



Symptom patterns and clinical outcomes in women versus men with systolic heart failure and depression

Sven M. Piepenburg^{1,2} · Hermann Faller³ · Stefan Störk¹ · Georg Ertl¹ · Christiane E. Angermann¹

Received: 22 May 2018 / Accepted: 31 July 2018 / Published online: 10 August 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Background Depression is more common in females than in males and is 3–5 times more prevalent in patients with heart failure (HF) than in the general population. The 9-item Patient Health Questionnaire (PHQ-9) is a validated depression screening instrument; higher sum-scores predict adverse clinical outcomes. Sex- and gender differences in PHQ-9 symptom profile, diagnostic and prognostic properties, and impact on health-related quality of life (HRQOL) have not been comprehensively studied in HF patients.

Methods and results This post hoc analysis from the Interdisciplinary Network Heart Failure program enrolled 852/1022 participants (67 ± 13 years, 28% female) who completed the PHQ-9 at hospital discharge after cardiac decompensation. All had a left ventricular ejection fraction $\leq 40\%$. Women had a higher mean PHQ-9 sum-score than men (8.4 ± 5.6 vs. 7.4 ± 5.5 ; $p = 0.027$), and higher proportions rated the following items ≥ 2 (i.e., present on $\geq 50\%$ of days): ‘feeling down, hopeless’ (25.8 vs. 18.0%; $p = 0.011$); ‘fatigue’ (51.9 vs. 37.2%; $p < 0.001$); and ‘trouble concentrating’ (21.6 vs. 15.4%; $p = 0.032$). A PHQ-9 sum-score ≥ 10 predicted increased mortality in women [hazard ratio 1.91 (95% confidence interval 1.06–3.43); $p = 0.030$] and men [2.10 (1.43–3.09); $p < 0.001$] and was associated with worse HRQOL ($p < 0.001$ for all comparisons). Sum-scores ≥ 10 predicted higher re-hospitalization rates in men only [1.35 (1.08–1.69); $p = 0.008$].

Conclusions Differences in several PHQ-9 items indicated sex- or gender-specific depression symptomatology in HF. For both sexes, HRQOL and survival were worse when PHQ-9 sum-score was ≥ 10 , but higher sum-scores predicted higher re-hospitalization rates in men only. Considering these specific aspects might help optimize care strategies in HF.

Keywords Heart failure · Depression · Sex · Mortality · Morbidity

Introduction

Increasing longevity in industrialized countries and better treatment of acute cardiovascular conditions contribute to increases in heart failure (HF) prevalence. Although the

lifetime risk of HF appears comparable in elderly women and men [1], HF phenotype and age of HF onset differ between sexes with women surpassing male prevalence rates when older than 75 years. Furthermore, baseline risk factors and predominant HF aetiologies vary between sexes, with possible differential impact on prognosis [2]. For example, diabetes has been shown to be a stronger risk factor for HF in women [3], who are also at higher risk of developing HF in the presence of hypertension [4]. In the past, women have been under-represented in most HF treatment trials [5]. Therefore, evidence on whether females respond differently from males to HF therapies is limited, and sex-specific mortality data from large clinical trials are inconsistent [2, 6]. Remarkably, patient sex was not considered even in the most recent systematic review of the main mechanisms of action of HF disease management interventions [7].

In the general population, depression is more common in women than in men [8]. It has been suggested that this

Sven M. Piepenburg, Hermann Faller contributed equally.

✉ Christiane E. Angermann
Angermann_c@ukw.de

¹ Department of Medicine I, Comprehensive Heart Failure Center, University Hospital and University of Würzburg, Am Schwarzenberg 15, 97078 Würzburg, Germany

² Department of Cardiology and Angiology I, Heart Center, University Hospital Freiburg, Freiburg, Germany

³ Department of Medical Psychology, Medical Sociology and Rehabilitation Sciences, University of Würzburg, Würzburg, Germany

difference might mainly be due to higher rates of sleep and appetite disorders and fatigue (‘somatic’ depressive symptoms) in women, while sex differences in other criteria, such as loss of interest or guilt (termed ‘pure’ depressive symptoms by the authors), were found to be much smaller [9]. In HF, depression is one of the most common comorbidities, affecting 20–40% of patients depending on HF severity, and prevalence rates are also higher in females [10]. Sex difference data are not consistent, however. For example, Heo et al. found in HF patients that only in women functional status measured by the New York Heart Association (NYHA) class mediated the effects of depression on HRQOL, while in men depression affected HRQOL in multivariable analysis [11]. When investigating predictors of depression, Eastwood et al. showed that correlates differed between sexes, with financial status, functional capacity, health perception and anxiety constituting major determinants in men, while body mass index, perceived control and anxiety were associated with depression in women [12]. When the 9-item Patient Health Questionnaire (PHQ-9) [13] was employed to assess depressive symptom patterns in patients with coronary disease, only minor gender differences were observed [14].

The PHQ-9 is often used in patients with cardiovascular disorders, and recommended by the American Heart Association for depression screening [15]. PHQ-9 items reflect Diagnostic and Statistical Manual of Mental Disorder (DSM) depression criteria. The PHQ-9 sum score is a powerful predictor of prognosis in HF patients, with adverse clinical outcome rates proportional to symptom severity [16–18].

To our knowledge, no studies have so far focused specifically on sex differences in single item PHQ-9 scores in patients with HF, and it is unknown whether the prognostic impact of PHQ-9-assessed depressive symptoms varies between women and men. This study sought to clarify to what extent differences in HF characteristics between sexes are accompanied by emotional differences, and whether depressive symptoms relate to clinical outcomes differentially in women versus men. We, therefore, compared baseline demographics, clinical features, laboratory findings, and depressive symptom patterns according to the PHQ-9 between female and male patients hospitalized for acute systolic HF and undergoing psychometric assessment before discharge. Sex differences in the relationship of depression with death and re-hospitalization rates over 540-days’ follow-up and with HRQOL were also investigated.

Methods

Study flow

The Interdisciplinary Network Heart Failure (INH) program (ISRCTN 23325295) evaluated telephone-based,

nurse-coordinated disease management (*HeartNetCare-HF™*) after discharge compared with usual care in patients hospitalized for cardiac decompensation [19]. Of 1022 consecutive participants recruited at nine hospitals, 852 completed the PHQ-9 at baseline and qualified for this post hoc analysis. Eligibility criteria were the same as in the primary INH Study, including a left ventricular ejection fraction (LVEF) $\leq 40\%$ at discharge [19]. All responsible ethics committees approved the INH study protocol, and the investigation conforms with the principles outlined in the Declaration of Helsinki.

Follow-up was centralized and performed 6-monthly either during an outpatient visit or using a structured telephone interview. No patient was lost to follow-up. Medical records were used to track hospital readmissions, and death certificates to ascertain the date of death in deceased patients.

Baseline examination

All participants underwent standardized clinical evaluation before discharge. In addition to psychometric assessment, medical history, physical examination, electrocardiogram, routine laboratory testing, and standardized echocardiography were recorded.

Depressive symptoms were assessed using the PHQ-9 (German version) [13]. The questionnaire asks how often nine of the most important symptoms of depression according to DSM criteria were present in the past fortnight. Possible answers are ‘not at all’, ‘several days’, ‘more than half the days’, and ‘nearly every day’. Each PHQ-9 item yields a score of 0–3 (sum-score 0–27), with higher values indicating more severe depression.

HRQOL was measured using the German version of the Kansas City Cardiomyopathy Questionnaire (KCCQ) [20], a 23-item self-assessment questionnaire (score range, 0–100), with higher scores indicating better HRQOL.

Statistical analyses

Baseline demographics, physical status, symptoms and diagnostic variables were compared between sexes, and in subgroups with and without depression (PHQ-9 sum-score ≥ 10 and > 10 , respectively) using Student’s *t* test, Mann–Whitney *U* test or Pearson Chi-square test as appropriate. Mean PHQ-9 sum-scores and the proportion of patients with clinically relevant score elevation on each individual PHQ-9 item (≥ 2 , indicating symptom presence on $\geq 50\%$ of days) were also compared. Analyses were repeated for both sexes in the non-depressed and depressed subgroups.

Cox proportional hazard regression analysis was used to identify differences in all-cause mortality and re-hospitalization risk between depressed and non-depressed patients of

both sexes. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated, and Kaplan–Meier curves created. Associations between continuous PHQ-9 sum-scores and clinical outcome variables were assessed. Event-free patients were censored at 540 days. To study relationships between depression, sex and HRQOL, we used linear regression analysis with depression, sex and their interaction as independent variables and HRQOL as the dependent variable. IBM SPSS version 23.0 software (Armonk, NY) was used. A two-tailed p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics overall and by sex are detailed in Table 1. The majority of participants were male (71.4%). Women were significantly older and half of them were living alone compared with $< 20\%$ of men. Coronary artery disease (CAD) was the most common HF aetiology in both sexes, but ischemic HF was significantly less common in women. Various comorbidities were significantly more prevalent in women, who had also more severe HF symptoms, higher PHQ-9 sum-scores, used more antidepressants and had worse HRQOL.

Table 2 compares baseline characteristics for non-depressed and depressed patients by sex. Diabetes, anaemia, higher heart rate, lower blood pressure, higher high-sensitivity C-reactive protein levels, greater use of diuretics and less use of beta-blockers were linked with depression in men only. History of depression, more severe HF symptoms, higher amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and worse HRQOL were associated with depression in both sexes. Depressed women were less frequently taking renin–angiotensin–aldosterone blockers and received the *HeartNetCare-HF*TM intervention less often, a trend also observed in men.

Depression profiling

Figure 1A shows proportions of patients with clinically relevant scores (≥ 2 , indicating symptom presence on $\geq 50\%$ of all days) for individual PHQ-9 items. Except for item 8 ('psychomotor disturbance'), more women scored items ≥ 2 . The difference between sexes reached statistical significance for items 2 ('feeling down, depressed or hopeless'), 4 ('fatigue') and 7 ('trouble concentrating'). Women also had a higher mean PHQ-9 sum-score than men (8.4 ± 5.6 vs. 7.4 ± 5.5 ; $p = 0.027$).

In non-depressed patients, higher proportions of men scored items 1 ('loss of interest') and 8 ('psychomotor

disturbance') ≥ 2 , while significantly more women experienced item 4 ('fatigue') on $\geq 50\%$ of days (Fig. 1B). For depressed patients, proportions of scores ≥ 2 were similar in women and men except that significantly more men experienced item 8 ('psychomotor disturbance') on $\geq 50\%$ of days (Fig. 1C).

Clinical outcomes

Forty-five women (19.1%) and 104 men (16.9%) died during follow-up. Cumulative survival rates in women and men with and without depression are shown in Fig. 2A. Mortality risk was comparable between sexes, but mortality was higher in subjects with versus without depression [26.1% and 25.3% for depressed women and men versus 14.6% and 12.6% for non-depressed women and men; corresponding HR values, 1.91 (95% CI 1.06–3.43; $p = 0.030$) and 2.10 (95% CI 1.43–3.10; $p < 0.001$)], respectively. The PHQ-9 sum-score also predicted all-cause mortality risk in both sexes when considered as a continuous variable (women: HR 1.06 per score point, 95% CI 1.01–1.12, $p = 0.014$, and men: HR 1.07 per score point, 95% CI 1.03–1.10, $p < 0.001$).

Similar proportions of patients [346/616 men (56.2%) and 133/236 women (56.4%)] were hospitalized at least once during follow-up. Interestingly, hospitalization rates for women with PHQ-9 sum-scores ≥ 10 and < 10 were comparable (57.6% and 54.3%, respectively; HR 0.95, 95% CI 0.67–1.35, $p = 0.793$), while depressed men were hospitalized significantly more often than non-depressed men (61.9% vs. 53.2%, $p = 0.043$, HR 1.35, 95% CI 1.08–1.69, $p = 0.008$) (Fig. 2b). When PHQ-9 sum-scores were considered as continuous variables, only depressed men had an increased re-hospitalization risk (HR 1.03 per score point, 95% CI 1.02–1.06, $p < 0.001$ vs. HR 1.01, 95% CI 0.98–1.04, $p = 0.71$ in women).

Health-related quality of life

HRQOL was seriously impaired in the overall study population. Irrespective of mood, KCCQ Overall and Clinical Summary Scores were always significantly lower in women, indicating worse HRQOL. Furthermore, there was a major adverse impact of depression on HRQOL in both sexes ($p < 0.001$ for both comparisons) (Fig. 3A, B).

Linear regression analysis revealed that both female sex and PHQ-9 depression had adverse effects on HRQOL (Table 3), but no interaction was apparent. Thus, the effect of depressive symptoms on HRQOL appeared comparable in women and men.

Table 1 Patient characteristics at baseline, overall and by patient sex

	Overall (<i>n</i> =852)	Females (<i>n</i> =236)	Males (<i>n</i> =616)	<i>p</i> value
Age, years	67±13	70±13	66±12	<0.001 ^a
Living alone, <i>n</i> (%)	229 (26.9)	117 (49.6)	112 (18.2)	<0.001 ^b
Heart rate, beats/min	80±19	84±21	78±18	<0.001 ^a
Mean arterial pressure, mmHg	86.7 (80.0–96.7)	86.7 (80.0–96.7)	86.8 (80.0–96.7)	0.750 ^c
Predominant HF aetiology, <i>n</i> (%)				
Coronary artery disease	425 (49.9)	101 (42.8)	324 (52.6)	0.001 ^b
Other	427 (50.1)	135 (57.2)	292 (47.4)	
HF characteristics and biomarkers				
NYHA class III–IV, <i>n</i> (%)	360 (42.3)	126 (53.4)	234 (38.0)	<0.001 ^b
LVEF, % ^d	31.0 (25.0–37.0)	30.0 (25.0–37.0)	31.0 (25.0–36.0)	0.906 ^c
NT-proBNP, pg/mL	2800.5 (1026.0–6545.0)	3639.0 (1377.0–8173.0)	2563.0 (925.5–6220.5)	0.004 ^c
hsCRP, mg/L	8.9 (3.2–23.6)	9.1 (3.5–23.3)	8.7 (3.1–23.8)	0.597 ^c
Comorbidities, <i>n</i> (%)				
COPD	149 (17.5)	40 (16.9)	109 (17.7)	0.798 ^b
Diabetes mellitus	290 (34.0)	97 (41.1)	193 (31.3)	0.007 ^b
Anaemia	273 (32.0)	71 (30.1)	202 (32.8)	0.449 ^b
Hypertension	653 (76.2)	184 (78.0)	469 (71.8)	0.453 ^b
Chronic kidney disease	337 (39.6)	123 (52.1)	214 (34.7)	<0.001 ^b
History of depression	92 (10.8)	45 (19.1)	47 (7.6)	<0.001 ^b
HF treatment, <i>n</i> (%)				
Diuretics	737 (86.5)	210 (89.0)	527 (85.6)	0.190 ^b
Beta-blockers	716 (84.0)	194 (82.2)	522 (84.7)	0.366 ^b
ACE inhibitor/ARB	764 (89.7)	212 (89.8)	552 (89.6)	0.925 ^b
Antidepressants	65 (7.6)	29 (12.3)	36 (5.8)	<0.001 ^b
Allocation to <i>HeartNetCare-HF</i> TM	420 (49.3)	117 (49.6)	303 (49.2)	0.919 ^b
Psychometric assessment				
KCCQ overall summary score	56.8 (38.9–75.0)	47.9 (29.8–65.2)	59.4 (41.9–78.1)	<0.001 ^c
KCCQ clinical summary score	61.5 (42.6–79.7)	54.2 (32.0–70.1)	65.1 (46.3–83.3)	<0.001 ^c
PHQ-9 sum-score	7.7±5.5	8.4±5.6	7.4±5.5	0.027 ^a

Values are mean ± standard deviation, median (interquartile range) or number of patients (%), with percentage based on the number of patients with a non-missing value for that characteristic

ACE angiotensin-converting enzyme, ARB angiotensin-2 receptor blocker, HF heart failure, HNC HeartNetCare-HFTM, hsCRP high-sensitivity C-reactive protein, KCCQ Kansas City Cardiomyopathy Questionnaire, LVEF left ventricular ejection fraction, NT-proBNP amino-terminal pro-brain natriuretic peptide, NYHA New York Heart Association

^aBased on *t* test for continuous variables

^bBased on Chi-square test for categorical variables

^cBased on Mann–Whitney U test for non-normally distributed values

^dMeasured by two-dimensional echocardiography (*n*=859)

Discussion

This study identified significant differences in demographic and HF characteristics and symptom patterns between sexes. Although depressive symptom patterns were similar overall, frequencies of several items differed, indicating diverging symptom perception between women and men. While associations of PHQ-9 sum-scores with the risk of all-cause death were comparable between sexes, men showed a link between depressed mood and higher re-hospitalization risk, whereas women did not.

Less than 30% of our study sample were female, although epidemiological data show that more than half of German HF patients are women [21]. Lower enrolment rates in clinical trials may be at least partly due to greater prevalence of HFpEF among women, making them ineligible for studies with reduced LVEF as an inclusion criterion [2]. Existing evidence suggests a specific female HF phenotype, and that baseline risk may, outside the development of HF, impact differentially on prognosis in both sexes [2]. Similar to findings from the Italian Network on CHF [22] and from pharmacological trials in HFpEF

Table 2 Patient characteristics at baseline, by patient sex and presence (PHQ-9 sum-score ≥ 10) or absence (PHQ-9 sum-score < 10) of depression

	Females			Males		
	Non-depressed (<i>n</i> = 144)	Depressed (<i>n</i> = 92)	<i>p</i> value	Non-depressed (<i>n</i> = 423)	Depressed (<i>n</i> = 193)	<i>p</i> value
Age, years	70 ± 12	71 ± 14	0.622 ^a	65 ± 13	67 ± 11	0.208 ^a
Living alone, <i>n</i> (%)	65 (27.5)	52 (22.0)	0.713 ^b	77 (12.5)	35 (5.7)	0.945 ^b
Heart rate, beats/min	83 ± 22	84 ± 19	0.821 ^a	77 ± 19	81 ± 17	0.032 ^a
Mean arterial pressure, mmHg	87.8 (79.5–96.7)	86.7 (80.0–93.3)	0.555 ^c	88.3 (80.3–96.7)	86.7 (77.2–94.2)	0.048 ^c
Predominant HF aetiology, <i>n</i> (%)						
Coronary artery disease	66 (45.8)	35 (38.0)	0.238 ^b	218 (51.5)	106 (54.9)	0.435 ^b
Other	78 (54.2)	57 (62.0)		205 (48.5)	87 (45.1)	
HF characteristics and biomarkers						
NYHA class III–IV, <i>n</i> (%)	68 (47.2)	58 (63.0)	0.017 ^b	125 (29.6)	109 (56.5)	< 0.001 ^b
LVEF, % ^d	30.0 (24.8–37.0)	30.0 (25.0–34.0)	0.257 ^c	32.0 (25.0–37.0)	30.0 (25.0–36.3)	0.536 ^c
NT-proBNP, pg/mL	2509.0 (1029.0–6444.0)	4709.0 (2314.0–10535.0)	< 0.001 ^c	2313.5 (820.5–5132.5)	3487.0 (1031.5–8114.5)	0.010 ^c
hsCRP, mg/L	8.1 (3.4–19.4)	11.3 (3.5–26.4)	0.128 ^c	7.7 (2.6–18.8)	14.5 (4.3–31.6)	< 0.001 ^c
Comorbidities, <i>n</i> (%)						
COPD	19 (12.8)	40 (26.8)	0.054 ^b	69 (16.3)	40 (13.2)	0.183 ^b
Diabetes mellitus	60 (41.7)	37 (40.2)	0.825 ^b	117 (27.7)	76 (39.4)	0.004 ^b
Anaemia	41 (17.4)	30 (12.7)	0.499 ^b	123 (20.0)	79 (12.8)	0.004 ^b
Hypertension	113 (78.5)	71 (77.2)	0.814 ^b	320 (75.6)	149 (77.2)	0.617 ^b
Chronic kidney disease	70 (48.6)	53 (57.6)	0.177 ^b	137 (32.4)	77 (39.9)	0.069 ^b
History of depression	19 (13.2)	26 (28.3)	< 0.001 ^b	17 (4.0)	30 (15.5)	< 0.001 ^b
HF treatment, <i>n</i> (%)						
Diuretics	130 (90.3)	80 (87.0)	0.427 ^b	347 (82.0)	180 (90.3)	< 0.001 ^b
Beta-blockers	121 (84.0)	73 (79.3)	0.359 ^b	367 (86.8)	155 (80.3)	0.039 ^b
ACE inhibitor/ARB	135 (93.8)	77 (83.7)	0.013 ^b	379 (89.6)	173 (89.6)	0.988 ^b
Antidepressants	14 (9.7)	15 (16.3)	0.133 ^b	12 (2.8)	24 (12.4)	< 0.001 ^b
Allocation to <i>HeartNetCare-HF</i> TM	80 (55.6)	37 (40.2)	0.022 ^b	219 (51.8)	84 (43.5)	0.057 ^b
Psychometric assessment						
KCCQ overall summary score	59.0 (47.2–74.0)	27.5 (17.6–40.1)	< 0.001 ^c	68.0 (53.9–83.7)	39.1 (25.5–53.6)	< 0.001 ^c
KCCQ clinical summary score	62.1 (47.9–76.0)	31.6 (16.7–47.4)	< 0.001 ^c	74.0 (57.7–88.5)	45.8 (29.2–60.4)	< 0.001 ^c
PHQ-9 sum-score	4.5 ± 2.7	14.4 ± 3.4	< 0.001 ^a	4.3 ± 2.6	14.3 ± 3.6	< 0.001 ^a

Values are mean ± standard deviation, median (interquartile range) or number of patients (%), with percentage based on the number of patients with a non-missing value for that characteristic

ACE angiotensin-converting enzyme, ARB angiotensin-2 receptor blocker, HF heart failure, HNC HeartNetCare-HFTM, hsCRP high-sensitivity C-reactive protein, KCCQ Kansas City Cardiomyopathy Questionnaire, LVEF left ventricular ejection fraction, NT-proBNP amino-terminal pro-brain natriuretic peptide, NYHA New York Heart Association

^aBased on *t* test for continuous variables

^bBased on Chi-square test for categorical variables

^cBased on Mann–Whitney *U* test for non-normally distributed values

^dMeasured by two-dimensional echocardiography (*n* = 859)

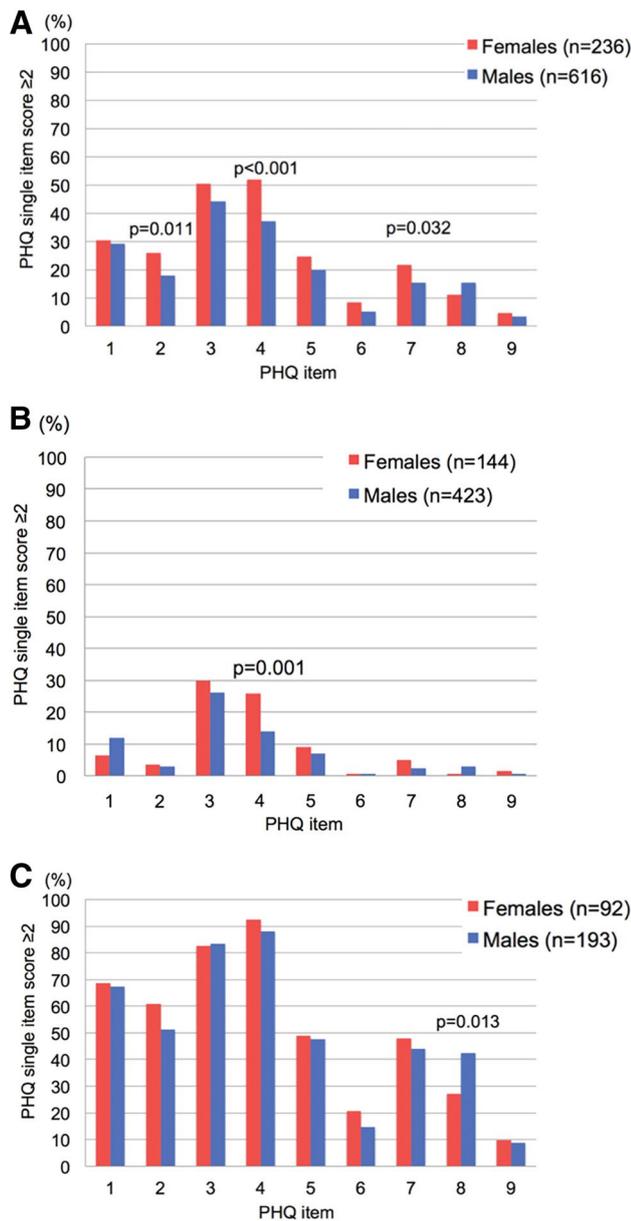
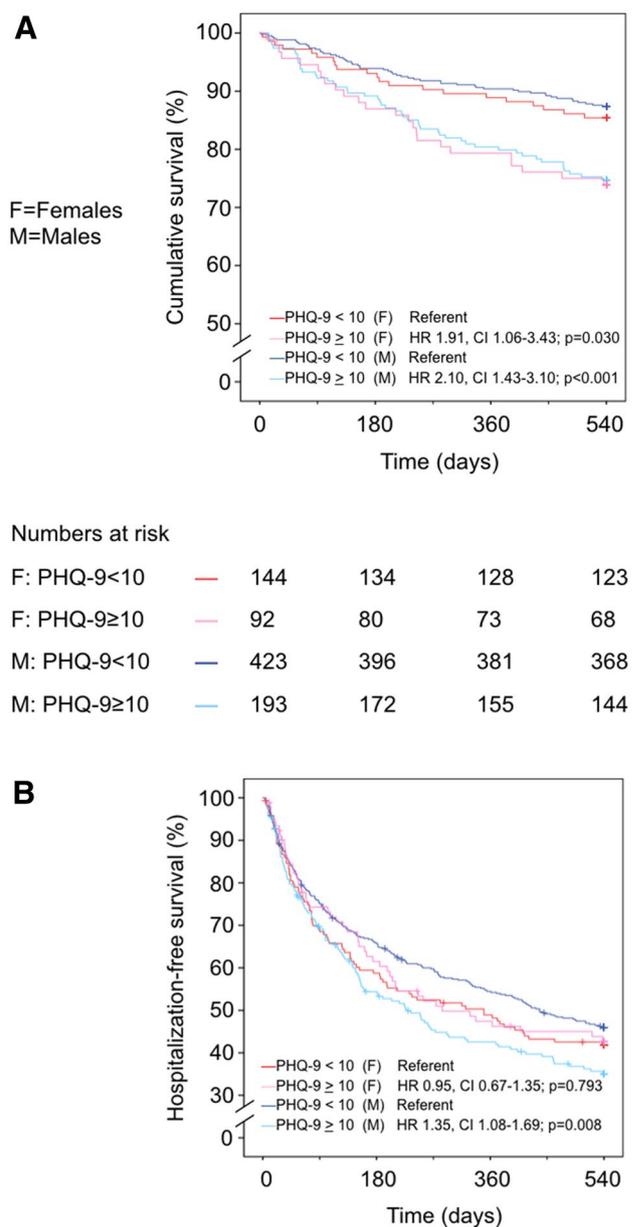


Fig. 1 Proportion of females and males who scored any of the nine individual Patient Health Questionnaire (PHQ-9) items ≥ 2 . Symptoms are: (1) Loss of interest; (2) Feeling down, depressed or hopeless; (3) Sleeping problems; (4) Fatigue, loss of energy; (5) Appetite change; (6) Feelings of failure; (7) Trouble concentrating; (8) Psychomotor changes; (9) Suicidal ideation. **A** Entire study cohort ($n = 852$); **B** non-depressed patients (PHQ-9 sum-score < 10 ; $n = 567$); **C** depressed patients (PHQ-9 sum-score ≥ 10 ; $n = 275$)

populations (reviewed by Jessup and Pina) [2], female participants were significantly older, less likely to have an ischemic HF aetiology, and had worse HF symptoms, higher NT-proBNP levels and heart rate, and more diabetes and renal dysfunction than males, while LVEF did not differ between sexes. Mortality rates in males and females were similar despite lower age and less severe HF in men,



Numbers at risk

F: PHQ-9<10	144	134	128	123
F: PHQ-9 \geq 10	92	80	73	68
M: PHQ-9<10	423	396	381	368
M: PHQ-9 \geq 10	193	172	155	144

F: PHQ-9<10	144	84	69	58
F: PHQ-9 \geq 10	92	53	40	35
M: PHQ-9<10	423	271	222	186
M: PHQ-9 \geq 10	193	97	74	59

Fig. 2 Prediction of all-cause death (**A**) and re-hospitalization (**B**) for females and males according to PHQ-9 sum-scores. *CI* confidence interval, *HR* hazard ratio, *PHQ* Patient Health Questionnaire

which is consistent with previous reports of comparatively better survival in female HF patients [2].

To our knowledge, this analysis is the first to compare depressive symptom patterns and the impact of depression

Fig. 3 Boxplots of Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall (A) and Clinical (B) Summary Scores by sex and presence/absence of depression (9-item Patient Health Questionnaire Score [PHQ-9] ≥ 10 or < 10, respectively)

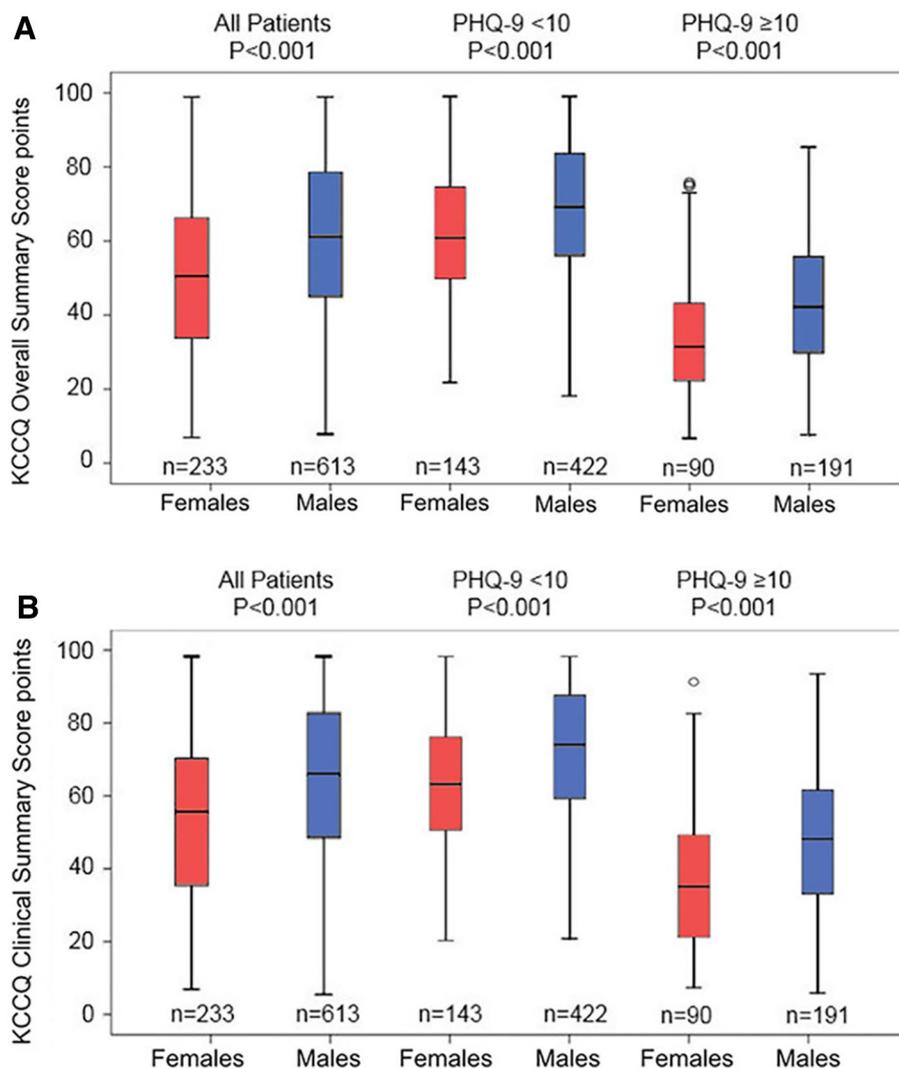


Table 3 Linear regression analysis of the impact of sex and depressive symptoms and their interaction with quality of life as measured by the Kansas City Cardiomyopathy Questionnaire

	Beta	B	SE	p value
KCCQ: OSS ($R^2=0.35$)				
Sex (male = 1, female = 2)	0.15	8.07	1.54	<0.001
Depressive symptoms (PHQ-9 sum score ≥ 10)	-0.57	-28.56	1.54	<0.001
Interaction of sex × depressive symptoms	0.01	1.28	3.08	0.68
KCCQ: CSS ($R^2=0.30$)				
Sex (male = 1, female = 2)	0.17	9.68	1.68	<0.001
Depressive symptoms (PHQ-9 sum score ≥ 10)	-0.51	-26.98	1.68	<0.001
Interaction of sex × depressive symptoms	0.01	0.68	3.37	0.84

B unstandardized regression coefficient, Beta standardized regression coefficient, KCCQ CSS Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, KCCQ OSS Kansas City Cardiomyopathy Questionnaire Overall Summary Score, PHQ-9 9-item Patient Health Questionnaire, R^2 R-squared to assess goodness-of-fit, SE standard error

on all-cause mortality and re-hospitalization risk and HRQOL between sexes in a HF population. Overall depression prevalence rates were similar to that reported in a meta-analysis for women and men [10]. Frequencies of individual

depressive symptoms based on proportions of PHQ-9 items rated ≥ 2 varied widely, consistent with data suggesting that the diagnosis of depression is based on a heterogeneous array of symptoms that can vary between individuals [14].

Given that many common complaints are also typical HF symptoms, our findings underscore the difficulty of diagnosing and classifying depression in HF populations. Symptom patterns varied proportionally with PHQ-9 sum-scores < 10 or ≥ 10 in our cohort, and none of the PHQ-9 items stood out specifically in the depressed subgroup to help explain increased mortality risk.

Overall, significantly more women scored PHQ-9 items 2, 4 and 7 ≥ 2 , consistent with existing data in patients with coronary artery disease [14] and with observations that women generally report ‘somatic’ depressive symptoms more often [9], explaining higher overall depression prevalence. The significantly higher sum-score in women occurred because they also scored most other items ≥ 2 slightly more often. Differences between women and men in single items largely disappeared, however, when considering only depressed people. We and others have shown that, in addition to a history of depression, NYHA class and various comorbidities (e.g., systemic inflammation, chronic obstructive pulmonary disease, anaemia or diabetes) are powerful predictors of depression [14, 23], thus linking its prevalence and severity to typical somatic features and symptom severity of the HF syndrome [14, 18, 23–25]. Our analysis demonstrates that many predisposing factors were more common in women, but also that these characteristics predict depression in both sexes. Previous multivariable analyses in a similar cohort demonstrated that sex no longer provided incremental information when a history of depression and NYHA class were entered into the model [23]. Sex-related differences in individual characteristics and clinical symptom patterns of the HF syndrome may thus contribute to explaining the higher PHQ-9 sum-scores in our female participants.

There is evidence that patients with cardiovascular disease and comorbid depression experience higher mortality and hospitalization rates compared with their non-depressed counterparts [10, 16–18, 26]. Our results demonstrate that, independent of sex, depressive symptoms (according to baseline PHQ-9) double all-cause mortality risk over the next 540 days. Mortality rates did not differ between sexes, although women were significantly older, had a higher comorbidity burden, more severe HF, higher PHQ-9 sum-scores, and worse functional status. This confirms previous reports of a relative survival advantage of women with symptomatic HFrEF compared with men [2], and is also in line with a meta-analysis showing that the association between depression and cardiac prognosis was worse for men than for women after myocardial infarction [26]. However, our data do not provide a clue to the underlying mechanisms.

Depressed men had an increased re-hospitalization risk, and gender-related differences may have played a role here given that significantly fewer men lived alone. Thus, patients’ female partners might have interpreted their

depressive symptoms as indicators of worsening HF and urged them to seek medical advice more often. In addition psychomotor changes, which were more frequent in depressed men, might have impacted unfavourably on re-hospitalization rates. Whether the lack of statistical significance for the association between depression and the risk of re-hospitalization in women indicates a true sex difference cannot be clarified conclusively from this analysis. Given the smaller size of the female sample, the risk of type II error was increased due to limited power.

Interestingly, higher proportions of both women and men allocated to *HeartNetCare-HF*TM were in the non-depressed subgroups. Randomization took place prior to any study-related procedures, and therefore patients knew their therapeutic allocation when undergoing psychometry. Our observations could indicate that patients were hoping for symptom relief from *HeartNetCare-HF*TM, which was explained to them before randomization, and that this impacted positively on their mood. They raise again questions regarding the nature of the depression construct captured by the PHQ-9 and individual symptom perception. As our data indicate, most participants were unaware that they had depression prior to psychometry and may have interpreted their emotional status as related to their medical illness. Although a validated tool frequently employed in HF research [12, 16–19, 23–25, 27], the PHQ-9 was probably not capable of thoroughly disentangling the diverse mechanisms underlying our patients’ complaints. Its prognostic utility was confirmed by our analysis, but higher sum-scores in women did not translate into augmented mortality risk. Considering the uncertain pathogenesis of many symptoms, therapeutic strategies targeting individual PHQ-9 profiles might be more appropriate than focusing on depression based on a sum-score. Thus, clinicians might address PHQ-9 symptom patterns with their patients during individualized treatment planning and self-care education. Such a person-centered pragmatic approach might prove superior to antidepressant pharmacotherapy in many patients, given that evidence for efficacy of specific antidepressants is lacking in patients with HF. For example, selective serotonin re-uptake inhibitors neither ameliorated depression nor improved clinical outcomes in previous randomized controlled trials in HF populations [27, 28].

Patients with HF experience compromised HRQOL [10, 25], which decreases with increasing HF severity [25]. KCCQ scores ≤ 75 were previously associated with significant HF symptoms, limited functional status and worse outcomes [29], and between-group differences and intra-individual changes of ≥ 5 points are considered clinically relevant [30]. Therefore, the difference of > 10 points in KCCQ Summary Scores indicated substantially worse HRQOL in our female versus male participants. Patients with depression in addition to HF had even lower KCCQ scores. In a prospective study, a 5-point

change in KCCQ Summary Scores was associated with an 11% change in the multivariable-adjusted hazard ratio for hospitalization and cardiovascular death [31]. Our findings confirm that depression is associated with severely compromised HRQOL and worse clinical outcomes [25, 31, 32]. Whether the independent negative impact of female sex on HRQOL was primarily mediated by more severe HF symptoms or partly due to more impaired health perception cannot be clarified from our data, which illustrate, however, that worse HRQOL in women did not translate into excess mortality.

Strengths and limitations

Strengths of our study include the large size, comprehensive clinical characterization and complete follow-up of our sample, which approximates a population-based HF cohort because the INH program had few exclusion criteria [19]. However, we may not have captured all gender- or sex-related differences, because the INH program did not record various demographic, psychosocial and behavioural factors shown to differentially correlate with depression in women and men [12]. Furthermore, our findings cannot be generalized to patients with new-onset structural heart disease or HFpEF, who were not eligible for INH participation. Although the PHQ-9 represents a well-established research tool in HF populations [12, 16–19, 23–25, 27], its exclusive use without confirmation by Structured Clinical Interview poses a risk to construct validity in symptomatic HF patients, as also suggested by our results. We operationalized depression as a PHQ-9 score ≥ 10 because Kroenke et al. reported a sensitivity (specificity) of 88% (88%) for the diagnosis of major depressive disorder when using a PHQ-9 sum-score of ≥ 10 compared with Structured Clinical Interview [13], and meta-analysis reported no significant differences in sensitivity or specificity within the 8–11 range [33]. Furthermore, the relationship between PHQ-9 sum-score and all-cause mortality risk was maintained when PHQ-9 sum-score was used as a continuous variable. It therefore seems unlikely that higher cut-off values would have materially altered our results. As in many previous studies [10, 16–18], depressive symptoms were only assessed once. We were thus unable to investigate whether they changed over time, whether *HeartNetCare-HF*TM impacted differentially on depression in women and men, and whether changes in depression were associated with changes in mortality and re-hospitalization risk, although others have not found this to be the case [34].

Conclusion

This study demonstrated sex differences in clinical HF characteristics, comorbidities, and symptom patterns in a large consecutive cohort of patients after acute cardiac decompensation. Although females had more severe HF, lower

HRQOL and more depressive symptoms than males, their mortality risk was similar. Depressive symptoms predicted worse survival in both sexes. Our findings suggest that using information from single PHQ-9 items may offer opportunities to develop individualized care strategies targeting both HF and depressive symptoms. This could potentially be a more effective approach to enhance outcomes and wellbeing than specific antidepressants that have been shown to neither ameliorate depression nor reduce clinical endpoints in these patients. Mediators and mechanisms underlying the differences between women and men remain unclear and require further evaluation in prospective controlled studies.

Acknowledgements English language editing assistance was provided by Nicola Ryan, BSc, independent medical writer.

Funding This study was funded by the Federal Ministry of Education and Research (BMBF), Grant 01GL0304, by the Competence Network Heart Failure Germany (grants 01GI0205 and 01GI1202A), and by the Comprehensive Heart Failure Center Würzburg (Grants 01EO1004 and 01EO1504).

Compliance with ethical standards

Conflict of interest None of the authors report any conflicts of interest, including any financial relationship with industry, relevant to this manuscript.

References

1. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH (2004) Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 25:1614–1619
2. Jessup M, Pina IL (2004) Is it important to examine gender differences in the epidemiology and outcome of severe heart failure? *J Thorac Cardiovasc Surg* 127:1247–1252
3. Peters SA, Huxley RR, Sattar N, Woodward M (2015) Sex differences in the excess risk of cardiovascular diseases associated with type 2 diabetes: potential explanations and clinical implications. *Curr Cardiovasc Risk Rep* 9:36
4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK (1996) The progression from hypertension to congestive heart failure. *JAMA* 275:1557–1562
5. Vitale C, Fini M, Spoletini I, Lainscak M, Seferovic P, Rosano GM (2017) Under-representation of elderly and women in clinical trials. *Int J Cardiol* 232:216–221
6. Meyer S, Teerlink JR, Metra M, Ponikowski P, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Hua TA, Severin T, Qian M, Voors AA (2017) Sex differences in early dyspnea relief between men and women hospitalized for acute heart failure: insights from the RELAX-AHF study. *Clin Res Cardiol* 106:280–292
7. Clark AM, Wiens KS, Banner D, Kryworuchko J, Thirsk L, McLean L, Currie K (2016) A systematic review of the main mechanisms of heart failure disease management interventions. *Heart* 102:707–711
8. Murray JLLA (1996) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries

- and risk factors in 1990 and projected to 2020. Summary. Harvard School of Public Health, World Health Organization, Boston
9. Silverstein B, Levin E (2014) Differences in the developmental patterns of depression with and without additional somatic symptoms. *Psychiatry Res* 220:254–257
 10. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ (2006) Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 48:1527–1537
 11. Heo S, Moser DK, Widener J (2007) Gender differences in the effects of physical and emotional symptoms on health-related quality of life in patients with heart failure. *Eur J Cardiovasc Nurs* 6:146–152
 12. Eastwood JA, Moser DK, Riegel BJ, Albert NM, Pressler S, Chung ML, Dunbar S, Wu JR, Lennie TA (2012) Commonalities and differences in correlates of depressive symptoms in men and women with heart failure. *Eur J Cardiovasc Nurs* 11:356–365
 13. Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 16:606–613
 14. Kohlmann S, Gierk B, Murray AM, Scholl A, Lehmann M, Lowe B (2016) Base rates of depressive symptoms in patients with coronary heart disease: an individual symptom analysis. *PLoS One* 11:e0156167
 15. Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasura-Smith N, Kaufmann PG, Lesperance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES (2009) AHA science advisory. Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee to the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care Outcomes Research. Endorsed by the American Psychiatric Association. *Prog Cardiovasc Nurs* 24:19–26
 16. Faller H, Stork S, Schowalter M, Steinbuechel T, Wollner V, Ertl G, Angermann CE (2007) Depression and survival in chronic heart failure: does gender play a role? *Eur J Heart Fail* 9:1018–1023
 17. Moraska AR, Chamberlain AM, Shah ND, Vickers KS, Rummans TA, Dunlay SM, Spertus JA, Weston SA, McNallan SM, Redfield MM, Roger VL (2013) Depression, healthcare utilization, and death in heart failure: a community study. *Circ Heart Fail* 6:387–394
 18. Piepenburg SM, Faller H, Gelbrich G, Stork S, Warrings B, Ertl G, Angermann CE (2015) Comparative potential of the 2-item versus the 9-item patient health questionnaire to predict death or rehospitalization in heart failure. *Circ Heart Fail* 8:464–472
 19. Angermann CE, Stork S, Gelbrich G, Faller H, Jahns R, Frantz S, Loeffler M, Ertl G, Competence Network Heart F (2012) Mode of action and effects of standardized collaborative disease management on mortality and morbidity in patients with systolic heart failure: the Interdisciplinary Network for Heart Failure (INH) study. *Circ Heart Fail* 5:25–35
 20. Faller H, Steinbuechel T, Schowalter M, Spertus JA, Stork S, Angermann CE (2005) [The Kansas City Cardiomyopathy Questionnaire (KCCQ)—a new disease-specific quality of life measure for patients with chronic heart failure]. *Psychother Psychosom Med Psychol* 55:200–208
 21. Stork S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S (2017) Epidemiology of heart failure in Germany: a retrospective database study. *Clin Res Cardiol* 106:913–922
 22. Opasich C, Tavazzi L, Lucci D, Gorini M, Albanese MC, Cacciatore G, Maggioni AP (2000) Comparison of one-year outcome in women versus men with chronic congestive heart failure. *Am J Cardiol* 86:353–357
 23. Angermann CE, Gelbrich G, Stork S, Schowalter M, Deckert J, Ertl G, Faller H (2011) Somatic correlates of comorbid major depression in patients with systolic heart failure. *Int J Cardiol* 147:66–73
 24. Faller H, Stork S, Schuler M, Schowalter M, Steinbuechel T, Ertl G, Angermann CE (2009) Depression and disease severity as predictors of health-related quality of life in patients with chronic heart failure—a structural equation modeling approach. *J Card Fail* 15:286–292 e282
 25. Schowalter M, Gelbrich G, Stork S, Langguth JP, Morbach C, Ertl G, Faller H, Angermann CE (2013) Generic and disease-specific health-related quality of life in patients with chronic systolic heart failure: impact of depression. *Clin Res Cardiol* 102:269–278
 26. Doyle F, McGee H, Conroy R, Conradi HJ, Meijer A, Steeds R, Sato H, Stewart DE, Parakh K, Carney R, Freedland K, Anselmino M, Pelletier R, Bos EH, de Jonge P (2015) Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: a MINDMAPS study. *Psychosom Med* 77:419–428
 27. Angermann CE, Gelbrich G, Stork S, Gunold H, Edelmann F, Wachter R, Schunkert H, Graf T, Kindermann I, Haass M, Blankenberg S, Pankuweit S, Prettin C, Gottwik M, Bohm M, Faller H, Deckert J, Ertl G (2016) Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *Jama* 315:2683–2693
 28. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R (2010) Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol* 56:692–699
 29. Heidenreich PA, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, Rathore SS, Peterson ED, Masoudi FA, Krumholz HM, Havranek EP, Conard MW, Williams RE, Cardiovascular Outcomes Research C (2006) Health status identifies heart failure outpatients at risk for hospitalization or death. *J Am Coll Cardiol* 47:752–756
 30. Spertus JA, Jones PG, Kim J, Globe D (2008) Validity, reliability, and responsiveness of the Kansas City Cardiomyopathy Questionnaire in anemic heart failure patients. *Qual Life Res* 17:291–298
 31. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, Spertus JA (2007) Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation* 115:1975–1981
 32. Sullivan M, Levy WC, Russo JE, Spertus JA (2004) Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. *J Card Fail* 10:390–396
 33. Manea L, Gilbody S, McMillan D (2012) Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ* 184:E191–E196
 34. Lesperance F, Frasura-Smith N, Talajic M, Bourassa MG (2002) Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 105:1049–1053