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Health-Related Quality of Life and Mortality in Heart Failure

The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries

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BACKGROUND: Poor health-related quality of life (HRQL) is common in heart failure (HF), but there are few data on HRQL in HF and the association between HRQL and mortality outside Western countries.

METHODS: We used the Kansas City Cardiomyopathy Questionnaire–12 (KCCQ-12) to record HRQL in 23 291 patients with HF from 40 countries in 8 different world regions in the G-CHF study (Global Congestive Heart Failure). We compared standardized KCCQ-12 summary scores (adjusted for age, sex, and markers of HF severity) among regions (scores range from 0 to 100, with higher score indicating better HRQL). We used multivariable Cox regression with adjustment for 15 variables to assess the association between KCCQ-12 summary scores and the composite of all-cause death, HF hospitalization, and each component over a median follow-up of 1.6 years.

RESULTS: The mean age of participants was 65 years; 61% were men; 40% had New York Heart Association class III or IV symptoms; and 46% had left ventricular ejection fraction ≥40%. Average HRQL differed between regions (lowest in Africa [mean± SE, 39.5±0.3], highest in Western Europe [62.5±0.4]). There were 4460 (19%) deaths, 3885 (17%) HF hospitalizations, and 6949 (30%) instances of either event. Lower KCCQ-12 summary score was associated with higher risk of all outcomes; the adjusted hazard ratio (HR) for each 10-unit KCCQ-12 summary score decrement was 1.18 (95% CI, 1.17–1.20) for death. Although this association was observed in all regions, it was less marked in South Asia, South America, and Africa (weakest association in South Asia: HR, 1.08 [95% CI, 1.03–1.14]; strongest association in Eastern Europe: HR, 1.31 [95% CI, 1.21–1.42]; interaction $P<0.0001$). Lower HRQL predicted death in patients with New York Heart Association class I or II and III or IV symptoms (HR, 1.17 [95% CI, 1.14–1.19] and HR, 1.14 [95% CI, 1.12–1.17]; interaction $P=0.13$) and was a stronger predictor for the composite outcome in New York Heart Association class I or II versus class III or IV (HR 1.15 [95% CI, 1.13–1.17] versus 1.09 [95% CI, [1.07–1.11]; interaction $P<0.0001$). HR for death was greater in ejection fraction ≥40 versus <40% (HR, 1.23 [95% CI, 1.20–1.26] and HR, 1.15 [95% CI, 1.13–1.17]; interaction $P<0.0001$).

CONCLUSION: HRQL is a strong and independent predictor of all-cause death and HF hospitalization across all geographic regions, in mildly and severe symptomatic HF, and among patients with preserved and reduced ejection fraction.

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Key Words: health status ■ heart failure ■ prognosis ■ quality of life ■ ventricular function, left

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Clinical Perspective

What Is New?

- The G-CHF study (Global Congestive Heart Failure) is the largest study to systematically examine health-related quality of life (HRQL; measured by the Kansas City Cardiomyopathy Questionnaire–12) and its association with heart failure (HF) outcomes across 8 major geographic regions spanning 5 continents.
- HRQL differs considerably among geographic regions, with markedly lower quality of life related to HF in Africa than elsewhere.
- HRQL is a strong predictor of death and HF hospitalization in all regions, irrespective of symptoms class and with both preserved and reduced ejection faction.

What Are the Clinical Implications?

- HRQL is an inexpensive and simple prognostic marker that is useful in characterizing symptom severity and prognosis in patients with HF.
- There is a need to address disparities that affect HRQL in patients with HF in different regions of the world.

Mortality in patients with heart failure (HF) is high.[1] The key goals of HF therapy are to prevent progression of symptoms, improve quality of life, and prolong survival.[2,3] Health-related quality of life (HRQL) is poor in HF, but it is unknown whether this varies among different regions of the world. Poor HRQL has been associated with worse prognosis but given that most studies were conducted in Western (and high-income) countries, it is not known whether the prognostic importance of HRQL varies in patients with HF from different geographic regions.[4] This is important to document given that >80% of cardiovascular disease (and also likely HF) occurs in non-Western low- and middle-income countries. Most data on HRQL are based on patients with HF and reduced ejection fraction (EF <40%) or patients with more advanced symptoms,[4,5] with fewer data available in patients with midrange or preserved EF (≥40%) or patients with mild symptoms.[6–10]

The Kansas City Cardiomyopathy Questionnaire–12 (KCCQ-12) is a simple, widely available, and inexpensive tool that characterizes a patient's HF-related health status. Showing that it can be used as a marker to predict major clinical outcomes in a wide spectrum of patients with HF across the world would confirm its usefulness in research as well as in clinical practice. In this study, we used the KCCQ-12 to examine regional differences in HRQL and whether HRQL predicts outcomes in HF overall, by geographic region, by New York Heart Association (NYHA) class, by EF ≥40% versus <40%, and in patients who had or had not been hospitalized recently.

Nonstandard Abbreviations and Acronyms

ACTION-HF	A Controlled Trial Investigating Outcomes of Exercise Training in Heart Failure
ASCEND-HF	A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure
CHAMP-HF	Change the Management of Patients With Heart Failure
EF	ejection fraction
G-CHF	Global Congestive Heart Failure
HF	heart failure
HRQL	health-related quality of life
HR	hazard ratio
KCCQ-12	Kansas City Cardiomyopathy Questionnaire–12
KCCQ-12-SS	Kansas City Cardiomyopathy Questionnaire–12 Summary Score
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
Tele-HF	Telemonitoring to Improve Heart Failure Outcomes

METHODS

The data that support the findings of this study are not available to be shared with third parties because the study is ongoing.

Study Population

The design of the G-CHF study (Global Congestive Heart Failure) has been described.[11] G-CHF is a prospective multinational cohort study that enrolled >23 000 patients from 40 countries between December 20, 2016, and November 19, 2020, across 8 geographic regions (North America [n=2710], Western Europe [n=3826], Eastern Europe [n=1814], the Middle East [n=1824], South Asia [2974], East Asia [n=1894], Africa [n=5352], and South America [n=2897]). The patients from each country are described in Table I in the Data Supplement. All patients ≥18 years of age with a clinical diagnosis of HF seen in outpatient clinics or inpatient hospital wards were eligible and were selected for participation by means of convenience sampling. Information about demographic characteristics, clinical status, medication use, and echocardiographic data was recorded at the baseline visit.

The diagnosis of HF was established by the local physician caring for the patient, using all available clinical, laboratory, radiographic, echocardiographic, and imaging data. Information on the most recent echocardiogram done within 12 months of enrollment was used for this analysis.

HRQL Assessment

Self-reported HRQL was measured with the KCCQ-12 at baseline for 99.5% (n=23 291) of all patients enrolled in G-CHF. This brief, self-administered questionnaire reflects activities of daily living, HF symptoms, and perceived HRQL over the past 2 weeks. The KCCQ-12 has been validated in multiple HF-related conditions. It has proven to be reliable, responsive, and able to predict prognosis in studies involving small groups of patients with HF[4,5,12–17] with reduced and preserved left ventricular function.[4,5,10,12] Although originally developed as a 23-item questionnaire, the 12-item version used in the current study has been validated and can be used interchangeably with the original version.[18] KCCQ-12 quantifies 4 domains of HF-related health status: physical limitation (question 1a through 1c), symptom frequency (questions 2 through 5), general quality of life (questions 6 and 7), and social limitation (question 8a through 8c; Figure I in the Data Supplement). Answers are recorded on a Likert scale and subsequently converted into scores ranging from 0 to 100 for each domain (higher scores reflect better HRQL). The KCCQ-12 summary score (KCCQ-12-SS; averaged from the 4 domains) ranges from 0 to 100. For clinical applicability, the KCCQ-12 scores are often summarized in ranges of 25 points reflecting HF-related health status (0 to 24, very poor to poor; 25 to 49, poor to fair; 50 to 74, fair to good; 75 to 100, good to excellent).[19] G-CHF used culturally and linguistically validated versions of the KCCQ-12 in all countries where available (https://www.cvoutcomes.org/licenses).

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes were first HF hospitalization and a composite of all-cause mortality or first HF hospitalization. Patients were followed every 6 months up to 2 years (annual clinic visits and interim telephone calls at 6 and 18 months), with assessment of vital status and HF hospitalizations at each contact. The median duration of follow-up for the current analysis was 1.6 years (interquartile range, 1.3–2.0 years). Follow-up rates were 97% at 1 year and 96% at 18 months; 99% had completed at least 1 follow-up visit (at 6, 12, 18, or 24 months follow-up) or had died. Deaths were recorded and ascertained by local investigators through review of relevant source documents. HF hospitalization events were identified through physician or self-report and confirmed by local review of available documentation. HF hospitalization required the hospital stay to be longer than 24 hours.

Statistical Analysis

The KCCQ-12 domain and summary scores were analyzed as continuous variables (score 0 to 100) and grouped into 4 categories of scores: 0 to 24, 25 to 49, 50 to 74, and ≥75. Categorical variables are summarized as counts and proportions. Continuous variables are summarized as mean±SD if normally distributed and median and interquartile range if non-normally distributed. Between-group differences were tested using analyses of variance for continuous variables and χ^2 tests for categorical ones. KCCQ-12 scores were compared among the 8 world regions after adjusting for age, sex, enrollment as an inpatient or outpatient, and EF ≥40% or <40% using a generalized linear model. Average scores are presented as adjusted mean±SE. Patients with mildly reduced EF (40% to 49%) and preserved EF (≥50%) were combined into 1 group to allow for a comparison between more equally sized groups (EF ≥40% versus <40%).

Age- and sex-adjusted 12-month mortality rates were calculated using a generalized linear model and are presented with their 95% CIs. The associations between KCCQ-12-SS and all-cause mortality, HF hospitalization, and the composite of the two were examined as cumulative incidence rates using the Kaplan-Meier method. Patients were censored at the last date of follow-up (maximum of 2 years) or death. We used multivariable Cox proportional hazard regression models to assess the associations of baseline KCCQ-12-SS and the primary and secondary outcomes. Baseline KCCQ-12-SS was included in the model as a continuous variable. A 10-unit (10-U) difference has previously been shown to reflect moderate to large clinical change and was considered to be clinically important.[19–21] In separate Cox models, KCCQ-12-SS was included as a 4-group categorical variable (0 to 24, 25 to 49, 50 to 74 and ≥75), with the highest score category (≥75 points) as the reference group. The 25-point ranges have been reported previously and can be readily applied in clinical practice.[19] We prespecified variables to include in the models on the basis of demographic factors and clinical measures known to be associated with worse outcomes[22] and checked the proportionality assumption with standard log(-log [survival]) plots. Two different models were used. The first model was adjusted for age, sex, and region (8 regions; South America was the reference because event rates were lowest in this region). The second model, in addition to region, sex, and age, included 8 of the 13 demographic, clinical, and treatment-related factors known to be associated with worse outcomes in HF from the MAGGIC criteria (Meta-Analysis Global Group in Chronic Heart Failure),[22] plus socioeconomic variables (education and urban/rural dwelling) and 3 echocardiographic measures (left ventricular function, right ventricular enlargement, and valvular dysfunction) as detailed in Table II in the Data Supplement. We restricted the number of covariates to 15 to allow using the same multivariable model for all subgroups. Sensitivity analyses including the full set of the MAGGIC HF criteria, additional socioeconomic covariates such as marital status, health and medication insurance, and additional comorbidities, and objective signs of HF did not alter the observed strength of associations in the overall analyses (data not shown). After tests for interaction using the fully adjusted model (model 2) were performed, stratified analyses were also undertaken using Cox proportional hazards models to examine whether the associations between KCCQ-12-SS and outcomes differed among several subgroups of patients (different geographic regions, NYHA class I or II versus III or IV, EF ≥40% versus <40%, and inpatients versus outpatients). An additional subgroup analysis was performed in patients stratified by HF with preserved, mildly reduced, and reduced EF (Table III in the Data Supplement).

A 2-tailed *P* value <0.05 was considered statistically significant. All analyses were performed with SAS (version 9.4).

Ethical Considerations

The study protocol was approved by each center's ethics committee. Written informed consent was obtained from every study participant before study enrollment.

RESULTS

Patient Characteristics

A total of 23 291 patients from 8 world regions were enrolled (Table 1). The mean (SD) age was 65±15 years, 61% were men, and 32% were inpatients; 40% were in NYHA functional class III or IV and 46% had EF ≥40%. There were considerable variations in patient characteristics among different regions. Mean age was lowest in Africa (57±17 years) and highest in Western Europe (71±12 years). Women accounted for 54% of patients in Africa and ≤41% in other regions. Fewer patients from North and South America were recruited from an inpatient setting (16% and 14%, respectively) compared with other regions (average 32% and as high as 52% in South Asia). Patients with NYHA class III or IV symptoms were most frequent in East Asia (59%) and Africa (50%), less frequent in South Asia (43%), and the least frequent in other regions (<36%). Among patients with EF recorded (n=19 355 [83%]), the percent with EF ≥40% was 66% in Eastern Europe; 60% in East Asia; between 46% and 49% in Africa, South America, and Western Europe; less in North America (41%); and was least frequent in South Asia (34%) and the Middle East (27%).

Variations in Baseline HRQL

Table 1 describes KCCQ-12 summary and domain scores overall and by different regions. The mean±SE KCCQ-12-SS in the overall population was 55.0±0.2. After adjusting for age, sex, and markers of HF severity (inpatient versus outpatient and EF), the lowest scores were seen in Africa and in Eastern Europe (39.5±0.3 and 51.3±0.6, respectively). Higher, adjusted HRQL ratings were observed in the other regions, ranging from 54.9±0.6 in East Asia to 62.5±0.4 in Western Europe. Regional differences in scores were largely consistent across the 4 KCCQ-12 domains. The domain reflecting general quality of life had the lowest scores in all regions and the domain reflecting symptom burden had the highest scores (ie, the least affected HRQL ratings). This pattern was also consistent in the subgroups by NYHA class, EF ≥40% and <40%, and in inpatients and outpatients.

KCCQ-12-SS was lower in patients with worse NYHA class. Adjusted mean score ±SE in NYHA class I was 77.9±0.5; in NYHA class II, 61.1±0.2; in NYHA class III, 41.5±0.3; and in NYHA class IV, 29.4±0.5 (P<0.0001; Table 2). The adjusted mean KCCQ-12-SS was comparable in patients with EF ≥40% and EF <40% (54.6±0.3 and 52.8±0.2, respectively; P<0.0001; Table 3). Inpatients had lower adjusted mean KCCQ-12-SS compared with outpatients (38.8±0.3 versus 61.2±0.2; P<0.0001; Table IV in the Data Supplement), with similar differences within each region.

KCCQ-12 and Clinical Outcomes

The median follow-up time was 1.6 (1.3–2.0) years, during which 4460 (19.2%) patients had died, 3885 (16.7%) had been hospitalized for HF, and 6949 (29.8%) had had either of the 2 events. As described in Table 4 and Figure 1, mortality rates were inversely related to KCCQ-12-SS in a graded manner (1-year adjusted death rates: lowest category [scores 0 to 24], 27.8%; second category [scores 25 to 49], 15.0%; third category [scores 50 to 75], 8.8%; and the highest category [score ≥75], 4.6%). Similar associations were observed for first HF hospitalization and for the composite of mortality or HF hospitalization (20.3%, 16.7%, 11.1%, and 5.2% and 40.6%, 27.2%, 17.4%, and 8.8%, respectively). The adjusted hazard ratio (HR) for all-cause mortality by 10-U decrement in KCCQ-12-SS was 1.18 (95% CI, 1.17–1.20). When KCCQ-12-SS was grouped into 4 categories, compared with the highest category (≥75), adjusted HRs were 2.52 (95% CI, 2.23–2.85) for the lowest category, 1.86 (95% CI, 1.66–2.08) for the second category, and 1.38 (95% CI, 1.23–1.55) for the third category (P value for trend <0.0001).

The association between KCCQ-12-SS and outcomes differed between regions (interaction P<0.0001). Stratified analyses showed a significant inverse association between poorer HRQL and higher risk of all-cause death in all world regions (Figure 2): the strongest associations were seen in the Middle East and in Eastern Europe (HR for 10-U decrement, 1.22 [95% CI, 1.15–1.25] and 1.31 [95% CI, 1.21–1.42], respectively); intermediate associations were seen in North America, East Asia, and Western Europe (HR, 1.17 [95% CI, 1.12–1.24], 1.19 [95% CI, 1.12–1.27], and 1.20 [95% CI, 1.15–1.26], respectively); and the weakest associations were seen in South Asia, South America, and Africa (HR, 1.08 [95% CI, 1.03–1.14], 1.11 [95% CI, 1.06–1.16], and 1.11 [95% CI, 1.08–1.14], respectively).

As depicted in Figure 3 and Table 2, although the adjusted mortality rates were higher in NYHA classes III and IV than in classes I or II, the graded inverse correlation between KCCQ-12-SS category and all-cause death was observed in both groups. The mortality rate for patients with milder symptoms (NYHA class I or II) but reporting the lowest HRQL (KCCQ-12-SS scores 0 to 24) was 29%, whereas the mortality rate was only 16.1% for patients with severe symptoms (NYHA class III or IV) who reported the best HRQL (KCCQ-12-SS scores ≥75). The inverse association with all clinical outcomes persisted after adjustment for clinical, demographic, and echocardiographic characteristics (fully adjusted model); HRs for all-cause mortality per 10-U decrements in KCCQ-12-SS in NYHA class I and II was 1.17 (95% CI, 1.14–1.19) and in NYHA class III and IV it was 1.14 (95% CI, 1.12–1.17; interaction P=0.13). The HRs for 10-U decrement in the KCCQ-12-SS for

Table 1. Baseline Characteristics and Health-Related Quality of Life Overall and by Region

Variable	Overall	Missing	North America	Western Europe	Eastern Europe	East Asia	South Asia	Africa	South America	Middle East
No. of patients	23 291		2710	3826	1814	1894	2974	5352	2897	1824
Demographic and clinical characteristics										
Age, y	65±13		65±13	71±12	66±12	66±15	59±13	57±17	67±12	58±14
Male sex	14 186 (61)		1904 (70)	2610 (68)	1157 (64)	1125 (59)	1897 (64)	2444 (46)	1806 (62)	1243 (68)
Recruited as hospital inpatient	7362 (32)	4	437 (16)	1097 (29)	637 (35)	880 (47)	1532 (52)	1851 (35)	406 (14)	522 (29)
Primary heart failure, ischemic	8871 (40)	1208	1164 (46)	1523 (43)	975 (57)	909 (50)	1427 (54)	621 (12)	1269 (46)	983 (55)
Body mass index, kg/m^2	27 (23–31)	564	29 (25–34)	28 (25–32)	30 (26–34)	24 (21–26)	24 (21–27)	24 (21–29)	28 (24–31)	29 (25–33)
Ejection fraction ≥40%	8850 (46)	3936	836 (41)	1435 (49)	1071 (66)	908 (60)	831 (34)	2276 (47)	1031 (46)	462 (27)
NYHA functional class III or IV	9208 (40)	117	920 (35)	1224 (32)	565 (31)	1116 (59)	1276 (43)	2685 (50)	820 (28)	602 (33)
Hemoglobin, g/L	129±22	4157	129±22	132±19	137±19	129±24	125±21	125±21	134±21	129±20
Creatinine, μmol/L	97 (77–124)	3745	103 (82–135)	101 (81–131)	95 (80–115)	87 (71–108)	97 (80–126)	93 (71–124)	96 (80–120)	92 (73–124)
Systolic blood pressure, mm Hg	118±19	64	118±19	124±19	128±16	125±19	123±20	124±26	123±21	124±22
Hypertension	15 283 (66)	2	1811 (67)	2756 (72)	1507 (83)	1089 (58)	1502 (51)	3249 (61)	2260 (78)	1109 (61)
Coronary artery disease	8756 (38)	1	1325 (49)	1672 (44)	1110 (61)	859 (45)	1565 (53)	337 (6)	1191 (41)	697 (38)
Diabetes	7188 (31)	2	1069 (39)	1241 (32)	625 (34)	474 (25)	1258 (42)	667 (12)	959 (33)	895 (49)
Atrial fibrillation or flutter	6387 (27)	2	1174 (43)	1772 (46)	817 (45)	588 (31)	371 (12)	662 (12)	677 (23)	326 (18)
Chronic obstructive pulmonary disease	2438 (10)	1	485 (18)	548 (14)	232 (13)	245 (13)	248 (8)	202 (4)	321 (11)	157 (9)
Pharmacologic treatment										
β-Blocker	18 669 (80)	8	2393 (88)	3387 (89)	1604 (88)	1451 (77)	2210 (74)	3423 (64)	2480 (86)	1721 (94)
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/sacubitril/valsartan	17 923 (77)	7	2149 (79)	3187 (83)	1572 (87)	1351 (71)	1686 (57)	4076 (76)	2396 (83)	1506 (83)
Mineralocorticoid antagonist	12 907 (55)	10	2149 (79)	3187 (83)	1572 (87)	1351 (71)	1686 (57)	4076 (76)	2396 (83)	1506 (83)
Loop diuretic	18 427 (79)	10	1959 (72)	2929 (77)	1405 (77)	1497 (79)	2442 (82)	4936 (92)	1814 (63)	1445 (79)
Health-related quality of life; region estimates are adjusted mean±SE*										
KCCQ-12 summary score	55±0.2		58.2±0.5	62.5±0.4	51.3±0.6	54.9±0.6	61±0.5	39.5±0.3	56.2±0.5	61.6±0.6
KCCQ-12 physical limitation score	56±0.2	545	61.6±0.6	63.5±0.5	51.6±0.6	58.8±0.7	62±0.5	39.5±0.4	57.6±0.6	61.7±0.7
KCCQ-12 symptoms frequency score	62.1±0.2	3	63.1±0.6	66.8±0.5	57.0±0.6	64.8±0.6	71.2±0.5	48.5±0.4	62.4±0.5	68.5±0.6
KCCQ-12 general quality of life score	46.1±0.2	15	51.1±0.6	55.4±0.5	42.8±0.7	43.6±0.7	45.2±0.6	31.6±0.4	48.2±0.6	53.3±0.7
KCCQ-12 social limitation score	55.5±0.2	979	56.2±0.7	63.7±0.6	53.5±0.7	54.3±0.8	65.9±0.6	38.2±0.4	56.2±0.6	62.1±0.7

Values are n (%), mean±SD, or median (interquartile range). *P* values for regional comparison are all <0.0001. KCCQ-12 indicates Kansas City Cardiomyopathy Questionnaire–12; and NYHA, New York Heart Association.

*Mean KCCQ-12 scores are adjusted for age, sex, left ventricular ejection fraction, and inpatient or outpatient status at enrollment.

the composite of death and HF hospitalization among patients with NYHA class I or II was 1.15 (95% CI, 1.13–1.17), which was considerably stronger than the association in patients with NYHA class III or IV 1.09 (95% CI, 1.07–1.11; interaction *P*<0.0001; Table 2). A similar pattern was observed for the association between KCCQ-12-SS and HF hospitalization between patients in NYHA class I or II versus III or IV.

The inverse relationship between KCCQ-12-SS category and all outcomes was also observed in patients with EF ≥40% and <40% (Figure 4 and Table 3). Whereas higher mortality rates were observed in patients with EF <40% than in patients with EF ≥40% among patients with better HRQL (KCCQ-12-SS scores ≥50), all-cause mortality rates were similarly worse in patients at different EF levels with the worst HRQL (KCCQ-12-SS scores ≤49). In the fully adjusted model, HRs per 10-U decrement in KCCQ-12-SS for all-cause death were larger in EF ≥40% than EF <40% (1.23 [95% CI, 1.20–1.26] versus 1.15 [95% CI, 1.13–1.17]; interaction *P*<0.0001; Table 3). By contrast, there was no difference in association between lower KCCQ-12-SS and the risk of HF

Table 2. Adjusted Mean Baseline KCCQ-12-SS and Adjusted HRs for All-Cause Mortality, First HF Hospitalization, and All-Cause Mortality or HF Hospitalization by NYHA Class

KCCQ-12-SS	Mean* ± SE			*P* value	
NYHA class				<0.0001	
I	77.9±0.5				
II	61.1±0.2				
III	41.5±0.3				
IV	29.4±0.5				
Outcomes by KCCQ-12-SS 10-U decrements	**No. of patients**	**No. of events**	**HR (95% CI)**	***P* value**	***P* interaction comparing adjusted HRs (model 2)**
All-cause mortality					
NYHA I or II KCCQ-12 per 10-U decrements					0.13
Model 1	13 964	1806	1.19 (1.17–1.21)	<0.0001	
Model 2	11 172	1427	1.17 (1.14–1.19)	<0.0001	
NYHA III or IV					
KCCQ-12 per 10-U decrements					
Model 1	9206	2629	1.16 (1.14–1.18)	<0.0001	
Model 2	7590	2129	1.14 (1.12–1.17)	<0.0001	
HF hospitalization					
NYHA I or II					<0.0001
KCCQ-12 per 10-U decrements					
Model 1	13 964	1704	1.19 (1.17–1.22)	<0.0001	
Model 2	11 172	1398	1.15 (1.12–1.18)	<0.0001	
NYHA III or IV					
KCCQ-12 per 10-U decrements					
Model 1	9206	2161	1.12 (1.10–1.14)	<0.0001	
Model 2	7590	1866	1.06 (1.04–1.08)	<0.0001	
All-cause mortality or HF hospitalization					
NYHA I or II					<0.0001
KCCQ-12 per 10-U decrements					
Model 1	13 964	2965	1.19 (1.17–1.21)	<0.0001	
Model 2	11 172	2384	1.15 (1.13–1.17)	<0.0001	
NYHA III or IV					
KCCQ-12 per 10-U decrements					
Model 1	9206	3946	1.14 (1.12–1.16)	<0.0001	
Model 2	7590	3298	1.09 (1.07–1.11)	<0.0001	

Model 1 adjusted for age, sex, and region. Model 2 adjusted for demographic and clinical variables: sex, age, region, care level (inpatient or outpatient), baseline body mass index, diabetes, chronic pulmonary obstructive disease, treatment with β-blockade, treatment with angiotensin-converting enzyme/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, systolic blood pressure, living location (urban/rural), education, echocardiographic parameters, left ventricular ejection fraction, right ventricular function, and valvular dysfunction. HF indicates heart failure; HR, hazard ratio; KCCQ-12-SS, Kansas City Cardiomyopathy Questionnaire–12 Summary Score; and NYHA, New York Heart Association.

*Means adjusted for age, sex, inpatient or outpatient at enrollment, and ejection fraction.

hospitalization between patients with EF ≥40% versus <40% (1.14 [95% CI, 1.12–1.17] versus 1.14 [95% CI, 1.02–1.16]; interaction *P*=0.23; Table 3).

The inverse relationship between KCCQ-12-SS and all-cause death was also consistent irrespective of whether patients were enrolled as outpatients or inpatients. There was a similar association between lower KCCQ-12-SS and the risk of death, HF hospitalization, and the risk of the composite of either event in outpatients versus inpatients (fully adjusted HRs for all-cause death per 10-U decrement in KCCQ-12-SS for outpatients, 1.17 [95% CI, 1.15–1.19]; for inpatients, HR, 1.19 [95% CI, 1.17–1.25]; interaction *P*=0.06; Table IV in the Data Supplement).

Table 3. Adjusted Mean Baseline KCCQ-12-SS and Adjusted HRs for All-Cause Mortality, First HF Hospitalization, and All-Cause Mortality or HF Hospitalization by EF ≥ or <40%

KCCQ-12-SS	Mean* ± standard error			*P* value	
EF ≥40%	54.6±0.3			<0.0001	
EF <40%	52.8±0.2				
Outcomes by KCCQ-12-SS 10-U decrements	**No. of patients**	**No. of events**	**HR (95% CI)**	***P* value**	***P* interaction comparing adjusted HRs (model 2)**
All-cause mortality					
EF ≥40%					
KCCQ-12 per 10-U decrements					
Model 1	8850	1579	1.25 (1.23–1.28)	<0.0001	
Model 2	8634	1513	1.23 (1.20–1.26)	<0.0001	
EF <40%					<0.0001
KCCQ-12 per 10-U decrements					
Model 1	10 504	2168	1.19 (1.17–1.21)	<0.0001	
Model 2	10 194	2059	1.15 (1.13–1.17)	<0.0001	
HF hospitalization					
EF ≥40%					
KCCQ-12 per 10-U decrements					
Model 1	8850	1420	1.21 (1.18–1.24)	<0.0001	
Model 2	8634	1386	1.14 (1.12–1.17)	<0.0001	
EF <40%					0.23
KCCQ-12 per 10-U decrements					
Model 1	10 504	1934	1.18 (1.16–1.20)	<0.0001	
Model 2	10 194	1891	1.14 (1.12–1.16)	<0.0001	
All-cause mortality or HF hospitalization					
EF ≥40%					
Model 1	8850	2484	1.24 (1.22–1.26)	<0.0001	
Model 2	8634	2403	1.18 (1.16–1.20)	<0.0001	
EF <40%					<0.001
KCCQ-12 per 10-U decrements					
Model 1	10 504	3434	1.19 (1.17–1.20)	<0.0001	
Model 2	10 194	3302	1.14 (1.13–1.16)	<0.0001	

Model 1 was adjusted for age, sex, and region. Model 2 was adjusted for demographic and clinical variables: sex, age, region, care level (inpatient or outpatient), baseline body mass index, diabetes, chronic pulmonary obstructive disease, treatment with β-blockade, treatment with angiotensin-converting enzyme/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, systolic blood pressure, living location (urban/rural), education, echocardiographic parameters, right ventricular function, and valvular dysfunction. EF indicates ejection fraction; HF, heart failure; HR, hazard ratio; and KCCQ-12-SS, Kansas City Cardiomyopathy Questionnaire–12 Summary Score.

*Means adjusted for age, sex, and inpatient or outpatient at enrollment.

DISCUSSION

Patient-reported HRQL optimally gives fast, comprehensive, and standardized information regarding a patient's current health status and its prognostic implications. Showing that results from a simple patient-administered HRQL tool such as the KCCQ-12 is associated with major clinical outcomes in a wide spectrum of patients with HF across different regions of the world is important in assessing whether it can be of value in different settings. Our study has systematically examined HRQL and its association with outcomes across most geographic regions. We include 5000 patients from 9 African countries where data on HF are sparse. The key findings are that self-reported HRQL is inversely correlated with the risk of all-cause death and HF hospitalization in all regions represented in the G-CHF population and irrespective of HF symptoms class or EF.

Geographic Variations in HRQL

The population we studied is a diverse group of patients with HF, with few exclusions drawn from both

Table 4. Adjusted 12-Month Event Rate, 95% CI, and Crude and Adjusted HRs for All-Cause Mortality, First HF Hospitalization, and the Composite of Either Event Within 24 Months by KCCQ-12-SS in the Overall Population

Health-related quality of life estimates	Adjusted 12-month event rate, % (95% CI)	24-month outcomes, HR (95% CI)	
		Model 1 (n=23 291)	Model 2 (n=18 828)
All-cause mortality			
KCCQ-12-SS by 10-U decrements		1.22 (1.20–1.23)	1.18 (1.17–1.20)
KCCQ-12 category			
75 to 100	4.6 (3.8–5.3)	1	1
50 to 74	8.8 (8.0–9.5)	1.65 (1.49–1.83)	1.38 (1.23–1.55)
25 to 49	15.0 (14.2–15.8)	2.54 (2.30–2.80)	1.86 (1.66–2.08)
0 to 24	27.8 (26.8–28.8)	4.09 (3.7–4.53)	2.52 (2.23–2.85)
P value for trend	<0.0001	<0.0001	<0.0001
HF hospitalization			
KCCQ-12-SS by 10-U decrements		1.20 (1.19–1.22)	1.14 (1.13–1.16)
KCCQ-12 category			
75 to 100	5.2 (4.5–6.0)	1	1
50 to 74	11.1 (10.3–11.8)	1.96 (1.77–2.18)	1.75 (1.56–1.97)
25 to 49	16.7 (15.8–17.5)	3.03 (2.74–3.35)	2.38 (2.12–2.67)
0 to 24	20.3 (19.3–21.3)	3.76 (3.37–4.20)	2.55 (2.24–2.91)
P value for trend	<0.0001	<0.0001	<0.0001
All-cause mortality or HF hospitalization			
KCCQ-12-SS by 10-U decrements		1.21 (1.2–1.22)	1.16 (1.15–1.17)
KCCQ-12 category			
75 to 100	8.8 (7.8–9.7)	1	1
50 to 74	17.4 (16.5–18.4)	1.77 (1.64–1.91)	1.56 (1.42–1.70)
25 to 49	27.2 (26.2–28.2)	2.72 (2.52–2.94)	2.11 (1.93–2.31)
0 to 24	40.6 (39.3–41.8)	3.99 (3.68–4.32)	2.60 (2.36–2.87)
P value for trend	<0.0001	<0.0001	<0.0001

Model 1 adjusted for age, sex, and region. Model 2 adjusted for demographic and clinical variables: sex, age, region, care level (inpatient or outpatient), baseline body mass index, diabetes, chronic pulmonary obstructive disease, treatment with β-blockade, treatment with angiotensin-converting enzyme/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, systolic blood pressure, living location (urban/rural), education, echocardiographic parameters, left ventricular ejection fraction, right ventricular function, and valvular dysfunction. HF indicates heart failure; HR, hazard ratio; and KCCQ-12-SS, Kansas City Cardiomyopathy Questionnaire–12 Summary Score.

outpatients and inpatients in 40 countries at different country income levels. These countries are at various stages of epidemiologic transition, have varying health care systems, and have different levels of access to care.[23–25] In poorer countries, patients may present only when their symptoms are more advanced. The quality of their treatments may also differ. This can be expected to be reflected in HRQL ratings. We observed significant differences in average KCCQ-12-SS between regions; however, these variations remained after adjusting for markers of disease severity such as inpatient versus outpatient, EF, and age and sex. This suggests that additional factors may affect HRQL. In Africa and Eastern Europe, where we observed the worst HRQL ratings, adjusted mean KCCQ-12-SS were ≈20 and ≈10 points lower, respectively, than in the regions with the highest self-rated HRQL (Western Europe, South Asia, and the Middle East). A difference of 10 points is clinically important and has previously been associated with an 18% relative difference in risk of mortality or HF hospitalization,[10] and by 16% difference in our study. This makes HRQL as important a risk predictor as other commonly used prognostic markers, such as EF, NYHA class, and natriuretic peptides.[10,19–21] These variations may reflect true differences in HRQL for patients living with HF in different parts of the world that can be captured only by formal questionnaires such as the KCCQ-12. Another possibility is that HRQL has different meanings and different implications in different cultures around the world. The KCCQ has previously been validated in HF populations from North and South America, Western Europe, and some parts of Asia and Africa,[4,14–17,26] but not in Eastern Europe or the Middle East. A few studies have reported on HRQL

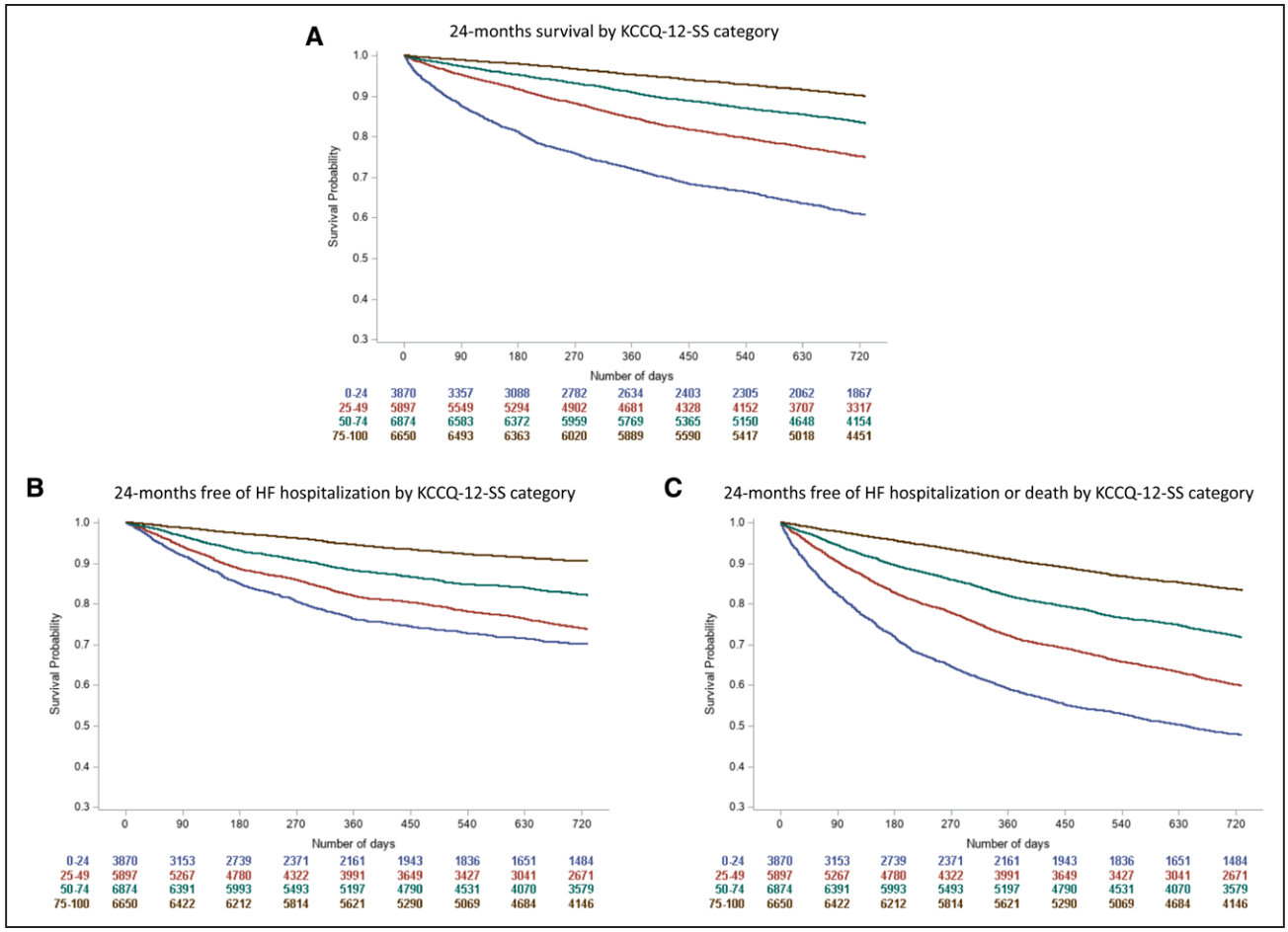

Figure 1. Clinical outcomes, by KCCQ-12-SS category.
Kaplan-Meier curves for all-cause mortality (**A**), HF hospitalization (**B**), and all-cause mortality or HF hospitalization (**C**). KCCQ-12-SS category ranges are 0 to 24, 25 to 49, 50 to 74, and 75 to 100, with higher score indicating better health-related quality of life. HF indicates heart failure; and KCCQ-12-SS, Kansas City Cardiomyopathy Questionnaire–12 summary score.

across different geographic regions or ethnicities. The PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) analyzed HRQL in 8399 patients with EF <45% and compared average HRQL ratings among North America, Central/Eastern Europe and Russia, Latin America, and Asia-Pacific, with the poorest HRQL observed in Central/Eastern Europe and Russia and the highest in Latin America and Asia-Pacific.[27] Another study compared HRQL among patients from multiple ethnicities in a combined analysis of 5697 patients with EF ≤35% from ACTION-HF (A Controlled Trial Investigating Outcomes of Exercise Training in Heart Failure; a randomized trial of 1998 patients with left ventricular EF ≤35% and moderate to severe HF from 83 centers in the United States, Canada, and France) and ASIAN-HF (a prospective observational registry of 3688 patients with HF with EF ≤35% from 46 sites in 11 Asian countries).[28] The worst KCCQ scores were observed in patients of Malay and Chinese ethnicity; patients of Japanese, Korean, or White ethnicity had the highest KCCQ scores. These findings are consistent with ours in that HRQL ratings varied among geographic locations and patient ethnicities and the regions where HRQL ratings were poorer were somewhat similar for the regions or ethnicities represented. Two other studies of North American HF cohorts (the CHAMP-HF registry [Change the Management of Patients with Heart Failure; n=3494] and the Tele-HF trial [Telemonitoring to Improve Heart Failure Outcomes; n=1427]) have examined differences in HRQL ratings among Hispanic, Black, and White patients[29] and non-Hispanic Black and non-Hispanic White patients[30] and found only slight differences in self-reported HRQL. The current observations expand on previous findings by simultaneously including patients from 5 continents and 40 countries. We include the first data from several African countries. By including large numbers of patients with both EF ≥40% and <40% and by including patients who were hospitalized or ambulant with HF and patients with different levels of symptoms, our results are likely to be widely generalizable.

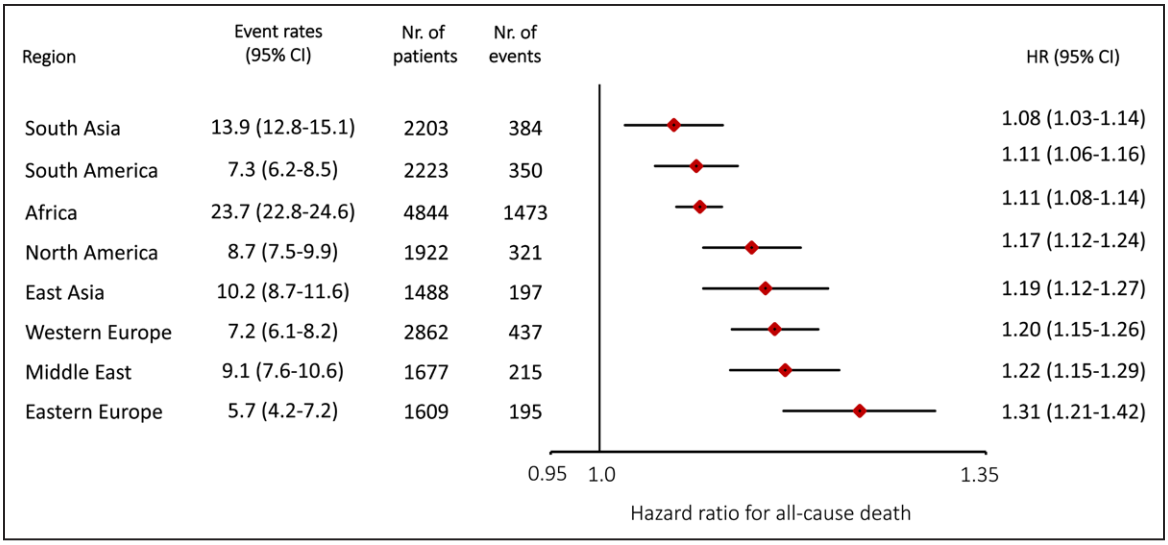

Figure 2. Regional variation in death rates and association between KCCQ-12-SS and death.
Age- and sex-standardized 12-month all-cause death rates and adjusted HRs and 95% CIs for the risk of all-cause mortality within 24 months by 10-U decrements in KCCQ-12-SS in each world region are shown. HRs are adjusted for sex, age, care level (inpatient or outpatient), baseline body mass index, systolic blood pressure, history of diabetes, history of chronic pulmonary obstructive disease, echocardiographic parameters, left ventricular ejection fraction, right ventricular function, valvular dysfunction, treatment with β-blockers or angiotensin-converting enzyme/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitors, living location (urban/rural), and education. HR indicates hazard ratio; and KCCQ-12-SS, Kansas City Cardiomyopathy Questionnaire–12 summary score.

Despite the variations in HRQL by different geographic region and symptom severity, general quality of life was the domain that consistently generated the worst KCCQ-12 score. This observation is consistent with previous ones in smaller studies[16,28,30,31] and likely reflects the best summary of patient experiences.

HRQL and Clinical Outcomes

Although there is evidence that HRQL predicts mortality in patients with HF, previous data predominantly come from high-income countries and mostly, although not exclusively, based on studies involving patients with reduced EF.[5,10,13,20,28,32–35] Two exceptions are the multiethnic comparison of the ACTION-HF (n=1998) and ASIAN-HF (n=3688) cohorts[28] and a retrospective analysis of ASCEND-HF (A Study Testing the Effectiveness of Nesiritide in Patients with Acute Decompensated Heart Failure; a multinational randomized study of 7141 hospitalized patients with acute HF from Asia-Pacific, Central Europe, Latin America, North America, and Western Europe).[32] The results from these studies are similar to ours. HRQL was a strong predictor of mortality even after adjusting for factors related to physical symptoms and socioeconomic parameters known to affect HF prognosis.[22,36] The large size of our study enabled robust analyses in subgroups. We demonstrate that KCCQ-12-SS predicts mortality and HF hospitalization irrespective of NYHA class,[37,38] in both inpatients and outpatients,[13,17,20,33,39] as well as in patients with EF ≥40% and <40%.[10,12] Poor HRQL was a stronger predictor of adverse outcomes in the group with milder HF symptoms compared with more severe symptoms (NYHA class I or II versus III or IV). The mortality rate for patients with milder symptoms (NYHA class I or II) who reported the lowest HRQL was 29%, whereas the mortality rate was only 16% for patients with severe symptoms (NYHA class III or IV) who reported the best HRQL. This suggests that self-reported HRQL is a better indicator of prognosis in HF compared with the commonly used NYHA class, which is an assessment of symptom severity elicited by physicians. To our knowledge, this has not been reported previously on such a large scale.

We found that HRQL was a stronger predictor of all-cause death and the composite of death or HF hospitalization in patients with preserved or mildly reduced EF (≥40%) compared with reduced EF (<40%). Based on these observations, HRQL measures such as the KCCQ-12 may be particularly informative for clinical practice when trying to risk stratify patients with HF with milder symptoms or patients with HF and preserved EF. HRQL is a simple and strong added risk predictor that can be used in most clinical settings around the world to identify patients in need of further attention to prevent death or HF hospitalizations. This is of particular interest because obtaining markers such as natriuretic peptides or echocardiograms are less widely available or affordable in many parts of the world. This supports the inclusion of HRQL estimation as an important outcome in future clinical trials and registries.

We found that the importance of HRQL in predicting worse outcomes varied by region. The weakest associations were observed in South Asia, South America, and Africa, and the strongest in Eastern Europe. The reasons

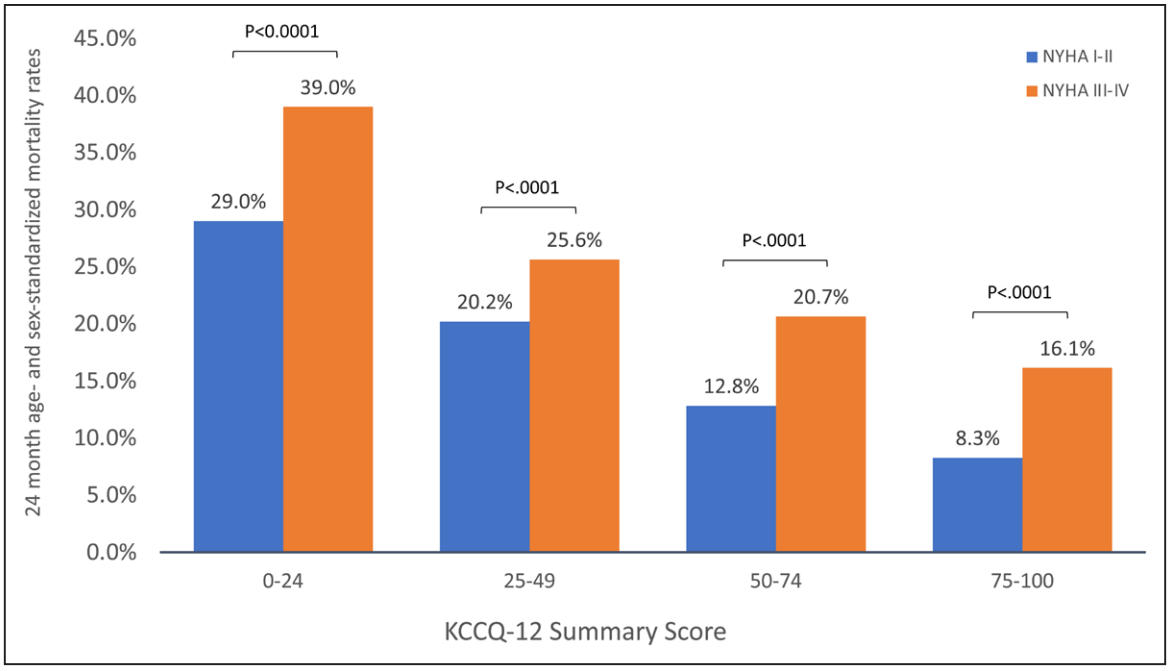

Figure 3. Adjusted death rate, by NYHA class and KCCQ-12 summary score category.
All-cause death rates adjusted for age and sex in patients with NYHA class I and II versus III and IV by KCCQ-12 summary score category (0 to 24, 25 to 49, 50 to 74, and 75 to 100, with higher score indicating better health-related quality of life). KCCQ-12 indicates Kansas City Cardiomyopathy Questionnaire–12; and NYHA, New York Heart Association.

why the associations between HRQL and outcomes were weaker in South Asia, Africa, and South America are not known. It is possible that patients' responses to disease-specific health status questionnaires such as the KCCQ-12 differ across cultures with varying levels of health literacy. This may have an effect even though the KCCQ has been validated for prognostic prediction in many different populations, including in sub-Saharan Africa, Asia, and South America.[4,17,28] It is possible that patients in South Asia, Africa, and South America more

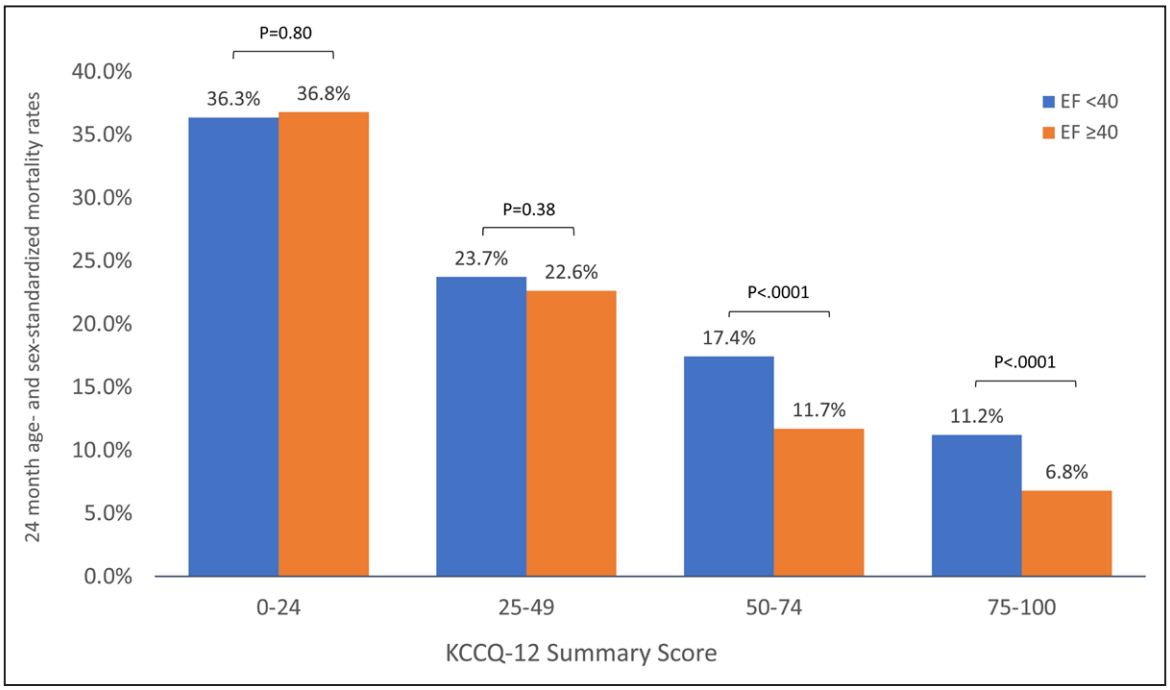

Figure 4. Adjusted death rate, by EF and KCCQ-12 summary score category.
All-cause death rates adjusted for age and sex in patients with EF ≥40% versus <40% by KCCQ-12 summary score category (0 to 24, 25 to 49, 50 to 74, and 75 to 100, with higher score indicating better health-related quality of life). EF indicates ejection fraction; and KCCQ-12, Kansas City Cardiomyopathy Questionnaire–12.

often had HF with reduced EF, and KCCQ-12-SS was a weaker predictor in patients with EF <40%. It is also possible that factors unrelated to HF (eg, social factors, poverty, deprivation) may have a larger effect on mortality than the severity of HF per se in these regions of the world. The associations between HRQL attributable to HF and outcomes may thus be weaker, although the multivariable adjustments at least in part should account for such confounding. The large sample size and considerable number of events in all regions decreases the likelihood of this being a chance finding. However, the large sample size also means that there is a possibility that these regional variations, while being statistically significant, may not necessarily indicate clinically important differences in the strength of association between HRQL and clinical outcomes in different regions. Nevertheless, the more important finding from a clinical perspective is that KCCQ-12-SS strongly and independently predicts patient-important outcomes in all regions, across the spectrum of HF severity, even after taking anthropometric, sociodemographic, and clinical characteristics into consideration. This points to the potential benefit of using KCCQ-12 or similar metrics as simple, readily available, and inexpensive prognostic tools in routine clinical care versus some other tests such as advanced imaging or biomarkers.

Strengths and Limitations

The G-CHF represents a diverse HF population, but comparisons of patients' characteristics and outcomes between regions were possible because of standardized protocol and approach. Patients were selected by convenience rather than random sampling. However, to our knowledge, no systematic differences in approaches to enrollment between regions occurred. Therefore, although the large sample size provides generalizability, it is important to note that observed differences in HRQL and other characteristics reflect diversities in the sample of patients from 8 regions of the world studied, which may or may not be representative of all patients with HF from all regions. The completeness of data on HRQL in the total G-CHF population (99.5%) and high follow-up rate (97% had completed 12 months follow-up) provide further confidence in our findings. EF was not known in 17% of the participants (missing ranging from 8% in the Middle East to 9% in Africa to 25% in North America), but the strength of association between KCCQ-12-SS and all outcomes was not altered when excluding EF from the Cox model. Therefore, this should not affect the interpretation of our results. We used HF hospitalization as a secondary end point, knowing that factors determining whether patients with HF are hospitalized vary by region, health systems, and economic circumstances.[40]

Although the KCCQ-12 was translated into each language and validated in several (but not all) countries,[4,14–17] there may be cultural differences in how patients interpret symptoms as well as their effects in different cultures and social context. Comprehension of and ability to respond accurately to questionnaires may vary by region. Nevertheless, our data showing a strong relationship between KCCQ-12-SS and clinical outcomes in all regions indicates the applicability of the measure to a wide range of social and cultural settings.

CONCLUSIONS

HRQL in HF is a strong and independent predictor of mortality and HF hospitalizations in all regions represented in the G-CHF population, in mildly and severe symptomatic HF, and among patients with preserved and reduced EF. Assessment of HRQL will be of value in characterizing patients with HF in addition to other clinical markers.

ARTICLE INFORMATION

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Supplemental Material

Data Supplement Tables I–IV
Data Supplement Figure I

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