Sex differences in heart failure

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Chapter 5

Sex-specific acute heart failure phenotypes and outcomes from PROTECT.

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Abstract

Aims

Differences in manifestation, treatment, and outcomes of acute heart failure between men and women have not been well studied. The objective of this analysis was to characterize differences in clinical presentation, and in-hospital and post-discharge outcomes between sexes in acute heart failure patients.

Methods and results

Clinical profiles, treatment characteristics, and outcomes were compared between sexes in 2033 patients hospitalized for acute heart failure and impaired renal function. Women comprised 33% of the study population and were older, had higher body mass index, LVEF, and systolic blood pressure, and a greater prevalence of diabetes. At baseline, women showed signs and symptoms of congestion comparable with men, but more often had rales, orthopnoea, and worse renal function. Women were less intensively diuresed, as indicated by lower oral and intravenous diuretic doses used, fewer dose increases, and less total weight loss during hospitalization. Furthermore, hospitalization was slightly but significantly prolonged in women (11.04 ± 7.8 vs. 10.65 ± 8.86 days; P = 0.024). Age-adjusted 180-day mortality was lower in women (15.8% vs. 18.5%, hazard ratio 0.74; 95% confidence interval 0.59-0.93, P = 0.010), but multivariable risk-adjusted mortality was similar in both sexes, mainly attributable to lower blood urea nitrogen, higher LVEF, and higher systolic blood pressure in women compared with men.

Conclusions

Women with acute heart failure present with a clinical profile different from that of men, with more hypertension, diabetes, and depression, and a preserved LVEF. During hospitalization, they were less intensively diuresed. Nevertheless, risk-adjusted 180-day outcome was similar between sexes.

Introduction

Women with cardiovascular disease have a distinct clinical manifestation and outcome compared with males.[1] Women less often undergo preventive measures and are underdiagnosed, undertreated, and understudied, although cardiovascular disease is the major cause of death in women above the age of 65 years. Suboptimal care for women with ischaemic heart disease translates into increased morbidity and mortality.[1] In chronic heart failure, the sex-specific outcomes are paradoxical and women consistently show better survival than men.[2] This might be explained by disparities in aetiology and co-morbidities, but differences in the prevalence of LV systolic dysfunction and treatment or response to treatment modalities are also considered as potential explanations for the sex difference in mortality. However, most of the evidence is based on stable outpatients with chronic heart failure and reduced LVEF enrolled in long-term clinical trials.[3] Much less is known about sex differences in acute heart failure.[4,5] Limited registry and survey data show substantial sex differences in baseline characteristics and in-hospital treatment between women and men. However, no mortality difference was found during hospitalization or by 1-year follow-up, when adjusting for these variables.[6–8] There are almost no data available for contemporary populations focusing on patients who are hospitalized with acute heart failure. In addition, no data are available on sex-specific patients' response to in-hospital decongestive treatment regarding signs and symptoms of heart failure. We therefore studied differences in clinical presentation, and in-hospital and post-discharge outcomes in women compared with men admitted for acute heart failure.

Methods

Study design and population

The 'Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion' (PROTECT) was a multicentre,

randomized, placebo-controlled trial in 2033 patients hospitalized with acute heart failure and impaired renal function. Details on the rationale, design, and results have been reported elsewhere.[9,10] Patients with the full continuum of LVEF were enrolled. Eligible patients, showing signs and symptoms of fluid overload with concomitant dyspnoea NYHA III–IV, systolic blood pressure ≥ 95 mmHg, and need for i.v. diuretic therapy were enrolled within 24 h of presentation.

Ethics

The study met all requirements of local Ethics Committees and complied with the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients.

Endpoints

We analysed the original primary endpoint of PROTECT and its individual components. The original primary endpoint of PROTECT was trichotomous, evaluating treatment response by success, unchanged status, or failure. Treatment success was defined by rapid symptom improvement within 48 h, treatment failure was defined as symptom recurrence indicative of worsening heart failure, persistent renal impairment, and death, during 7 days, and unchanged status referred to neither of these. Treatment success was assessed via patient-reported moderate or marked improvement in dyspnoea within 48 h compared with study start, measured by a 7-point Likert scale. Notably, persistent renal impairment was defined as an increase in serum creatinine ≥ 0.3 mg/dL from randomization to day 7, confirmed at day 14, or the initiation of haemofiltration or dialysis by day 7.

We additionally analysed the original secondary endpoints of PROTECT, i.e. the proportions of patients with persistent worsening renal function, defined as an increase in serum creatinine ≥ 0.3 mg/dL from randomization to day 7 confirmed at day 14, and readmission for cardiovascular or renal

cause or death within 60 days after the start of study intervention, as adjudicated by an independent clinical endpoint committee.

For the present study, we also analyzed the 180-day mortality, which was a safety endpoint of the study, and health status, which was assessed using the EQ-5D questionnaire at day 14.

Statistical analyses

Mean ± SD or medians with interquartile range refer to continuous variables. Counts and percentages denote categorical variables. Student's t-test or Mann–Whitney test, as appropriate, were used for comparisons of continuous variables; the $\chi 2$ test was used for analysis of categorical variables. Univariable and multivariable Cox proportional hazards regressions were used to analyse the association between sex and 180-day mortality and covariates.

First, univariable analyses were performed, assessing the association of individual covariates with 180-day mortality and additionally adjusting for age when analysing the sex effect on outcome.

Secondly, multivariable Cox models were fitted using the two-sided significance threshold of $P < 0.1$ for entry in the models. In a first multivariable model (Model 1), the influence of all univariable outcome-related covariates on the risk-predictive value of sex on 180-day mortality was assessed. In addition, another multivariable model (Model 2) was used, adjusting for a priori confounders, which have previously been appraised in the PROTECT population.

Model 1 comprises the following covariates with age-adjusted univariate outcome relationship ($P < 0.1$): age, weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, LVEF, oedema, ischaemic heart disease, myocardial infarction, peripheral vascular disease, depression,

CRT, implantable cardioverter defibrillator (ICD), ACE inhibitor, ARB, beta-blocker, calcium antagonists, creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), total cholesterol, sodium, and hyponatraemia.

Model 2, the pre-established PROTECT risk model, comprises: age, creatinine, BUN, serum albumin, sodium, bicarbonate, glucose, systolic blood pressure, pulmonary rales, NYHA class 1 month before admission, and previous heart failure hospitalization.

Statistical analyses were performed using STATA (version 11.0, STATA Corp, College Station, TX, USA) and R (version 2.15.1, R Foundation for Statistical Computing, Vienna, Austria) software. A two-sided P-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The proportion of women in PROTECT was 33% (669 of 2033 patients). Table 1 provides a detailed overview of the sex distribution of baseline characteristics.

Table 1

Baseline characteristics

	Men (*n* = 1364)	Women (*n* = 669)	*P*-value
Demographics and measurements			
Age, mean ± SD, years	69 ± 12	73 ± 11	<0.001
Weight, kg	85 ± 19	75 ± 18	<0.001
BMI, mean ± SD, kg/m^2	29 ± 6	29 ± 7	0.008
SBP, mean ± SD, mmHg	123 ± 18	127 ± 17	<0.001
DBP, mean ± SD, mmHg	74 ± 12	74 ± 12	0.964
LVEF, mean ± SD, %	30 ± 12	37 ± 14	<0.001
HFpEF, *n* (%)	11	28	<0.001
Signs and symptoms of HF (%)			
Orthopnoea	95	97	0.04
Rales	89	93	<0.001
Oedema	86	86	0.961
JVP	89	87	0.209
History (%)			
Ischaemic heart disease	72	66	0.012
Myocardial infarction	53	43	<0.001
Diabetes	43	50	0.007
Hypertension	76	86	<0.001
COPD	21	16	0.009
Smoking	27	9	<0.001
Peripheral vascular disease	12	8	0.002
Atrial fibrillation	55	54	0.645
Stroke	9	9	0.898
Depression	6	9	0.006
Pacemaker	12	13	0.295
CRT	12	6	<0.001
ICD	20	9	<0.001
Medication (%)			
ACE inhibitor	58	62	0.177
ARB	13	11	0.223
ACEi or ARB (%)	70	72	0.389
Beta-blocker (%)	69	68	0.672
Aldosterone antagonists (%)	47	43	0.074
Calcium antagonists (%)	8	14	<0.001
Laboratory values			
Creatinine, mg/dL	1.5 (1.2–1.9)	1.2 (1.0–1.5)	<0.001
eGFR, mL/min/1.73 m^2	51 (38–66)	42 (32–55)	<0.001
BUN, mg/dL	31 (23–42)	27 (21–39)	<0.001
Total cholesterol, mmol/L	142 ± 42	157 ± 47	<0.001
Sodium, mmol/L	140 (137–142)	140 (137–143)	0.001
Hyponatraemia, %	2	2	0.924

BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; SBP, systolic blood pressure.

The analysis of demographic and clinical characteristics showed that women were on average 4.9 years [95% confidence interval (CI) 3.9–6.0 years] older (P < 0.001), had 0.8 kg/m2 (95% CI 0.2–

1.4 kg/m2) greater BMI (P = 0.008), 7% (95% CI 5.5–9.0 %) higher LVEF (P <0.001), and 4.4 mmHg (95% CI 2.8–6.0 mmHg) higher systolic blood pressure (P < 0.001), respectively, and they more frequently suffered from diabetes (P = 0.007) and depression (P < 0.007). Men more often had a history of ischaemic heart disease (P = 0.012) and myocardial infarction (P < 0.001) with more pre-existing congestive heart failure (P = 0.045) and respective previous hospitalizations (P = 0.004). Men had higher treatment rates with ICDs (P < 0.001) and biventricular pacemakers (P < 0.001). In women, calcium antagonists were more frequently used (P < 0.001).

Women showed signs and symptoms of congestion comparable with men, but more women had rales and suffered from orthopnoea (P < 0.001 and P = 0.040, respectively).

Women had consistently lower values than men in eGFR and BUN (all P < 0.001). Serum sodium was slightly higher in women (P = 0.004), whereas the proportion in hyponatraemia was equally distributed.

In-hospital treatment characteristics and clinical outcomes

Despite a comparable prevalence of peripheral oedema and elevated jugular venous pressure, women were treated with lower oral and i.v. diuretic doses and fewer dose increases. The administered dose of furosemide per kg weight change in women vs. men was 90.8 mg vs. 150.1 mg, respectively (P = 0.059). This was associated with 0.5 (95% CI 0.2–0.8) kg less total weight loss during hospitalization compared with men (P = 0.002). Treatment rates of renal replacement therapy comprising ultrafiltration, peritoneal dialysis, or haemodialysis did not differ between both sexes. Likewise, there were no differences regarding i.v. vasoactive treatment using inotropes, vasopressors, or vasodilators up to day 7.

Women more often showed improvement from rales than men (P = 0.006), but no different improvement rates could be detected for oedema, elevated jugular venous pressure, orthopnoea, and general well-being between both sexes.

When the changes in laboratory values were assessed between day 1 and 7, women had a comparable drop in eGFR. BUN increased more in female patients (P = 0.003), an effect that was also seen for total cholesterol (P = 0.001).

Hospitalization was slightly but significantly prolonged in women (P = 0.024) compared with men. No differences in medical therapy were observed at discharge or day 7, if earlier; except for calcium channel blockers, that were more often used in women.

Details of in-hospital treatment characteristics are shown in Table 2.

Table 2

Treatment and treatment response

	Men (n = 1364)	Women (n = 669)	P-value
Change of weight from day 1 to day 4 (kg)			
Weight loss	2.6 (1.1–4.5)	2.0 (4.0–1.0)	0.002
Symptoms of heart failure at day 7 (%)			
Improvement in orthopnoea	77	79	0.327
Improvement in dyspnoea	78	80	0.454
Improvement in well-being	77	78	0.779
Change in signs of heart failure at day 7 (%)			
Improvement in rales	81	87	0.006
Improvement in oedema	77	78	0.692
Improvement in JVP	75	72	0.269
Healthcare status at day 14 (EQ-5D™; no/some/absolute limitation, %)			
Mobility	38/58/4	25/71/4	<0.001
Self-care	65/30/5	46/47/6	<0.001
Usual activities	40/47/13	25/59/16	<0.001
Pain/discomfort	57/40/3	45/50/5	<0.001
Anxiety/depression	65/32/3	55/40/4	<0.001
Diuretics			
I.v. loop diuretics total dose (mg)			
Day 1	80 (40–160)	80 (40–120)	0.068
Day 7	120 (60–200)	80 (40–161)	0.063
Day 1	60 (40–80)	40 (40–80)	0.002
Day 7	80 (40–120)	60 (40–80)	<0.001
Oral loop diuretics total dose (mg)			
Total dose of diuretics, days 1–7	460 (280–820)	366 (240–610)	<0.001
Diuretic dose increase, days 1–7	360 (200–660)	270 (160–480)	<0.001
Medication at discharge or day 7, if earlier (%)			
ACE inhibitor	67	71	0.074
ARB	17	15	0.314
ACE inhibitor or ARB	81	85	0.055
Beta-blocker	85	83	0.143
Aldosterone antagonists	61	58	0.141
Calcium antagonists	10	16	<0.001
Change in laboratory values, baseline to day 7			
Creatinine, mg/dL	0 (−0.2 to 0.2)	0 (− 0.1 to 0.2)	0.124
eGFR, mL/min/1.73 m^2	−1.6 (−7.7 to 5.1)	−2.2 (−8.2 to 4.5)	0.301
BUN, mg/dL	2 (−4 to 10)	4 (−2 to 12)	0.002
Total cholesterol, mmol/L	6 (−8 to 22)	10 (−6 to 30.2)	0.001
Sodium, mmol/L	−1 (−3 to 1)	−1 (−4 to 1)	0.478

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; JVP, jugular venous pressure.

In-hospital and post-discharge outcomes are summarized in Table 3.

Table 3

In-hospital and post-discharge outcomes

	Men (n = 1364)	Women (n = 669)	P-value
Primary endpoint, %			
Trichotomous endpoint			0.705
Success	38	40	
Unchanged	40	39	
Failure	21	20	
Individual components of the primary endpoint, %			
Improvement in dyspnoea[a]	49	54	0.055
Treatment failure criteria (up to day 7)			
Creatinine increase	12	13	0.399
Persistent renal impairment	12	14	0.378
Worsening heart failure	10	8	0.193
Rehospitalization for heart failure	0	0	0.978
Death	2	2	0.951
Secondary endpoint, %			
Death or cardiovascular or renal rehospitalization within 60 days	30	27	0.168
Additional endpoints, %			
Length of hospital stay, days	10.65 $\pm$ 8.86	11.04 $\pm$ 7.8	0.024
Event-free[b] days	61 (57–63)	61 (58–63)	0.544
Heart failure rehospitalization or death at 60 days	23	20	0.132
Survival days	180 (178–180)	180 (178–180)	0.800
Mortality at 180 days	18	16	0.143

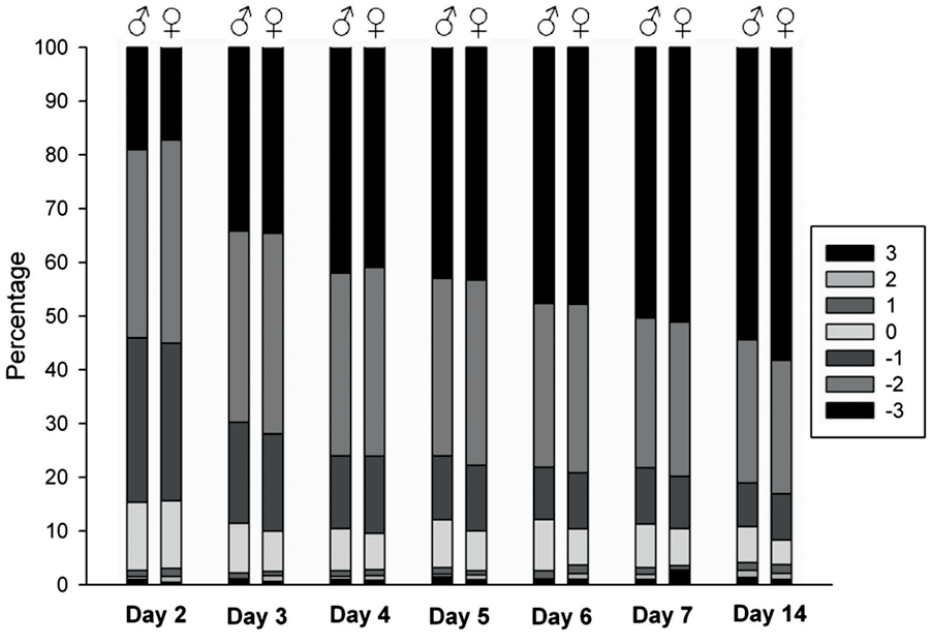
[a] Improvement in dyspnoea is defined as dyspnoea moderately or markedly improved on both days 2 and 3
[b] Events comprise heart failure rehospitalization or death.

Primary endpoint

No differences between the sexes regarding the trichotomous primary endpoint were detected by day 7. Correspondingly, improvement in dyspnoea, as defined by reaching moderate or marked improvement in a 7-point Likert scale, was comparable between women and men. The change in dyspnoea by day and sex group is shown in Figure 1. Treatment failure rates also did not differ between women and men by day 7, neither in terms of worsening renal function measures nor in terms of worsening heart failure or related rehospitalization or death.

Figure 1

Change in dyspnoea by day and sex group



Dyspnoea was quantified using the Likert scale:
-3 markedly worse; -2 moderately worse -1 minimally worse; 0 no change;
1 minimally better; 2 moderately better; 3 markedly better.

Secondary endpoints

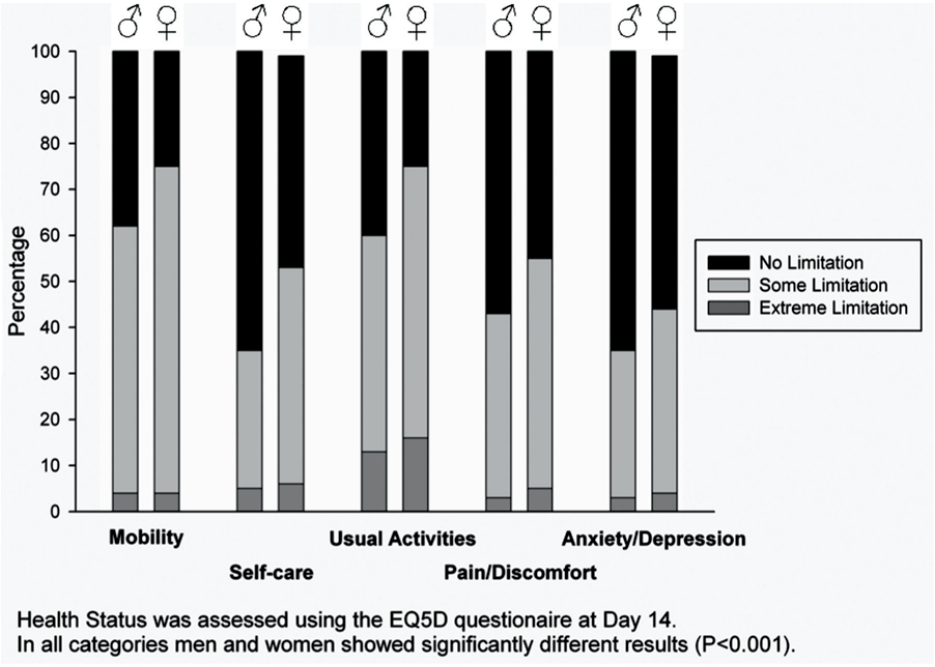
No differences were seen in readmissions and deaths or time to death or cardiovascular or renal rehospitalization up to day 60 between the sexes. Also, the proportion of patients who developed persistent renal impairment did not differ between women and men.

Additional endpoints

Women showed more limitation than men in all categories of the EQ-5D health status at day 14 ($P < 0.001$). Figure 2 shows the health status by category and sex group.

Figure 2

Health status by category and sex group



Age-adjusted 180-day mortality was lower in women [15.8% vs. 18.5%, hazard ratio (HR) 0.74; 95% CI 0.59–0.93, P = 0.010], but multivariable risk-adjusted mortality was similar in both sexes using different analytic approaches [Model 1 (univariate predictors), HR 0.84; 95% CI 0.53–1.34, P = 0.466; Model 2 (pre-established PROTECT risk model), HR 0.87; 95% CI 0.50–1.51, P = 0.615], which was mainly attributable to lower BUN, higher LVEF, and higher systolic blood pressure in women compared with men.

Discussion

This study demonstrates that women hospitalized with acute heart failure and impaired renal function more often have typical co-morbidities, and undergo less aggressive decongestion therapy than males, but the outcome is similar. The age-adjusted beneficial impact of female sex on 180-day mortality seems explainable by lower BUN, higher LVEF, and higher systolic blood pressure in women.

Unique aspects of acute heart failure and the PROTECT study

Whereas sex differences in chronic heart failure have been studied extensively over the last years,[3] far less is known about studies in the contemporary setting of acute heart failure. PROTECT allowed for analysis of the in-hospital journey of patients with symptomatic congestion and underlying renal dysfunction, who are known for their major symptomatic burden and mortality risk. In addition, PROTECT provided details on the change in laboratory data, symptom perception, and signs of heart failure, as well as patients' self-reported health status. Congestion and impaired renal function have well-known adverse effects on mortality,[11,12] but sex differences in treatment and response to decongestive therapy are insufficiently studied. This applies particularly for endpoints involving changes in signs and symptoms of heart failure, clinical status, and renal function.

Baseline disease differences

Overall, 95% of patients in PROTECT had a history of congestive heart failure, revealing acute decompensation of chronic heart failure to be by far the most common cause of hospitalization. Women showed typical demographic and clinical characteristics: they were older, and had higher BMI, LVEF, and systolic blood pressure. This pattern has consistently been reported in many studies as characteristic for women with heart failure,[6,7,13] usually manifesting as heart failure with preserved

ejection fraction (HFpEF), in comparison with the typical male phenotype, which basically refers to post-myocardial infarction heart failure with reduced ejection fraction (HFrEF).

In addition, women more frequently suffered from diabetes and had worse health-related quality of life. Among men, ischaemic heart disease and myocardial infarctions were the main aetiological factors for heart failure, which correspond to higher frequencies of pre-existing heart failure and more previous hospitalizations in men than in women. These relationships are in accordance with other studies[2,6–8] and reflect the natural sex difference in cardiovascular risk, which constitutes a relatively lower cardiovascular risk in pre-menopausal women, leading to later onset of systolic heart failure in women compared with men.[14]

With regard to symptoms and signs of heart failure, women more frequently showed pulmonary rales and perceived orthopnoea. This reflects a higher female symptomatic burden and an increased occurrence of pulmonary congestion in women with acute heart failure, matching the results from ADHERE, a US registry in 105 388 patients hospitalized for acutely decompensated heart failure.[6] Pathophysiologically, these findings may be explained by the typical female phenotype with rapid fluid redistribution and a higher prevalence of LV diastolic dysfunction and consecutive HFpEF. Borlaug et al. demonstrated elevated filling pressures to be the causal mechanism of cardiac dyspnoea in patients with HFpEF.[15] Hypervolaemia is frequently present in non-oedematous patients with chronic heart failure, being associated with increased cardiac filling pressures and worse patient outcomes.[16]

Treatment and response to therapy

Treatment rates with rolofylline and other vasoactive agents were similar between women and men, but significant differences in the usage and effect of diuretics were detected between women and

men. Women received lower oral and i.v. diuretic doses, fewer dose increases, had less total weight loss during hospitalization, and had a slightly increased length of hospital stay. These results could indicate undertreatment but may, more probably, simply reflect greater diuretic effectiveness in terms of weight and symptom reduction in women compared with men. However, this question cannot be definitely answered in our study, since in practice both of the latter criteria influence dose adjustments of diuretics, and no protocol for diuretic dose adjustments had to be followed in PROTECT. Generally, sex differences are common in everyday clinical practice in patients with heart failure. The EuroHeart Failure Survey II[7] reported on 3580 acute heart failure patients revealing typical differences in the usage of catheterization and inotropic agents, but no covariate-adjusted differences in use of cardiovascular medication, including diuretics. ADHERE[6] demonstrated comparable rates of i.v. diuretic use but a lower mean duration of such therapy in women. This translated into less in-hospital weight loss in women compared with men. Women also typically underwent fewer invasive procedures such as cardiac catheterizations and were less frequently treated with vasoactive agents, which is explainable by higher female prevalence of HFpEF. In PROTECT, women exhibited more compromised renal function than men at baseline. The reasons for this difference in PROTECT is unclear, but may, most probably, be explained by the natural sex difference in renal mass and relevant co-morbidity, such as hypertension and diabetes, in women. Lower eGFR values were seen in women despite higher blood pressures and a natural protective effect of female sex in chronic kidney disease of various origins.[17,18] Despite worse renal function in women, we observed lower mean BUN values in women compared with men. BUN is generally considered as a surrogate marker of neurohormonal activation in heart failure patients, and higher BUN values are mechanistically related to worsening GFR.[19] Elevated BUN was also related to increased mortality in several studies,[6,20,21] and has previously been proven to be the strongest predictor of short-term morbidity and mortality in PROTECT.[22] Because of these relationships, our observations of lower mean BUN values in women than men are remarkable, given the lower mean

GFR in women. This suggests a differential increase in BUN between men and women, a finding which is similar to that in the ADHERE population.[6] A trend for interaction of sex with the BUN association with mortality was suggested (P for interaction = 0.096).

Study limitations

This study needs a cautious interpretation, as required for retrospective subgroup analyses per se. The PROTECT study had not primarily been designed for analyses of sex differences, and thus no sufficient power is warranted. PROTECT was a prospective placebo-controlled randomized study, which are by nature known to be affected by selection bias limiting generalizability. Cardiac imaging for assessment of ventricular function was not mandatory for inclusion in PROTECT, consequently a categorization into heart failure with reduced vs. preserved LV function is limited by incomplete data availability. NT-proBNP measurements were technically restricted to an upper range of 3000 pg/mL and assessed in 1518 patients, whereas BNP levels were measured in 537 patients, which limits the overall interpretation of natriuretic peptides. Data on oestrogen levels or menopause are lacking and prevent consideration of these biological factors. Long-term follow-up beyond 180 days is not available and limits characterization of long-term effects. This exploratory and hypotheses-generating study is based on biological subgroup classification.

Conclusion

Women with acute heart failure present with a clinical profile different from men. They have a distinct disease entity with typical co-morbidities involving hypertension, diabetes, and depression, but more preserved LVEF. Nevertheless, risk-adjusted 180-day outcome is similar between both sexes.

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