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Quality of life in men and women with heart failure: association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire

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Aims	We sought to analyse quality of life (QoL) measures derived from two questionnaires widely used in clinical trials, the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQoL 5 dimensions (EQ-5D), and to compare their prognostic value in men and women with heart failure and reduced ejection fraction (HFrEF).
Methods and results	From the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) we compared KCCQ and EQ-5D at baseline and after 9 months in 1276 men and 373 women with new-onset or worsening symptoms of HFrEF, who were sub-optimally treated and in whom there was an anticipated up-titration of guideline-derived medical therapies. Women had significantly worse baseline QoL (median) as compared with men, both when assessed with KCCQ overall score (KCCQ-OS, 44 vs. 53, $P < 0.001$) and EQ-5D utility score (0.62 vs. 0.73, $P < 0.001$). QoL improved equally in women and men at follow-up. All summary measures of QoL were independently associated with all-cause mortality, with KCCQ-OS showing the most remarkable association with mortality up to 1 year compared to the EQ-5D scores (C-statistic 0.650 for KCCQ-OS vs. 0.633 and 0.599 for EQ-5D utility score and EQ-5D visual analogue scale, respectively). QoL was associated with all outcomes analysed, both in men and women (all P for interaction with sex >0.2).
Conclusion	Amongst patients with HFrEF, women reported significantly worse QoL than men. QoL was independently associated with subsequent outcome, similarly in men and women. The KCCQ in general, and the KCCQ-OS in particular, showed the strongest independent association with outcome.

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Graphical Abstract
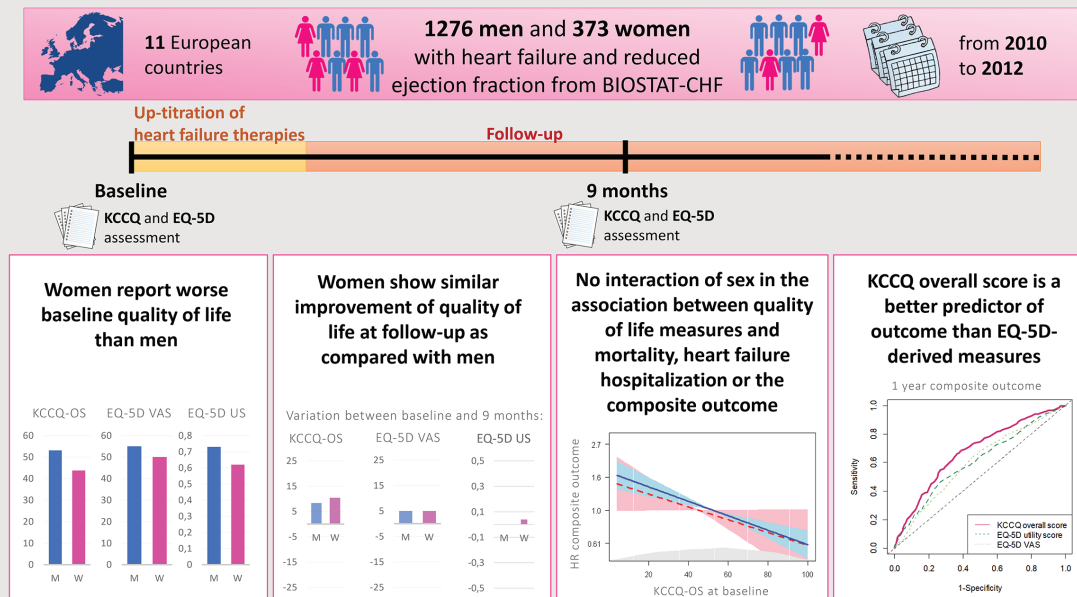
Sex differences in quality of life, in its relationship with outcomes, and predictive ability of different quality of life measures towards outcome. BIOSTAT-CHF, BIOlogy Study to TAilored Treatment in Chronic Heart Failure; EQ-5D, EuroQoL 5 dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; OS, overall score; US, utility score; VAS, visual analogue scale.

Introduction

Patients with heart failure (HF) suffer from debilitating physical symptoms, frequently associated with depressive symptoms, anxiety, and cognitive disorders that further affect their daily function and quality of life (QoL).[1] Notably, patients with HF generally have a poor QoL, which is much lower compared to healthy individuals and even to patients with other chronic illnesses.[1]

Previous analyses of trials and registries in HF highlighted several differences between men and women with regard to clinical features and event rates.[2] Of particular interest is the observed sex difference in QoL, with women experiencing poorer QoL and greater perceived disability as compared with men.[3,4] Lower QoL in HF with reduced ejection fraction (HFrEF) is associated with increased hospitalizations and mortality.[5–7] However, sex differences in the relationship of QoL to outcomes require further investigation.

Tools aimed at assessing patients' perception of their health status are widely used in research, and potentially approvable endpoints in medication development.[8] Various QoL surveys have been used for patients with HF, both generic and disease-specific.[9] The EuroQol 5 dimensions (EQ-5D) questionnaire is a widely used, standardized instrument for measuring generic health status,[10]

whereas the Kansas City Cardiomyopathy Questionnaire (KCCQ) was specifically designed and validated for health-related QoL assessment in patients with HF.[11] Head-to-head comparisons on the discriminative power and prognostic value of these two QoL assessment methods are limited.

We therefore sought to analyse sex differences in QoL as assessed with two widely used QoL questionnaires, and to assess whether there are sex differences in QoL variations after up-titration of HF therapies. Moreover, we analysed the relationship between different measures of QoL and outcomes, testing for the interaction of sex in this association. Finally, we compared the predictive ability of different QoL measures towards outcome.

Methods

Patient population

We studied patients from the index cohort of the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), whose design has been described in detail elsewhere.[12] Briefly, BIOSTAT-CHF was a multicentre, multinational, prospective, observational study. The index cohort included 2516 patients enrolled from 11 European countries between December 2010 and December 2012. To be enrolled in the study patients had to comply with protocol specified criteria.[12] The

main inclusion criteria were signs and/or symptoms of new-onset or worsening HF and sub-optimal (≤50% target dose; online supplementary *Table S1*) treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) and/or beta-blockers, with anticipated initiation or up-titration of these drugs according to the target doses recommended by the European Society of Cardiology (ESC) guidelines[13,14] (online supplementary *Table S1*). Patients could be enrolled either as inpatients or from outpatient clinics. Investigators were encouraged to optimize treatment with ACEi/ARB and beta-blockers during the first 3 months of the study.

All patients provided written informed consent to participate in the study and BIOSTAT-CHF complied with the Declaration of Helsinki. The study was approved by the ethics committees of the participating centres.

Study procedures and quality of life assessment

The first study assessment was performed at baseline, then a second visit was planned after 9 months. Medical history, current medication, and physical examination were recorded at both visits, and blood and urine samples were collected for subsequent analyses. QoL was assessed with EQ-5D and KCCQ, both at baseline and 9-month visits; details on the questionnaires are described in the online supplementary *Methods*. Six-minute walk test (6MWT) was also performed at both visits.[8]

In our analyses, only patients with HFrEF, thus with a left ventricular ejection fraction <40%, were included ($n = 1819$). Patients who did not complete both KCCQ and EQ-5D questionnaires at baseline were also excluded from the main analyses ($n = 170$). For the limited set of analyses considering the variation of QoL parameters at follow-up, we also excluded patients who did not complete both KCCQ and EQ-5D questionnaires at 9 months ($n = 407$). A flow diagram is displayed in online supplementary *Figure S1*.

Follow-up and outcomes

After the second study visit, patients were prospectively followed by ambulatory visits or telephone calls at 6-month intervals until the end of the study, in April 2015. The protocol of BIOSTAT-CHF used clear endpoint definitions, a structured case report form, and source data of all sites were closely monitored. All deaths and hospitalizations were recorded. The adjudication of HF hospitalization was performed by the treating physician. After the trial has ended, all medical reports of the deadly event were read and adjudicated by an independent committee of cardiologists. Median follow-up was 21 months [interquartile range (IQR) 11–32 months].[12]

Statistical analysis

Normally distributed continuous variables are presented as means ± standard deviation and non-normally distributed variables as median (IQR). Categorical variables are reported as numbers with percentages. Baseline clinical parameters were compared between men and women, and between patients with quartiles of KCCQ overall score (KCCQ-OS). Group comparisons were made using ANOVA, Student's *t*-tests, Chi-square tests and Mann−Whitney U tests as appropriate. QoL variation between different timepoints was compared using paired samples *t*-tests. Shift analysis was also performed to check for sex differences in QoL variation across the entire QoL spectrum. Baseline and 3-month HF therapies were also compared using shift analysis (details in online supplementary *Methods*).

Univariable and multivariable Cox proportional hazard models were used to evaluate the impact of QoL overall measures [KCCQ-OS; EQ-5D utility score (US), US; EQ-5D visual analogue scale (VAS)] on mortality, HF hospitalization and the composite outcome (death and/or HF hospitalization). Hazard ratios are expressed as mean and 95% confidence interval (CI). To account for potential confounding factors, the previously published multivariable risk models of BIOSTAT-CHF for mortality, HF hospitalization or the composite outcome at 1 year were used, as appropriate, for adjustment in the multivariable Cox and competing-risk regression models.[15] The covariates in each model are displayed in the online supplementary *Methods*. QoL measures were modelled as continuous variables: 5 point-change units for KCCQ-OS and EQ-5D VAS, and 0.1 point-change units for EQ-5D US were considered because of clinical meaning and comparable magnitude.[16] Univariable and multivariable Cox proportional hazard models were obtained for the total study population and for men and women separately. Additionally, for all relationships between QoL measures and outcome, interaction with sex was tested, and effect plots stratified by sex were obtained for immediate results visualization.

To compare the impact of each QoL measure on outcomes, between univariable Cox models the change in C-statistics was computed, time-dependent receiver operating characteristic (ROC) curves were plotted to study the strength of the association of each QoL measure to outcome over time, and net reclassification improvement (NRI) was calculated (details in online supplementary *Methods*). We finally tested the additive ability of each QoL measure to reclassify risk of each outcome beyond the BIOSTAT-CHF risk models, by examining categorical NRI.

Statistical analyses were performed using R, A Language and Environment for Statistical Computing, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS Statistics for Windows, version 23.0.0.3 (IBM Corp., Armonk, NY, USA).

Results
Clinical characteristics

A total of 1649 patients were studied, 373 (23%) of whom were women. Baseline characteristics of men and women are displayed in *Table 1* and online supplementary *Table S2*. At baseline, women were older (71 vs. 66 years, $P < 0.001$), had slightly higher left ventricular ejection fraction (29% vs. 27%, $P < 0.001$), and were less likely to have an ischaemic HF aetiology (49% vs. 64%, $P < 0.001$). Clinical signs and symptoms of HF and vitals were fairly similar between men and women. Notably, there was no significant sex difference in New York Heart Association (NYHA) class ($P = 0.688$), median HF duration (4 vs. 2 months, $P = 0.434$), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) ($P = 0.076$). Women were less likely to have most comorbidities, especially atherothrombotic disease in general. Baseline HF medications were similar in men and women, except for mineralocorticoid receptor antagonists (MRAs) and digoxin, that were more often prescribed in men (59% vs. 49%, $P < 0.001\%$ and 21% vs. 13%, $P = 0.002$, respectively). There was no significant sex difference in the fraction of target dose of ACEi/ARB or beta-blockers both at baseline and after the up-titration phase (online supplementary *Figure S5* and S6).

Table 1 Baseline characteristics stratified by sex

	Men	Women	*P*-value
No. of subjects	1276	373	
Demographics			
Age, years	66 ± 12	71 ± 12	<0.001
Race, *n* (%)			0.013
Caucasian	1261 (98.8)	367 (98.4)	
Other	15 (1.1)	6 (1.6)	
BMI, kg/m^2	27.80 (5.19)	27.11 (5.58)	0.027
Weight, kg	85 ± 18	72 ± 16	<0.001
Height, cm	174 ± 8	162 ± 7	<0.001
Clinical profile			
NYHA class, *n* (%)			0.688
I	31 (2.5)	6 (1.6)	
II	470 (37.5)	131 (35.8)	
III	611 (48.8)	188 (51.4)	
IV	140 (11.2)	41 (11.2)	
LVEF, %	26.8 ± 7	28.9 ± 6.3	<0.001
Systolic blood pressure, mmHg	122.4 ± 20.0	126.5 ± 23.4	0.001
Diastolic blood pressure, mmHg	75.6 ± 12.2	74.8 ± 13.5	0.280
Heart rate, bpm	79.6 ± 18.8	80.7 ± 18.3	0.352
Type of visit (%)			0.695
Outpatient	482 (37.8)	139 (37.2)	
Inpatient	794 (62.2)	234 (62.7)	
HF history			
Months since first diagnosis	3.70 [0.17−42.85]	1.90 [0.10−10.40]	0.434
HF aetiology, *n* (%)			
Ischaemic	734 (63.6)	158 (49.4)	<0.001
Valvular	498 (39)	145 (38.9)	0.320
Past HF hospitalization	431 (33.8)	117 (31.4)	0.420
Medical history, *n* (%)			
Hypertension	744 (58.3)	239 (64.1)	0.053
Atrial fibrillation	558 (43.7)	131 (35.1)	0.004
Myocardial infarction	530 (41.5)	105 (28.2)	<0.001
Diabetes mellitus	412 (32.3)	103 (27.6)	0.099
COPD	230 (18.0)	44 (11.8)	0.006
Peripheral artery disease	135 (10.6)	22 (5.9)	0.009
Stroke	109 (8.5)	30 (8.0)	0.842
Medication, *n* (%)			
ACEi or ARBs	962 (75.4)	268 (71.8)	0.189
Beta-blockers	1088 (85.3)	305 (81.8)	0.119
MRAs	752 (58.9)	181 (48.5)	<0.001
Laboratory			
Haemoglobin, g/dL	13.80 [12.30−14.90]	12.80 [11.75−13.72]	<0.001
Creatinine, mg/dL	1.20 [1.00−1.50]	1.00 [0.81−1.23]	<0.001
Urea, mmol/L	12.14 [8.00−19.99]	9.70 [7.20−16.00]	<0.001
Sodium, mmol/L	140.00 [137.00−142.00]	140.00 [138.00−142.00]	0.064
Potassium, mmol/L	4.30 [4.00−4.60]	4.20 [3.80−4.60]	0.002
NT-proBNP, ng/L	4148.00 [2288.00−8220.00]	4706.50 [2471.00−9992.00]	0.076

Continuous variables are presented as means ± standard deviation when normally distributed, or median [interquartile range] for non-normally distributed variables. Categorical variables are shown as *n* (%).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Sex differences in quality of life

Distributions of overall QoL measures at baseline and their change after 9 months are presented in *Figure 1*. Women reported lower QoL than men as assessed with KCCQ-OS (44 vs. 53, *P* < 0.001) and EQ-5D US (0.6 vs. 0.7, *P* < 0.001), with a similar tendency for EQ-5D VAS (50 vs. 55, *P* = 0.062). Similarly, women showed worse exercise capacity as assessed with 6MWT (180 vs. 281 m,

$P < 0.001$; online supplementary *Table S2*). Baseline KCCQ domain scores and answers to EQ-5D questions in men and women are displayed in *Figure 2*. Upon enrolment, women reported a significantly higher burden of limitation as captured by six (out of seven) KCCQ domains and all the five dimensions in the EQ-5D (*Figure 2B*). Notably, answers to KCCQ items show that the sex difference in perceived physical limitation increased as the considered activities became more demanding, with fatigue being the most limiting symptom in women as compared with men, and all social activities being more affected by HF symptoms in women (online supplementary *Figure S2*).

After 9 months, all QoL summary measures significantly improved in the total population, and in men and women separately (all $P < 0.001$; online supplementary *Table S5*). Likewise, 6MWT distance improved in the total population, and in men and women separately (all $P < 0.001$; online supplementary *Table S5*). The absolute change in QoL measures, more pronounced in KCCQ-OS and EQ-5D VAS, was similar in men and women (*Figure 1*). The magnitude of change in any QoL score at 9 months was neither dependent on sex (all $P > 0.1$) nor on the fraction of the target dose of ACEi/ARB or beta-blocker achieved after the up-titration period (all $P > 0.05$), with large QoL variability among each group (online supplementary *Tables S3* and *S4*, and *Figure S7*). In particular, KCCQ single answers and domain scores, and EQ-5D items at 9 months showed an improvement in QoL which was consistent across all the considered areas, and was slightly more pronounced in symptoms and physical limitation, similarly in men and women (online supplementary *Table S5*, and *Figures S3* and *S4*).

Quality of life and outcome

Table 2 shows the association of baseline QoL measures with outcomes. Univariable Cox regression showed that all QoL measures were significantly associated with all-cause mortality and the composite outcome in the entire study population and also in both sexes separately. After adjustment, all QoL measures were independently associated with mortality and the composite outcome in the total population and in men, with a similar tendency in women (*Table 2*). When considering HF hospitalization, in univariable Cox regression all QoL measures were significantly associated with both outcomes in the total population and in men, whereas in women KCCQ-OS was the only QoL measure significantly associated with this outcome (*Table 2*). In multivariable analyses, only KCCQ-OS and EQ-5D VAS were independently associated with HF hospitalization in the entire population and in men (*Table 2*). As for the other analysed outcomes, hazard ratios showed a similar tendency in women as compared with men. For all outcomes, there was no significant QoL-by-sex interaction (all $P > 0.2$). Additionally, effect plots showed similar predicted probability in men and women for all considered outcomes across the levels of QoL measures (online supplementary *Figures S8−S10*).

The 6MWT showed a significant association with all-cause mortality in the total population, and in men and women separately at univariable Cox regression; whilst only in the total population and in men after adjustment for the BIOSTAT-CHF risk model (online supplementary *Table S6*). When the other outcomes were considered, 6MWT showed a modest association with outcome only at univariable analysis (online supplementary *Table S6*). Interestingly, a significant interaction of sex in the association between 6MWT and all-cause mortality was observed, with women showing lower risk of death than men for similar 6MWT values (P for interaction: unadjusted 0.02, adjusted 0.046).

Univariable predictive power of KCCQ-OS for all-cause mortality was significantly better than the one of EQ-5D VAS, but not EQ-5D US, when models were compared using C-statistic (0.650 vs. 0.599 and 0.633, respectively, $P < 0.001$ and $P = 0.185$) and NRI (0.268, 95% CI 0.123−0.383 and 0.089, 95% CI −0.023 to 0.224, respectively; online supplementary *Table S8*). Conversely, univariable predictive power of KCCQ-OS towards HF hospitalization and the composite outcome was significantly better than those of both EQ-5D-derived measures, both when compared using C-statistic (all $P < 0.001$; *Table 3*) and NRI (online supplementary *Table S8*). Using time-dependent ROC curves, KCCQ-OS resulted the strongest univariable predictor of mortality up to 1 year (*Figure 3A*, and online supplementary *Table S7A*), and of HF hospitalization and the composite outcome up to 2 years (*Figure 3B* and *3C*, and online supplementary *Table S7B* and *S7C*). For all outcomes, adding any QoL measure did not significantly improve NRI compared to the corresponding BIOSTAT-CHF risk model (online supplementary *Table S8*).

Discussion

Assessment of QoL is an important tool that integrates physical examination with a comprehensive, reliable and reproducible characterization of HF patients' experience with their own illness.[9,17] QoL measures are useful for HF surveillance and prognostication, and constitute potential outcomes to support labelling claims for new drugs and devices.[1,17] Acknowledgement of sex differences in QoL and of their clinical impact is therefore important to correctly interpret QoL data. In our analysis of 1649 patients with HFrEF from 11 European countries, we confirmed that women with HFrEF report worse QoL than men; however, QoL equally improved in men and women during follow-up. QoL measures were independent predictors of mortality, HF hospitalization, and the combined outcome with no significant interaction of sex. Despite KCCQ-OS showed the best predictive value for all outcomes, there was no significant added prognostic value of QoL as assessed with this score to the predictive ability of the BIOSTAT-CHF risk models[15] (*Graphical Abstract*).

The larger impact of HFrEF on QoL in women confirms previous findings,[3,4] and is concordant with the worse performance of women in 6MWT, an objective measure of exercise capacity. We observed a large (9 point) sex difference in KCCQ-OS, with EQ-5D also capturing the worse QoL perceived by women, particularly when scored with EQ-5D US. Among KCCQ domains, the most remarkable sex differences were a 17 point difference in the physical limitation score and a 12 point difference in the social limitation score. The answers to EQ-5D questions also revealed that HF impacted more on women's health status also psychologically,
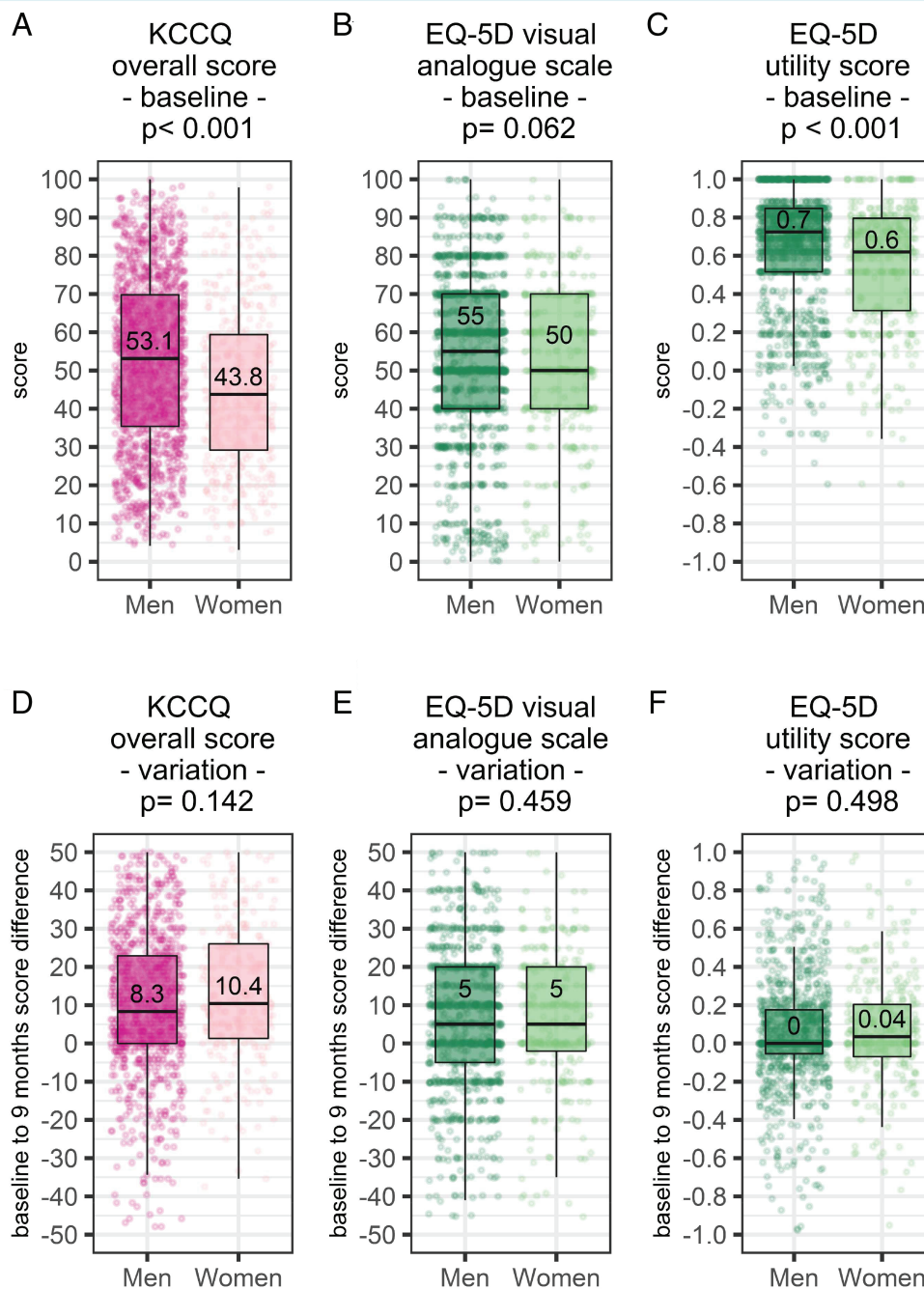
Figure 1 Sex differences in the distribution of baseline quality of life measures (*A−C*), and their difference between baseline and 9 months (*D−F*), boxplots showing median values and interquartile ranges. EQ-5D, EuroQoL 5 dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire.

with more than 60% of women reporting moderate to severe anxiety or depression at baseline. These differences were observed even though physician-assessed signs and symptoms of HF were fairly similar in men and women, and most comorbidities were more prevalent in men. Other markers of HF severity, including NT-proBNP and HF hospitalizations in the year before enrolment, were also not significantly different between men and women,

though women were older than men in our study population. This greater perceived physical and psychological disability of women despite similar physician-assessed signs and symptoms of HF highlights the importance of QoL assessment for a comprehensive HF patient characterization, while future studies may address these differences in evaluating potential personalized therapeutic strategies for women with HFrEF.
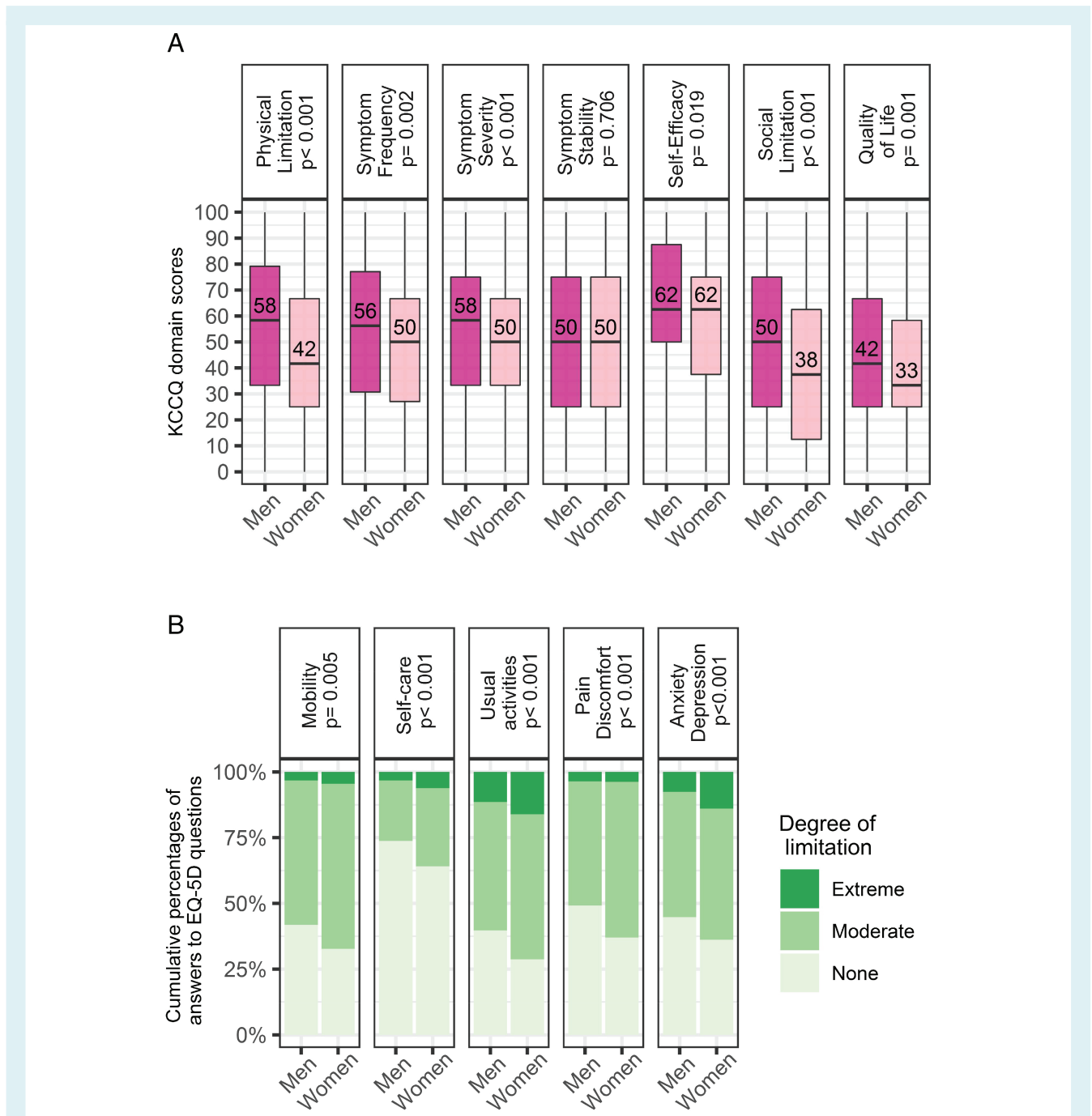
Figure 2 Sex differences in the baseline distribution of (A) the Kansas City Cardiomyopathy Questionnaire (KCCQ) domain scores (boxplot, medians and interquartile ranges), and (B) the answers to EuroQol 5 dimensions (EQ-5D) items (cumulative percentages).

At 9-month follow-up visit, both men and women showed a similar improvement in QoL, especially marked as assessed with KCCQ, regardless of sex or the fraction of target dose achieved, and consistent across all KCCQ domains and EQ-5D items. Several are the potential explanations for this overall QoL trend over time. First, patients in BIOSTAT-CHF were enrolled either with *de novo* or worsening HF symptoms,[12] thus maximizing the chances of capturing a QoL improvement at follow-up. Second, patients

enrolled in BIOSTAT-CHF might have benefited from the close follow-up entailed by the participation in a clinical study. However, QoL change over time was also evaluated in several of the pivotal trials of ACEi,[18,19] ARB[20,21] and beta-blockers[22,23] in HFrEF, showing an overall improvement in QoL with these drugs as compared to placebo in stable, symptomatic HFrEF patients. The QoL metrics used in these studies were heterogeneous and mainly HF-specific, and none of these analyses evaluated sex differences in QoL

Table 2 Association of baseline quality of life measures with mortality, heart failure hospitalization, and mortality and/or heart failure hospitalization

Population	n	Events (%)	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Mortality						
KCCQ-OS						
Total	1649	371 (22.5)	0.89 (0.87–0.92)	<0.001	0.95 (0.92–0.97)	<0.001
Men	1276	112 (23.4)	0.90 (0.87–0.92)	<0.001	0.94 (0.91–0.97)	<0.001
Women	373	33 (19.3)	0.86 (0.81–0.92)	<0.001	0.94 (0.88–1.00)	0.078
EQ-5D VAS						
Total	1649	371 (22.5)	0.94 (0.91–0.96)	<0.001	0.97 (0.93–0.99)	0.009
Men	1276	112 (23.4)	0.94 (0.92–0.96)	<0.001	0.97 (0.94–1.00)	0.024
Women	373	33 (19.3)	0.92 (0.87–0.97)	0.002	0.96 (0.91–1.02)	0.167
EQ-5D US						
Total	1649	371 (22.5)	0.88 (0.86–0.91)	<0.001	0.94 (0.90–0.96)	<0.001
Men	1276	112 (23.4)	0.87 (0.85–0.9)	<0.001	0.92 (0.89–0.96)	<0.001
Women	373	33 (19.3)	0.88 (0.82–0.94)	<0.001	0.96 (0.89–1.02)	0.229
Heart failure hospitalization						
KCCQ-OS						
Total	1649	374 (22.7)	0.9 (0.88–0.93)	<0.001	0.94 (0.92–0.97)	<0.001
Men	1276	293 (23)	0.90 (0.88–0.92)	<0.001	0.94 (0.91–0.96)	<0.001
Women	373	81 (21.7)	0.92 (0.87–0.97)	0.003	0.96 (0.90–1.01)	0.145
EQ-5D VAS						
Total	1649	374 (22.7)	0.95 (0.93–0.97)	<0.001	0.97 (0.95–0.99)	0.016
Men	1276	293 (23)	0.95 (0.92–0.97)	<0.001	0.97 (0.94–1.00)	0.022
Women	373	81 (21.7)	0.96 (0.91–1.00)	0.094	0.97 (0.92–1.03)	0.415
EQ-5D US						
Total	1649	374 (22.7)	0.93 (0.90–0.96)	<0.001	0.97 (0.94–1.00)	0.079
Men	1276	293 (23)	0.92 (0.89–0.96)	<0.001	0.96 (0.93–1.00)	0.063
Women	373	81 (21.7)	0.95 (0.89–1.00)	0.16	0.99 (0.92–1.06)	0.772
Mortality and/or heart failure hospitalization						
KCCQ-OS						
Total	1649	604 (36.6)	0.90 (0.88–0.93)	<0.001	0.95 (0.93–0.97)	<0.001
Men	1276	799 (37.4)	0.90 (0.88–0.92)	<0.001	0.95 (0.93–0.97)	<0.001
Women	373	127 (34)	0.89 (0.85–0.94)	<0.001	0.95 (0.91–1.00)	0.060
EQ-5D VAS						
Total	1649	604 (36.6)	0.95 (0.93–0.97)	<0.001	0.97 (0.95–0.99)	0.004
Men	1276	799 (37.4)	0.95 (0.93–0.96)	<0.001	0.97 (0.95–0.99)	0.012
Women	373	127 (34)	0.94 (0.9–0.98)	0.002	0.97 (0.93–1.01)	0.127
EQ-5D US						
Total	1649	604 (36.6)	0.93 (0.9–0.96)	<0.001	0.96 (0.94–0.99)	0.003
Men	1276	799 (37.4)	0.9 (0.88–0.93)	<0.001	0.96 (0.93–0.99)	0.003
Women	373	127 (34)	0.92 (0.87–0.97)	0.002	0.97 (0.92–1.03)	0.308

CI, confidence interval; EQ-5D, EuroQoL 5 dimensions; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall score; US, utility score; VAS, visual analogue scale.

improvement after treatment. Our study, conducted on a large prospective HF cohort including both inpatients and outpatients, with the specific aim of up-titrating ACEi/ARB and beta-blockers according to recent ESC guidelines, shows that sex influences the patients' instantaneous QoL perception, but not QoL variations over time. This finding remains consistent both when QoL is evaluated with EQ-5D, a general health status survey that allows the estimation of a health utility score particularly useful for economic analyses, and with KCCQ, one of the questionnaires that has the strongest overall clinical evidence supporting its use

in HF.[17] Even though its prospective cohort design does not allow causation inference on the underlying reasons for the observed QoL improvement, our study confirms that QoL benefit is equally present in men and women when managed according to recent ESC guidelines.

In the current study, all three baseline QoL measures were associated with mortality, HF hospitalization, and the combined outcome at univariable analysis. In multivariable analyses, KCCQ-OS and EQ-5D VAS were independently associated with all outcomes, while EQ-5D US only with mortality and the composite outcome.

Table 3 C-statistic for different baseline quality of life measure-based models for predicting mortality, heart failure hospitalization, and mortality and/or heart failure hospitalization

	C-statistic	SE	P for comparison with KCCQ-OS	P for comparison with EQ-5D US
Mortality				
KCCQ-OS	0.650	0.016	–	–
EQ-5D US	0.633	0.016	0.185	–
EQ-5D VAS	0.599	0.016	<0.001	0.025
Heart failure hospitalization				
KCCQ-OS	0.629	0.015	–	–
EQ-5D US	0.562	0.015	<0.001	–
EQ-5D VAS	0.574	0.015	<0.001	0.447
Mortality and/or heart failure hospitalization				
KCCQ-OS	0.636	0.012	–	–
EQ-5D US	0.587	0.012	<0.001	–
EQ-5D VAS	0.582	0.012	<0.001	0.674

EQ-5D, EuroQoL 5 dimensions; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall score; SE, standard error; US, utility score; VAS, visual analogue scale.

No significant interaction of sex was observed in any of these associations. Even though QoL surveys are still not routinely administered in clinical practice,[9] they are frequently used as surrogate endpoints in clinical trials, especially in phase 2 trials, and their use in phase 3 trials beside morbidity and mortality is currently encouraged by regulatory authorities.[8] The association with outcome of patient-reported health status assessed with KCCQ[6,7] and EQ-5D[5] measures in HFrEF was already established. However, this is the first study to our knowledge to specifically analyse sex differences in the association between QoL and outcome. Sex differences in HF have been overlooked for a long time, and clinical trials leading to drug approval in HFrEF enrolled predominantly men.[2] Mainly based on male-derived data, conclusions of clinical trials in HFrEF may thus be male-biased. Notably, we recently showed that women with HFrEF might even need lower doses of ACEi or ARBs and beta-blockers than men to achieve lowest hazards of death or HF hospitalization.[24] The observation that QoL measures carry the same prognostic meaning in women and men bears great importance for interpreting data from past trials, especially those of drugs approved for symptom relief indication without a clear survival benefit (e.g. digoxin, ivabradine), and to inform QoL survey use in future clinical trials. On the other hand, the different prognostic meaning of 6MWT, an objective measure of functional capacity, towards mortality in men and women, is a hypothesis-generating finding and warrants further investigation in other databases.

Although KCCQ and EQ-5D evaluate different aspects of HF patients' health status, KCCQ-OS showed the strongest association with all outcomes, also in the long term (1−2 years), though it conveyed no significant added prognostic value to the predictive ability of the previously validated set of clinical and laboratory variables in the BIOSTAT-CHF risk models.[15] However, this finding encourages the use of KCCQ both as surrogate endpoint in clinical trials, as it reliably reflects patients' health-related QoL and is independently associated with long-term clinical outcomes, but also in the clinical setting, periodically during HF patients' follow-up.

Overall, the findings from this study highlight the importance of evaluating patients' subjective QoL perception in the clinical setting, both in men and women, as it carries readily available prognostic information. Furthermore, these findings are especially important in the research setting, as they confirm the association of QoL with outcome in a broad HF population managed according to recent ESC guidelines, without any relevant interaction with sex in its prognostic meaning despite the sex differences observed in the overall QoL measures and the particular QoL domains. Finally, the head-to-head comparison of the features of KCCQ- and EQ-5D-derived measures provides important information for planning future clinical trials.

Limitations

Our study has several potential limitations. First, this was a *post-hoc* analysis even though carried out on a prospective HF cohort. Secondly, patients enrolled in BIOSTAT-CHF were predominantly Caucasian, thus limiting the generalizability of our findings to other ethnicities. In third place, we included in our analysis only patients that completed both KCCQ and EQ-5D questionnaires at baseline, thus introducing a potential selection bias on a population subset with less severe HF at baseline. Moreover, we focused on HFrEF while many women with HF have preserved left ventricular ejection fraction, and our study population included more men than women, though this is very common in studies on HFrEF. Finally, we compared a single generic and a single HF-specific QoL questionnaire, as more QoL surveys within each category were not available in our cohort.

Conclusions

While women with HFrEF had similar physician-assessed symptoms, they reported worse QoL than men. However, men and women showed a similar improvement in QoL after 9-month
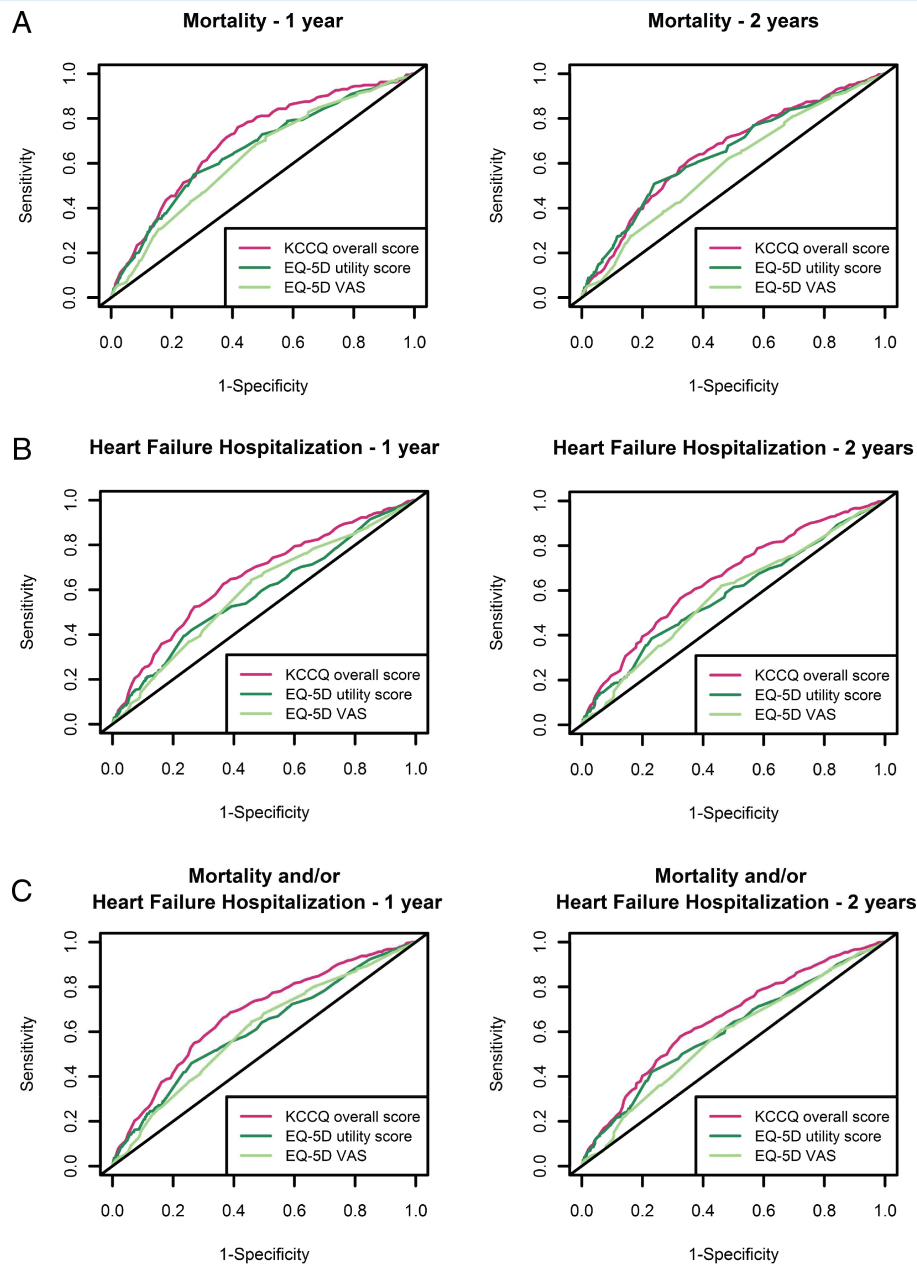
Figure 3 Time-dependent receiver operating characteristic curves for different quality of life measure-based models for predicting (*A*) mortality, (*B*) heart failure hospitalization, and (*C*) the composite outcome. EQ-5D, EuroQoL 5 dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; VAS, visual analogue scale.

follow-up. Baseline QoL was independently associated with subsequent mortality and HF hospitalization, similarly in men and women, with KCCQ-OS showing the strongest association with outcome.

Supplementary Information

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

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