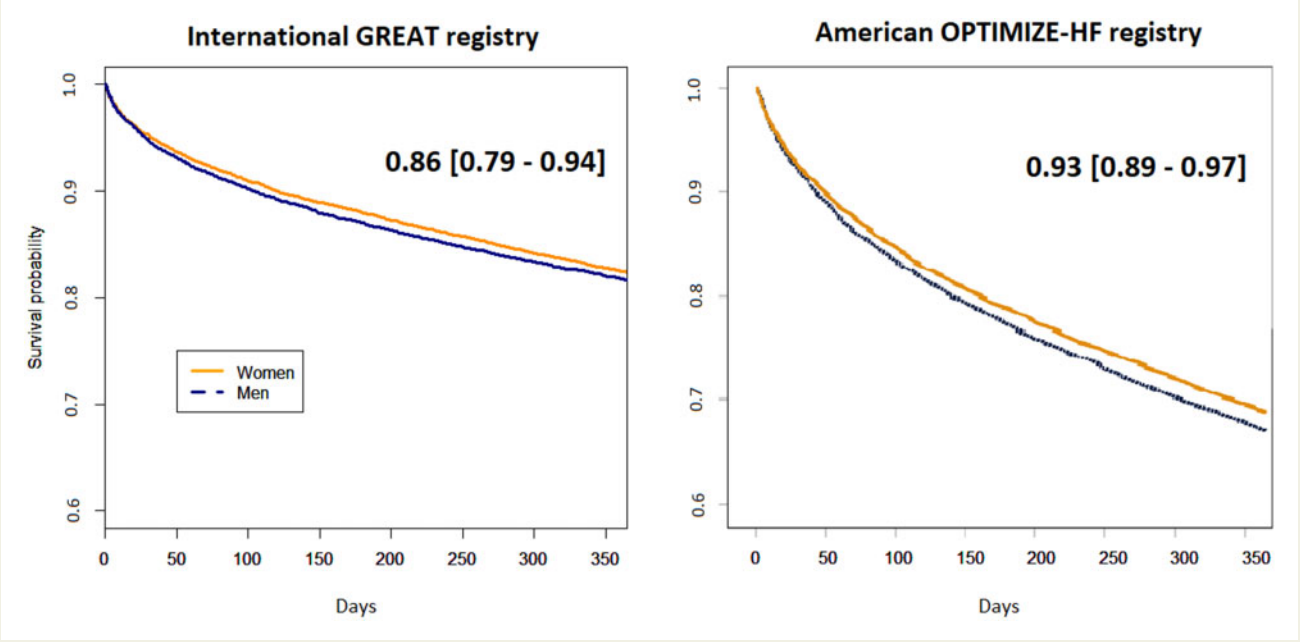

Figure 3 Graphical display of hazard ratio for long-term mortality according to biological sex of acute heart failure patients from different countries. Adjusted hazard ratios and 95% confidence intervals for the association between gender and long-term all-cause mortality in different countries around the world.

hypertension.[16,19] In our study, the greater incidence of HFpEF in women is supported by the greater prevalence of arterial hypertension.

There were also sex-related differences in comorbidities. Men more often presented with COPD, however, the prevalence of diabetes mellitus, coronary artery disease, and atrial fibrillation was similar in both sexes. Comparable results were found in ALARM-HF and ADHERE registries. In our study, the median length of hospital stay (LOS) was similar to EHFS II[2] and slightly longer than ADHERE.[20] Factors that might influence these differences in LOS are uncertain. Shorter length of stay in the US HF cohort is commonly reported and is more likely the result of variation in system administration.

Previous studies have stressed the phenomenon of undertreatment of patients with diagnosed HF.[21] Our data confirm this observation: even though a significant proportion of patients had a previous history of HF, optimal medical therapy rates were inadequate at admission and persisted at discharge. Compared to men, women were less likely to be prescribed with beta-blockers or MRAs. The reluctance to prescribe women with optimal HF therapy be explained by a few baseline differences. In our cohort, women were older than men. Previous studies[22] have highlighted a lower prescription rate of beta-blockers and ACEIs for patients older than 75 years. Yet the guidelines do not distinguish between age groups, and age alone should not influence therapeutic decisions. Women also had worse renal function compared to men, which may account for lower prescription rates of ACEIs and ARBs. What is more, women more often presented with preserved LVEF, a condition that has no guideline supported evidence-based therapeutic recommendations to this day. However, in the HFrEF subgroup, where guidelines have clear recommendations, women were still less often prescribed with evidence-based therapy than men. Therefore, our findings raise concern that gender bias persists regarding the prescription of evidence-based HF therapy.

Unadjusted 1-year mortality in the multinational GREAT (24%) registry was comparable to previous findings (20.5% in EHFS II[23] and 17% ATTEND[10]). The analysis of the OPTIMIZE-HF registry from the USA showed a higher unadjusted 1-year mortality (35%) which was comparable to the North American population in the GREAT registry (32%). This is in line with previous findings of other global AHF registries such as REPORT-HF.[24] In the latter study, the authors found inter-regional differences concerning AHF patient characteristics, precipitant factors, and initial treatment. In particular, the delay in intravenous therapy administration was longer in North America than in other studied regions. The REALITY-AHF[25] study found a correlation between time-to-furosemide and in-hospital mortality. Therefore, the lower survival in North America might be explained by differences in early AHF management. However, this observation needs further research.

When adjusted for age, LVEF, comorbidities, and other confounding factors, women had better 1-year survival than men in both GREAT and OPTIMIZE-HF registries.

We observed that the mortality benefit in the GREAT registry is mostly driven by the Northeast Asian HF patients, who accounted for almost half of the study population. Indeed, Asian AHF patients have better survival compared to other regions regardless of biological sex, as demonstrated by previous studies.[13] Our findings are supported by data from epidemiological studies: a recent study by Kontis *et al.*[26] demonstrated that South Korea and Japan had the highest life expectancy among 35 studied countries worldwide. They also demonstrated massive gains in South Korean and Japanese women's life expectancy. They attributed these gains to improved economic

Take home figure Towards further improvement in acute heart failure management: the importance of biological sex.

status and social capital (including education) as well as expanded access to health care and rapid advancement of new medical technologies. The authors also suggest that these countries have lower health inequalities between genders than their Western counterparts. The same factors might account for better female AHF survival in Asia. The heterogeneity of Asian patients in REALITY-AHF and ASIAN-HF cohorts might explain the difference in survival when compared to the GREAT study population. The Northeast Asian HF cohort from the GREAT registry had more women with HFpEF, which is known to have a better survival than HFrEF. In the other younger Asian cohorts there were less HFpEF patients, a possible explanation for why the sex differences in survival is not seen.

Limitations

Our study has several limitations. First of all, our study might carry some biases in inclusion of AHF patients. However, the proportion of women included and the baseline characteristics of the study population were comparable to previously described. What is more, our analysis is limited due to incomplete and missing data in the registry, especially concerning the data on natriuretic peptides as well as history of HF. In addition, the registry dataset did not include certain important confounding factors, such as the timing of when the echocardiography was performed for EF assessment. Moreover, the registry did not include information on inpatient medication strategies or post-baseline factors such as clinical worsening during the admission. Even though we adjusted for a number of covariates, there is the possibility that unmeasured confounders remain unaccounted for in our analysis. Another important limitation is the lack of knowledge on sacubitril/valsartan and ivabradine use. However, these particular medications were not guideline supported yet when the data were collected for the registry. Finally, rather than genetic sex, we stratified our results by self-reported sex status. How this may impact cardiovascular disease outcomes is unclear.

Conclusions

Our results confirm that women and men with AHF differ in baseline characteristics, comorbidities, and clinical presentation. However, even though women less often receive optimal medical therapy at discharge, they have better long-term outcomes. Survival differences were mostly pronounced in Northeast Asian and US patients compared to Europe. Significant geographic and biological sex differences in patient outcomes warrant further research aiming at understanding these differences. Our findings suggest that biological sex as well as geographical differences offer a valuable additional dimension of AHF trial heterogeneity and might have implications in the design of future global clinical trials. Prospective clinical trials are needed that

specifically analyse a female cohort or enrol a certain percentage of women in order to establish sex-specific guidelines for in-hospital as well as post-discharge management of HF (see *Take home figure*).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation* 2017;**135**:e146–e603.
2. Nieminen MS, Harjola VP, Hochadel M, Drexler H, Komajda M, Brutsaert D, Dickstein K, Ponikowski P, Tavazzi L, Follath F, Lopez-Sendon JL. Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. *Eur J Heart Fail* 2008;**10**:140–148.
3. Parissis JT, Mantziari L, Kaldoglou N, Ikonomidis I, Nikolaou M, Mebazaa A, Altenberger J, Delgado J, Vilas-Boas F, Paraskevaidis I, Anastasiou-Nana M, Follath F. Gender-related differences in patients with acute heart failure: management and predictors of in-hospital mortality. *Int J Cardiol* 2013;**168**:185–189.
4. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, Alhabib KF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A, Network G. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017;**19**:201–208.
5. Regitz-Zagrosek V, Brokat S, Tschope C. Role of gender in heart failure with normal left ventricular ejection fraction. *Prog Cardiovasc Dis* 2007;**49**:241–251.
6. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten Cate H, Nilsson PM, Huisman MV, Stam HC, Eizema K, Stramba-Badiale M. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J* 2011;**32**:1362–1368.
7. Vitale C, Fini M, Spoletini I, Lainscak M, Seferovic P, Rosano GM. Under-representation of elderly and women in clinical trials. *Int J Cardiol* 2017;**232**:216–221.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.

10. Kajimoto K, Minami Y, Sato N, Otsubo S, Kasanuki H. Acute decompensated heart failure syndromes r. gender differences in left ventricular ejection fraction and outcomes among patients hospitalized for acute decompensated heart failure. *Am J Cardiol* 2017;**119**:1623–1630.
11. Meyer S, van der Meer P, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, Cleland JGF, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL, Voors AA. Sex-specific acute heart failure phenotypes and outcomes from PROTECT. *Eur J Heart Fail* 2013;**15**:1374–1381.
12. Teixeira A, Parenica J, Park JJ, Ishihara S, AlHabib KF, Laribi S, Maggioni A, Miro O, Sato N, Kajimoto K, Cohen-Solal A, Fairman E, Lassus J, Mueller C, Peacock WF, Januzzi JL, Jr., Choi DJ, Plaisance P, Spinar J, Mebazaa A, Gayat E; on behalf of the GREAT (Global Research on Acute Conditions Team) Network. Clinical presentation and outcome by age categories in acute heart failure: results from an international observational cohort. *Eur J Heart Fail* 2015;**17**:1114–1123.
13. Akiyama E, Van Aelst LNL, Arrigo M, Lassus J, Miró Ò, Čelutkienė J, Choi D-J, Cohen-Solal A, Ishihara S, Kajimoto K, Laribi S, Maggioni AP, Motiejunaite J, Mueller C, Parenica J, Park JJ, Sato N, Spinar J, Zhang J, Zhang Y, Kimura K, Tamura K, Gayat E, Mebazaa A, Network G. East Asia may have a better 1-year survival following an acute heart failure episode compared with Europe: results from an international observational cohort. *Eur J Heart Fail* 2018;**20**:1071–1075.
14. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail* 2013;**15**:928–936.
15. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy C, Young JB; OPTIMIZE-HF Investigators and Hospitals. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). *Am J Cardiol* 2009;**104**:107–115.
16. Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. *Physiol Rev* 2017;**97**:1–37.
17. Zannad F, Mebazaa A, Juilliere Y, Cohen-Solal A, Guize L, Alla F, Rouge P, Blin P, Barlet MH, Paolozzi L, Vincent C, Desnos M, Samii K; EFICA Investigators. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. *Eur J Heart Fail* 2006;**8**:697–705.
18. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
19. Zsilinszka R, Shrader P, DeVore AD, Hardy NC, Mentz RJ, Pang PS, Peacock WF, Fonarow GC, Hernandez AF. Sex differences in the management and outcomes of heart failure with preserved ejection fraction in patients presenting to the emergency department with acute heart failure. *J Cardiac Fail* 2016;**22**:781–788.
20. Galvao M, Kalman J, DeMarco T, Fonarow GC, Galvin C, Ghali JK, Moskowitz RM. Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Cardiac Fail* 2006;**12**:100–107.
21. Greene SJ, Hernandez AF, Dunning A, Ambrosy AP, Armstrong PW, Butler J, Cerbin LP, Coles A, Ezekowitz JA, Metra M, Starling RC, Teerlink JR, Voors AA, O'Connor CM, Mentz RJ. Hospitalization for recently diagnosed versus worsening chronic heart failure: from the ASCEND-HF Trial. *J Am Coll Cardiol* 2017;**69**:3029–3039.
22. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola VP, Drexler H, Dickstein K, Tavazzi L, Nieminen M. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2008;**30**:478–486.
23. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail* 2010;**12**:239–248.
24. Filippatos GA, Cleland JGF, Lam CS, Dahlström U, Dickstein K, Ertl G, Hassanein M, Hart KW, Hu D, Lindsell CJ, Perrone SV, Guerin T, Ghadanfar M, Schweizer A, Obergfell A, Collins SP. Global differences in characteristics, precipitants and initial management of patients presenting with acute heart failure: an analysis of 18,553 patients from REPORT-HF. *JAMA Cardiol* 2019.
25. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Matsukawa R, Kato K, Suzuki S, Naruke T, Yoshioka K, Miyoshi T, Baba Y, Yamamoto M, Murai K, Mizutani K, Yoshida K, Kitai T. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol 2017;69:3042-3051*.
26. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet* 2017;**389**:1323–1335.