Health-Related Quality of Life Outcomes in PARADIGM-HF

BACKGROUND: Patients with heart failure and reduced ejection fraction have impaired health-related quality of life (HRQL) with variable responses to therapies that target mortality and heart failure hospitalizations. In PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubitril/valsartan reduced morbidity and mortality compared with enalapril. Another major treatment goal is to improve HRQL. Given improvements in mortality with sacubitril/valsartan, this analysis provides comprehensive assessment of impact of therapy on HRQL in survivors only.

METHODS AND RESULTS: Patients (after run-in phase) completed disease-specific HRQL using Kansas City Cardiomyopathy Questionnaire (KCCQ) at randomization, 4 month, 8 month, and annual visits. Changes in KCCQ scores were calculated using repeated measures analysis of covariance model that adjusted for treatment and baseline values (principal efficacy prespecified at 8 months). Among the 8399 patients enrolled in PARADIGM-HF, 7623 (91%) completed KCCQ scores at randomization with complete data at 8 months for 6881 patients (90% of baseline). At 8 months, sacubitril/valsartan group noted improvements in both KCCQ clinical summary score (+0.64 versus −0.29; P=0.008) and KCCQ overall summary score (+1.13 versus −0.14; P<0.001) in comparison to enalapril group and significantly less proportion of patients with deterioration (≥5 points decrease) of both KCCQ scores (27% versus 31%; P=0.01). Adjusted change scores demonstrated consistent improvements in sacubitril/valsartan compared with enalapril through 36 months.

CONCLUSIONS: Change scores in KCCQ clinical summary scores and KCCQ overall summary scores were better in patients treated with sacubitril/valsartan compared with those treated with enalapril, with consistency in most domains, and persist during follow-up beyond 8 months. These findings demonstrate that sacubitril/valsartan leads to better HRQL in surviving patients with heart failure.

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WHAT IS NEW?

- This study reports the primary quality of life outcomes for PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure), the largest pharmacological trial conducted in patients with heart failure and reduced ejection fraction.
- Sacubitril/valsartan improves health-related quality of life in comparison to enalapril by 4 months after randomization, and these improvements persisted throughout 36 months.
- There was a consistent effect of sacubitril/valsartan across all 8 quality of life domains, which is not typically seen in pharmacological interventions.
- Patients who were admitted to hospital have significant declines in the quality of life, but the severity of the decline was attenuated with sacubitril/valsartan.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Improving quality of life is an important stand-alone target of therapy for heart failure patients, and it is linked to increased risk for morbidity and mortality.
- Using sacubitril/valsartan improves quality of life to the same magnitude that was seen with cardiac resynchronization therapy in the MADIT-CRT study (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy).
- Several well-defined risk factors (such as higher body mass index and prevalent comorbid conditions) were associated with increased risk for worsening quality of life.
- Clinicians should consider monitoring quality of life in clinical practice among these higher risk patients.

Health-related quality of life (HRQL) is a key target of therapy in the management of patients with chronic heart failure (HF).[1] The HRQL of HF patients is more impaired than age-matched patients without chronic illnesses and those with other comorbidities,[2] and HRQL perceptions are predictive of future risk for morbidity and mortality.[3,4] For many patients with HF, in addition to prolonging life, improving HRQL is important.[5] Given this focus on HRQL by both patients and clinicians, it is relevant to determine the impact of novel interventions on these important patient-reported outcomes.

Angiotensin-converting enzyme (ACE) inhibitors have been the standard of care for management of patients with HF with reduced ejection fraction because of improved survival and reduced hospitalizations for HF.[6] ACE inhibitors and angiotensin receptor blockers have variable long-term effect on HRQL.[2,7,8] Neprilysin is a neutral endopeptidase that facilitates breakdown of natriuretic and other vasoactive peptides. Inhibition of this enzyme provides higher endogenous levels of vasoactive peptides, including natriuretic peptides, which may promote several changes that could improve HRQL.[9] Sacubitril/valsartan combines the neprilysin inhibitor, sacubitril, with the angiotensin receptor blocker, valsartan, to minimize the risk of serious angioedema previously seen with drugs that act to inhibit both neprilysin and ACE. The PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) demonstrated that sacubitril/valsartan was superior to enalapril with regards to reduction in cardiovascular death, HF hospitalizations, and all-cause death.[10] Sacubitril/valsartan also prevented the clinical progression of HF in surviving patients and risk of sudden cardiac death.[11,12] This article provides a comprehensive analysis of HRQL in PARADIGM-HF, a key prespecified secondary outcome measure.[9] The principal objective of this analysis was to determine whether sacubitril/valsartan was superior to enalapril on HRQL changes at 8 months. Secondary objective was to provide an assessment of long-term HRQL changes beyond 8 months.

METHODS

The details of PARADIGM-HF have been previously published.[9,10] Briefly, HF patients ≥18 years of age with New York Heart Association (NYHA) class II, III, or IV functional capacity, left ventricular ejection fraction (LVEF) ≤40%, and either a plasma BNP (B-type natriuretic peptide) >150 pg/mL or NT-proBNP (N-terminal pro-B-type natriuretic peptide) >600 pg/mL or a hospitalization for HF within past 12 months were eligible to be enrolled. Patients already taking ACE inhibitors or angiotensin receptor blockers were eligible if they were taking a daily dose equivalent to enalapril 10 mg and were on stable dose of β-blocker for a minimum of 4 weeks. Key exclusion criteria included symptomatic hypotension, systolic blood pressure <100 mm Hg at screening, estimated glomerular filtration rate <30 mL/(min 1.73 m^2), history of angioedema, or potassium >5.2 mmol/L. Eligible patients were entered (in a single blinded fashion) into a run-in phase where they took enalapril 10 mg twice daily for 2 weeks followed by sacubitril/valsartan 100 mg twice daily initially followed by 200 mg twice daily for a 4- to 6-week period. Patients without significant intolerances to either drug were randomized in 1:1 ratio to either enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily in a double-blinded fashion. The primary outcome was a composite of cardiovascular death or hospitalization for HF. The study was approved by an institutional review committee and informed consent was obtained.

Quality of Life Outcome Measures

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used as the HRQL instrument in PARADIGM-HF. The KCCQ

Table 1. Baseline Characteristics in Patient With and Without KCCQ Score at Baseline

	Patients With KCCQ (N=7623)	Patients Without KCCQ (N=776)	*P* Value
Age, y	64±11	60±12	<0.001
Female sex	1632 (21%)	200 (26%)	0.005
Region			<0.001
North America	600 (7.9%)	2 (0.3%)	
Latin America	1244 (16%)	189 (24%)	
Western Europe and Other	2015 (26%)	36 (4.6%)	
Central Europe	2801 (37%)	25 (3.2%)	
Asia Pacific	963 (13%)	524 (68%)	
Race			<0.001
White	5471 (72%)	73 (9.4%)	
Black	401 (5.3%)	27 (3.5%)	
Asian	993 (13%)	516 (67%)	
Other	758 (9.9%)	160 (21%)	
Systolic blood pressure, mm Hg	120 (110–130)	118 (108–130)	0.001
Body mass index, kg/m^2	27.8 (24.7–31.5)	24.9 (22.3–27.9)	<0.001
eGFR, mL/(min 1.73 m^2)	66 (54–79)	68 (55–81)	0.021
BNP, pg/mL	248 (154–456)	300 (160–639)	<0.001
NT-proBNP, pg/mL	1592 (881–3136)	1851 (948–4006)	<0.001
NYHA class			<0.001
1	319 (4.2%)	70 (9.0%)	
2	5316 (70%)	603 (78%)	
3	1917 (25%)	101 (13%)	
4	59 (0.8%)	1 (0.1%)	
Hypertension	5487 (72%)	453 (58%)	<0.001
Diabetes mellitus	2650 (35%)	257 (33%)	0.36
Atrial fibrillation	2914 (38%)	177 (23%)	<0.001
Hospitalization for HF	4815 (63%)	459 (59%)	0.028
Myocardial infarction	3373 (44%)	261 (34%)	<0.001
Stroke	663 (8.7%)	62 (8.0%)	0.50
Pretrial use of ACE-I	6073 (80%)	459 (59%)	<0.001
Pretrial use of ARB	1571 (21%)	321 (41%)	<0.001
Diuretic	6191 (81%)	547 (71%)	<0.001
Digitalis	2221 (29%)	318 (41%)	<0.001
MRA	4304 (57%)	367 (47%)	<0.001
ICD	1214 (16%)	29 (3.7%)	<0.001
CRT	552 (7.2%)	22 (2.8%)	<0.001
Time since diagnosis			<0.001
≤1 y	2175 (29%)	348 (45%)	
1–5 y	2958 (39%)	274 (35%)	
>5 y	2490 (33%)	154 (20%)	
LVEF, %	30 (25–35)	29 (24–33)	<0.001

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

is a 23-item, widely used, self-administered, disease-specific HRQL instrument that is valid in HF and has excellent psychometric properties, including reliability and responsiveness.[13] The 8 domains include physical limitation, symptom stability, symptom frequency, symptom burden, total symptom score, HRQL, self-efficacy, and social limitations. In addition, there is the KCCQ clinical summary score (KCCQ-CS) and KCCQ overall summary score (KCCQ-OS) that captures the overall health status of the patient. KCCQ-CS captures physical limitation and total symptom scores and KCCQ-OS captures physical limitation, total symptom score, HRQL, and social limitation scores. Each domain and summary score is scaled from 0 to 100, with higher scores indicating better HRQL and a clinically meaningful difference established as 5 points.[14,15] KCCQ was administered in 38 of the 46 countries, excluding countries without validated versions of the instrument.

KCCQ was administered at the time of randomization, which was after the run-in phase, and could have occurred between 5 and 10 weeks postenrollment and served as baseline visit. In addition, KCCQ was measured at 4 months, 8 months, 12 months, and annually thereafter through final visit. To minimize bias introduced by death with a resultant healthier cohort, the primary HRQL efficacy time point was at the 8-month follow-up visit.[9]

Statistical Analysis

Baseline characteristics of patients enrolled in the HRQL subset were compared with those who were not enrolled using descriptive statistics with means (standard deviation) and medians (first and third quartiles) for continuous variables (*t* test and Mann–Whitney test) and numbers and percentage for categorical variables (χ^2 and Mann–Whitney test). Among the patients in the HRQL subset, differences in patient baseline characteristics were assessed by randomization arm.

The KCCQ-CS and the KCCQ-OS served as the principal HRQL scores based on their use in other large HF trials.[4,16] The principal efficacy analysis was the change score between baseline and 8-month visit. The treatment effect of sacubitril/valsartan in comparison to enalapril on change KCCQ-CS and KCCQ-OS was compared using repeated measure analysis of covariance, and the difference was estimated using least squares mean, adjusted for baseline KCCQ score ($P<0.05$ is significant). Patients who died or did not complete the 8-month KCCQ score were excluded from the principal analysis.

Table 2. Baseline Characteristics Between Treatment Groups Among the Patients With Baseline KCCQ Data

	PARADIGM-HF With KCCQ		
	Enalapril (N=3826)	Sacubitril/Valsartan (N=3797)	*P* Value
Mean KCCQ-OS	72.27±19.43	73.48±19.51	0.007
Mean KCCQ-CS	75.30±19.31	76.56±19.32	0.004
Age, y	64±10	64±11	0.59
Female sex	857 (22%)	775 (20%)	0.034
Region			0.56
North America	291 (7.6%)	309 (8.1%)	
Latin America	626 (16%)	618 (16%)	
Western Europe and Other	1006 (26%)	1009 (27%)	
Central Europe	1421 (37%)	1380 (36%)	
Asia Pacific	482 (13%)	481 (13%)	
Race			0.86
White	2742 (72%)	2729 (72%)	
Black	205 (5.4%)	196 (5.2%)	
Asian	496 (13%)	497 (13%)	
Other	383 (10%)	375 (9.9%)	
Systolic blood pressure, mm Hg	120 (110–130)	120 (110–130)	0.48
Body mass index, kg/m^2	27.7 (24.7–31.6)	27.8 (24.7–31.5)	0.95
eGFR, mL/(min 1.73 m^2	66 (53–79)	66 (54–79)	0.99
BNP, pg/mL	245 (153–455)	251 (154–460)	0.68
NT-proBNP, pg/mL	1585 (882–3201)	1560 (880–3084)	0.72
NYHA class			0.11
1	168 (4.4%)	151 (4.0%)	
2	2620 (69%)	2696 (71%)	
3	1006 (26%)	911 (24%)	
4	27 (0.7%)	32 (0.8%)	
Hypertension	2757 (72%)	2730 (72%)	0.88
Diabetes mellitus	1318 (34%)	1332 (35%)	0.56
Atrial fibrillation	1494 (39%)	1420 (37%)	0.14
Hospitalization for HF	2449 (64%)	2366 (62%)	0.12
Myocardial infarction	1677 (44%)	1696 (45%)	0.46
Stroke	343 (9.0%)	320 (8.4%)	0.41
Pretrial use of ACE-I	3037 (79%)	3036 (80%)	0.53
Pretrial use of ARB	804 (21%)	767 (20%)	0.38
Diuretic	3104 (81%)	3087 (81%)	0.85
Digitalis	1143 (30%)	1078 (28%)	0.15
MRA	2213 (58%)	2091 (55%)	0.015
ICD	610 (16%)	604 (16%)	0.97
CRT	271 (7.1%)	281 (7.4%)	0.59
Time since diagnosis			0.27
≤1 y	1082 (28.3%)	1093 (28.8%)	
1–5 y	1467 (38.3%)	1491 (39.3%)	
>5 y	1277 (33.4%)	1213 (31.9%)	
LVEF	30.0 (25.0–35.0)	30.0 (25.0–34.7)	0.67

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CS, clinical summary; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and OS, overall summary.

Several secondary analyses were performed. First, the between-treatment effects of sacubitril/valsartan versus enalapril on KCCQ scores (including the 8 domains) were assessed through 36-month visit using analysis of covariance, adjusting for baseline values. Next, the proportion of patients with clinically meaningful changes in KCCQ-OS and KCCQ-CS scores was calculated at 8 months. Patients were classified as improved (KCCQ change score ≥5 point increase compared with baseline), stable (KCCQ change score between 5 and −5), or declined (KCCQ change score ≥5 point decrease compared with baseline), and *P* for trend was calculated. Next, the clinical factors that were independently associated with KCCQ-OS and KCCQ-CS change scores at 8 months were assessed from candidate variables and were entered using a forward ($P<0.05$) and backwards ($P<0.10$) stepwise selection procedure. Each predictive multivariate model was performed with and without NYHA classification given the overlap between NYHA and HRQL. Finally, the association of a hospitalization for HF on KCCQ-OS and KCCQ-CS change scores over 8 months were assessed. Patients were stratified based on presence or absence of confirmed HF hospitalization (adjudicated by central end point committee) between randomization and 8 months. Overall change scores in KCCQ-OS and KCCQ-CS as well as between-treatment differences of change scores were assessed using analysis of covariance.

A sensitivity analysis was performed in which KCCQ scores were imputed with a score of 0 for all subsequent visits that occurred after the patient died to account for the imbalance of death during follow-up between the 2 treatment arms. The treatment effect of sacubitril/valsartan in comparison to enalapril on change in KCCQ-CS and KCCQ-OS was then compared using repeated measure analysis of covariance at 8 months.

RESULTS

Among the 8399 patients enrolled in PARADIGM-HF, 7623 (91%) in 38 countries completed KCCQ scores at randomization. The baseline characteristics of the patients who completed the KCCQ were different than

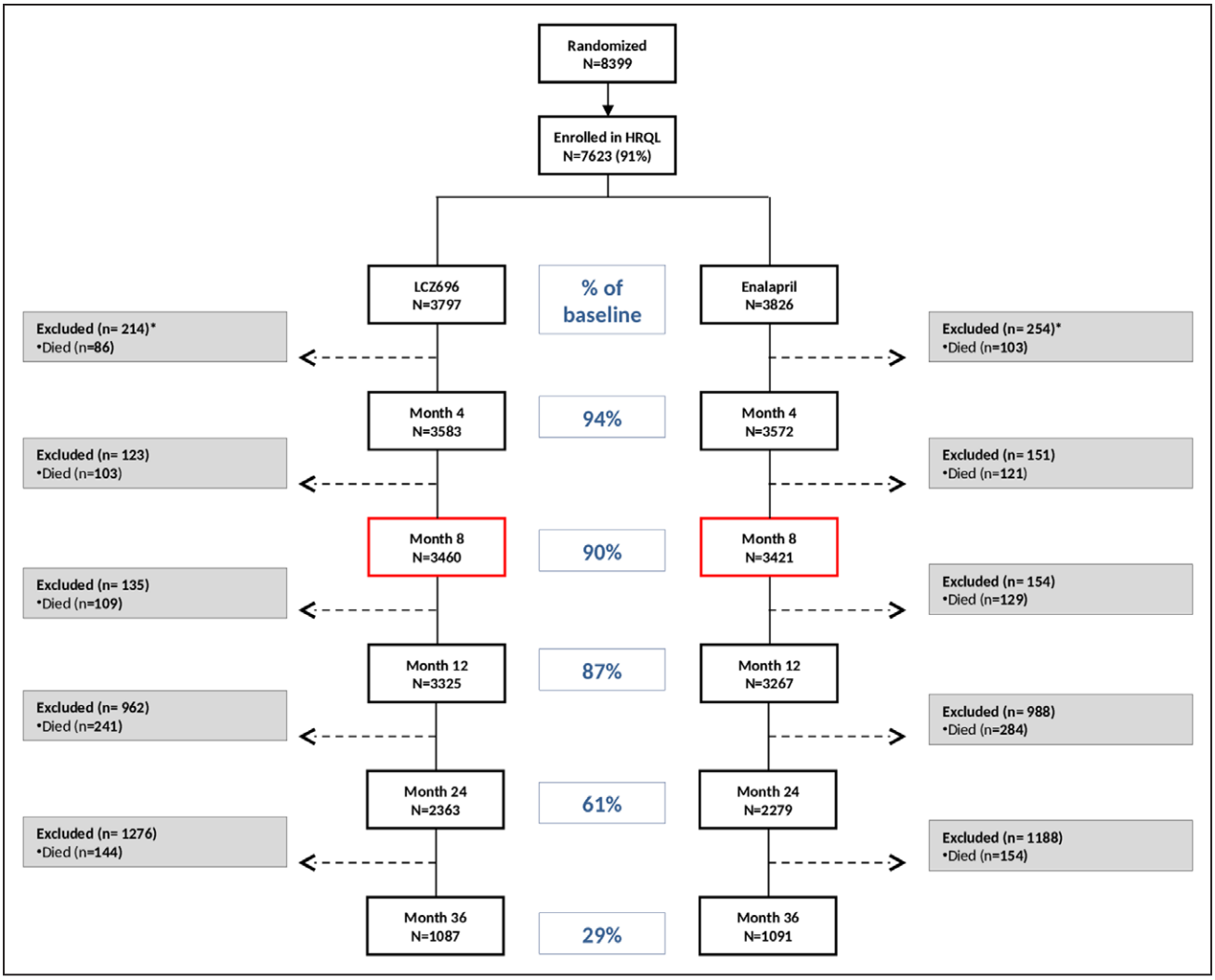

Figure 1. Proportion of patients who enrolled in quality of life substudy and completion of instruments through month 36.

HRQL indicates health-related quality of life. *Difference includes final visit, lack of completion of earlier HRQL instruments at earlier visits.

the 776 patients who did not complete KCCQ (Table 1). The characteristics of the patients who did not complete KCCQ include younger age, lower body mass index, less comorbid illnesses, higher percentage of women, and higher proportion from Asia Pacific region. Among patients who completed KCCQ, the patient characteristics in the 2 treatment groups were similar (Table 2). Compared with enalapril, the mean baseline KCCQ-CS scores (76.6±19 versus 75.3±19; *P*=0.004) and KCCQ-OS scores (73.5±20 versus 72.3±19; *P*=0.007) were higher in sacubitril/valsartan groups. The overall completion rate decreased to 90% at 8 months, 87% at 12 months, 61% at 24 months, and 29% at 36 months (Figure 1; Table I in the Data Supplement). The distribution of KCCQ scores are skewed toward the right (Figure 2).

At 8 months, the difference in change scores favored the patients in sacubitril/valsartan group in both KCCQ-CS score (+0.64 versus −0.29; *P*=0.008) and KCCQ-OS score (+1.13 versus −0.14; *P*<0.001) in comparison to those in enalapril group (Table 3). The patients in the sacubitril/valsartan group also noted improvements in all domains of KCCQ, with an exception of symptom stability with a 2.9-point decline (Table 3); notably, the enalapril group had a 4.3-point decline in that domain. In contrast, patients in the enalapril arm noted declines in most domains. There were consistent improvements in KCCQ-CS and KCCQ-OS scores in the sacubitril/valsartan group (in comparison to enalapril) for almost every subsequent visit point through 36 months (Table 4). At 8 months, the proportion of patients with clinically meaningful improvements in KCCQ-OS scores was significantly greater for sacubitril/valsartan group than for enalapril group (35% versus 33%), and the proportion with deterioration was less for sacubitril/valsartan (27% versus 31%; Table IIa and IIb in the Data Supplement).

Table 3. Between-Treatment Analysis of Change in KCCQ Summary Scores and All KCCQ Domains at 8 Months*

KCCQ Domain	8-Month KCCQ Change Scores			*P* Value
	Sacubitril/Valsartan	Enalapril	LSM Difference (95% CI)	
Physical limitation	0.83 (0.30)	−0.00 (0.30)	0.83 (0.00–1.66)	0.05
Symptom stability	−2.90 (0.35)	−4.31 (0.35)	1.40 (0.42–2.39)	0.005
Symptom frequency	0.75 (0.29)	−0.70 (0.29)	1.44 (0.63–2.26)	0.001
Symptom burden	0.36 (0.28)	−0.56 (0.28)	0.93 (0.14–1.71)	0.02
Total symptom score	0.53 (0.27)	−0.61 (0.27)	1.14 (0.39–1.89)	0.003
Quality of life	2.25 (0.31)	0.71 (0.31)	1.54 (0.68–2.41)	<0.001
Self efficacy	2.37 (0.28)	1.58 (0.28)	0.78 (0.00–1.56)	0.05
Social limitation	1.35 (0.36)	−0.56 (0.36)	1.91 (0.91–2.90)	<0.001
KCCQ-CS score	0.64 (0.25)	−0.29 (0.25)	0.92 (0.24–1.61)	0.008
KCCQ-OS score	1.13 (0.25)	−0.14 (0.25)	1.27 (0.58–1.96)	<0.001

CS indicates clinical summary; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSM, least squares mean; and OS, overall summary.

*Adjusted for baseline score and treatment.

In a multivariable model, several clinical factors were independently associated with deteriorations in both KCCQ-OS and KCCQ-CS scores, including higher body mass index, higher NT-proBNP, NYHA functional class III/IV, female sex, and history of myocardial infarction, atrial fibrillation, and diabetes mellitus (Table 5). Conversely, patients enrolled in Latin America and Asia noted improvements in these scores. Randomization to sacubitril/valsartan remained an independent predictor of improvements in KCCQ-OS and KCCQ-CS scores after adjustment for these factors. With an exception of older age, all factors were associated with changes in KCCQ scores with and without NYHA in the model.

Table 4. Between-Treatment Analysis of Change in KCCQ Overall Summary Scores and KCCQ Clinical Summary Scores Longitudinally*

	Sacubitril/Valsartan		Enalapril		Difference	*P* Value
	N	LSM Estimates (SE)	n	LSM Estimates (SE)		
Overall summary score						
Visit						
Month 4	3583	1.10 (0.2)	3572	0.44 (0.2)	0.66 (0.31)	0.03
Month 8	3460	1.13 (0.25)	3421	−0.14 (0.25)	1.27 (0.35)	<0.001
Month 12	3325	1.17 (0.26)	3267	0.08 (0.27)	1.09 (0.37)	0.004
Month 24	2363	0.69 (0.33)	2279	−0.64 (0.34)	1.33 (0.47)	0.005
Month 36	1087	0.36 (0.51)	1091	−1.92 (0.51)	2.28 (0.73)	0.002
Overall		0.80 (0.20)		−0.39 (−0.20)	1.19 (0.28)	<0.001
Clinical summary score						
Visit						
Month 4	3583	0.69 (0.22)	3572	0.21 (0.22)	0.48 (0.31)	0.12
Month 8	3460	0.64 (0.25)	3421	−0.29 (0.25)	0.92 (0.35)	0.008
Month 12	3325	0.60 (0.26)	3267	−0.39 (0.26)	0.99 (0.37)	0.008
Month 24	2363	−0.05 (0.33)	2279	−1.40 (0.33)	1.30 (0.47)	0.005
Month 36	1087	−0.89 (0.52)	1091	−2.50 (0.51)	1.60 (0.73)	0.03
Overall		0.23 (0.20)		−0.76 (0.20)	0.99 (0.28)	<0.001

ANCOVA indicates analysis of covariance; KCCQ, Kansas City Cardiomyopathy Questionnaire; and LSM, least squares mean.

*Adjusted for baseline score and treatment. Each visit's estimate is calculated using regression at the individual visit. The overall estimate is calculated using ANCOVA with adjustment for baseline score and treatment to provide the overall treatment effect.

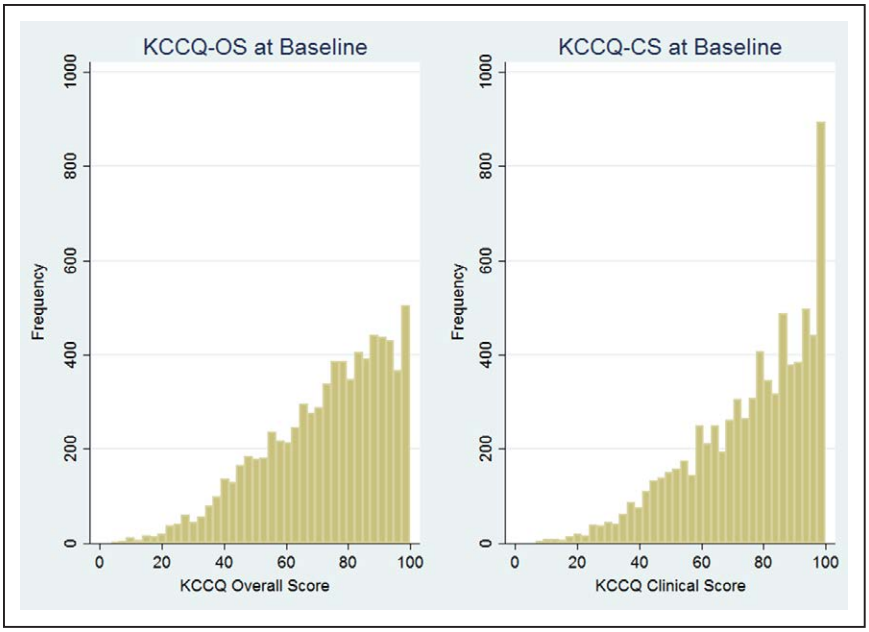

Figure 2. Histogram of Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores (Clinical Summary Score and Overall Summary Score) at baseline.

A total of 305 (4.4%) patients were hospitalized for HF between baseline and 8 months. The patients without a HF hospitalization had modest improvements in KCCQ scores in both sacubitril/valsartan and enalapril (Table 6). In contrast, patients with HF hospitalization had significant decreases in KCCQ scores at 8 months. In comparison to enalapril group, patients randomized to sacubitril/valsartan had a smaller decline in KCCQ-OS scores (5.66 point difference; *P*=0.003) and KCCQ-CS scores (5.14 difference; *P*=0.005). There was no difference in mean time between HF hospitalization and 8-month KCCQ assessment in sacubitril/valsartan (–4.0+2.3 months) and enalapril (–4.3+2.6 months) groups (*P*=0.27).

When imputing 0 for death during follow-up, there were significant differences favoring sacubitril/valsartan for KCCQ-CS, KCCQ-OS, and all 8 domains, with least square mean differences ranging from 1.41 to 2.56 points (Table III in the Data Supplement).

DISCUSSION

In a large, well-treated population with HF with reduced ejection fraction, sacubitril/valsartan was superior to enalapril in improving disease-specific HRQL. The principal HRQL end points of KCCQ-CS and KCCQ-OS were improved by 4 months, and these improvements persisted throughout 36 months. There were statistically significant differences favoring sacubitril/valsartan across all 8 KCCQ domains and extending to 36 months, adding further support for the principal findings. There was a significant proportion of patients receiving sacubitril/valsartan who noted clinically meaningful changes of HRQL, despite all patients receiving the drug during the run-in phase. Patients who were hospitalized for HF within the first 8 months noted significant deteriorations in KCCQ scores; however, randomization to sacubitril/valsartan attenuated this decline in comparison to enalapril.

The KCCQ scores at baseline are much higher than those of contemporary cohorts with HF evaluating novel interventions, including ivabradine,[4] iron replacement,[17] coronary artery bypass grafting,[16] cardiac rehabilitation,[18] sertraline use for treatment of depression,[19] and spironolactone.[20] This higher score likely reflects the unique features of the HRQL component of PARADIGM-HF, in that the patients did not complete instruments until the time of randomization, which occurred after the run-in phase with both enalapril and sacubitril/valsartan up to 10 weeks. It has been well established that HRQL perceptions can improve quickly in a clinical trial setting independent of any treatment effect because of potential extra attention, more intense management, and potential optimism for improved outcomes.[21,22] This higher baseline KCCQ score and prior exposure to sacubitril/valsartan possibly impacted the magnitude of improvement over time. Despite this limitation, randomization to sacubitril/valsartan still was consistently associated with improved HRQL. Despite a comparison with an active treatment rather than placebo, sacubitril/valsartan had similar magnitude of improvements of the KCCQ change scores as were seen with cardiac resynchronization therapy in the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy).[23]

Hospitalizations for HF are associated with increased risk for mortality.[24,25] Several studies have demonstrated worse HRQL after patients are discharged from the hospital. Sacubitril/valsartan appeared to attenuate the

Table 5. Clinical Factors Independently Associated With KCCQ Overall Summary Change Scores Between Baseline and 8 Months

Clinical Factor	Multivariable Model		
	Beta	95% CI	*Z* Score
KCCQ overall summary score			
With NYHA			
Baseline KCCQ-OS	–0.33	–0.35 to –0.31	33.17
Region (Latin America)	4.03	3.05 to 5.02	8.04
Region (Asia)	3.36	2.23 to 4.50	5.80
BMI (per 1 U)	–0.18	–0.25 to –0.11	5.18
NYHA (III/IV)	–2.00	–2.86 to –1.14	4.55
History of MI	–1.63	–2.34 to –0.92	4.49
Sex female	–1.80	–2.65 to –0.95	4.17
Sacubitril/valsartan	1.27	0.59 to 1.95	3.67
Log NT-proBNP	–0.68	–1.05 to –0.31	3.58
History of AF	–1.30	–2.05 to –0.55	3.41
Diabetes mellitus	–1.10	–1.84 to –0.36	2.92
Without NYHA			
Baseline KCCQ-OS	–0.32	–0.34 to –0.30	33.43
Region (Latin America)	4.22	3.24 to 5.20	8.45
BMI (per 1 U)	–0.20	–0.27 to –0.13	5.62
Region (Asia)	3.21	2.04 to 4.38	5.37
History of MI	–1.58	–2.30 to –0.86	4.29
Sex female	–1.77	–2.62 to –0.92	4.07
Log NT-proBNP	–0.72	–1.09 to –0.35	3.78
Sacubitril/valsartan	1.29	0.61 to 1.97	3.72
History of AF	–1.27	–2.03 to –0.51	3.27
Diabetes mellitus	–1.05	–1.79 to –0.31	2.77
Age (per year)	–0.03	–0.07 to 0.00	1.96
KCCQ clinical summary score			
With NYHA			
Baseline KCCQ-CS	–0.34	–0.36 to –0.32	33.29
Region (Latin America)	4.21	3.24 to 5.18	8.49
BMI (per 1 U)	–0.22	–0.29 to –0.15	6.26
Region (Asia)	3.26	2.10 to 4.42	5.51
Sex female	–2.10	–2.95 to –1.26	4.89
NYHA (III/IV)	–2.04	–2.89 to –1.18	4.68
History of MI	–1.57	–2.28 to –0.86	4.33
History of AF	–1.33	–2.08 to –0.58	3.47
Log NT-proBNP	–0.64	–1.01 to –0.27	3.42
Diabetes mellitus	–1.11	–1.84 to –0.39	3.00
Sacubitril/valsartan	0.93	0.26 to 1.60	2.73
Age	–0.03	–0.07 to 0.00	1.98
Without NYHA			
Baseline KCCQ-CS	–0.32	–0.34 to –0.31	33.64
Region (Latin America)	4.44	3.47 to 5.41	9.00
BMI (per 1 U)	–0.23	–0.30 to –0.16	6.41
Region (Asia)	3.31	2.15 to 4.48	5.59
Sex female	–2.11	–2.96 to –1.26	4.89
History of MI	–1.61	–2.32 to –0.90	4.44
History of AF	–1.46	–2.21 to –0.71	3.80
Log NT-proBNP	–0.71	–1.07 to –0.34	3.76
Diabetes mellitus	–1.11	–1.84 to –0.38	2.98
Sacubitril/valsartan	0.96	0.29 to 1.63	2.79
Age	–0.04	–0.07 to 0.00	2.15

AF indicates atrial fibrillation; BMI, body mass index; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire clinical summary score; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary score; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; and NYHA, New York Heart Association.

marked decline in HRQL in comparison to enalapril. It is unclear if the decline in HRQL among these patients with a HF hospitalization prompted the decision for admission or was a consequence of the progression of symptomatic HF. The greater magnitude of decline as a function of the time between the hospitalization and KCCQ assessment suggests that decisions that incorporate HRQL should be reassessed as patients stabilize in the outpatient setting.

There are several characteristics that were associated with impaired HRQL at baseline, including older age, female sex, higher body mass index, and comorbid illnesses. These variables are complex and may reflect the impact of symptom burden, patient perception, and disease severity on their overall sense of well-being.[26] Several studies have identified many of these factors in HF populations.[20,27,28] Some of these variables are modifiable and should be studied further with targeted interventions as we aim to improve HRQL. In the present study, there were multiple factors that consistently were associated with decreases in KCCQ scores by 8 months, including higher body mass index, higher NT-proBNP, older age, history of atrial fibrillation, diabetes mellitus, and higher NYHA class. This study expands on the study by Allen et al[27] that identified diabetes mellitus, older age, and arrhythmias as predictors of future unfavorable HRQL. Comorbidities affect self-care management and result in worse HRQL.[26] Exploration of these factors may identify a population who may be targeted for specific therapies directed specifically for preservation/improvements of HRQL and discussions about goals of care/advanced directives. Nevertheless, randomization to sacubitril/valsartan was an independent predictor of improved perceptions after adjusting for all other variables.

Table 6. Association of Heart Failure Hospitalizations on Changes in KCCQ-OS and KCCQ-CS Scores at 8 Months

	Non-HF	HF	Difference (95% CI)	*P* Value*	*P* Value†
8-mo KCCQ overall summary scores					
Sacubitril/valsartan	1.22 (0.24); n=3321	−5.11 (1.62); n=139	−6.33 (−8.73 to −3.95)	<0.001	0.003
Enalapril	0.60 (0.26); n=3251	−10.77 (1.15); n=170	−11.37 (13.69 to −9.06)	<0.001	
8-mo KCCQ clinical summary scores					
Sacubitril/valsartan	0.66 (0.24); n=3321	−4.02 (1.19); n=139	−4.69 (−7.06 to −2.31)	<0.001	0.005
Enalapril	0.35 (0.26); n=3251	−9.16 (0.26); n=170	−9.51 (−11.81 to 7.21)	<0.001	

HF indicates heart failure; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire clinical summary score; and KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary score.

*This *P* value represents the difference in change score between randomization and 8 mo in patients with and without a heart failure hospitalization that occurred between these time points.

†This *P* value represents the between-treatment differences in change scores in patients with and without a heart failure hospitalization. Patients receiving sacubitril/valsartan had less of a decline than those in enalapril group in KCCQ scores in setting of a heart failure hospitalization.

There are several limitations that should be highlighted. First, the KCCQ was initially measured after the run-in phase, which potentially resulted in a higher baseline score. Second, although the overall effect size might seem small, there are limited data assessing the clinical meaningfulness of change scores in patients who start with relatively good perceptions of their HRQL. Given the lack of validity of this instrument for some countries, we have limited experience of the impact of therapy in some parts of Asia. There may be >1 language in a given country, and thus, we cannot cross-validate responses by language. Nevertheless, KCCQ is the most well-validated instrument in HF, and the consistency of improvements of KCCQ scores across all domains suggest that patients can enjoy an improved survival and HRQL in comparison to ACE inhibitors, the long-standing standard of care.

CONCLUSIONS

In patients with HF with reduced ejection fraction who are well managed, HRQL specific to HF is significantly improved with sacubitril/valsartan compared with enalapril.

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FOOTNOTES

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