

Heterogeneity of health status treatment response with sacubitril/valsartan: insights from the CHAMP-HF registry

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Abstract

Aims The aim of our study was to investigate heterogeneity of health status treatment response of sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results We leveraged data from CHAMP-HF, an observational registry of 140 US clinics and 5026 outpatients with chronic HFrEF, where health status was serially assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 Overall Summary Scale (range from 0 to 100; ≥ 20 -point improvement is a very large improvement). In 334 patients newly initiated on sacubitril/valsartan, we used hierarchical multivariable logistic regression (13 patient-level characteristics as well as baseline KCCQ-12 score) to calculate the odds ratio (OR) of any characteristic being associated with a very large health status improvement. A total of 104/334 (31.1%) of patients achieved the primary endpoint, where only worse baseline health status [KCCQ-12 score of 0–60 points had an OR = 0.86/5-point higher score (CI 0.79, 0.93)], and those with a KCCQ-12 score of 60–80 points had an OR = 0.61/5-point higher score (0.45–0.82), which was associated with a very large benefit. No other patient characteristic was associated with a very large health status improvement ($P > 0.05$).

Conclusions We found that, after initiation of sacubitril/valsartan, only worse baseline health status was associated with very large health status improvement. Accordingly, a trial of therapy—particularly in those with worse symptoms, function, and quality of life—and assessing treatment response are likely to be the best prospective strategy.

Keywords Chronic heart failure; Health status; Quality of life; Angiotensin-neprilysin inhibitor

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Introduction

The primary treatment goal for patients with heart failure with reduced ejection fraction (HFrEF) is to improve their survival and to optimize their health status—their symptoms, function, and quality of life.¹ Sacubitril/valsartan has been shown to improve both outcomes,² and we recently demonstrated that a very large health status response [≥ 20 -point improvement in the Kansas City Cardiomyopathy Questionnaire

(KCCQ) Overall Summary Score] occurs in about one in five patients shortly after initiating this medication.³

Aims

The aim of this study was to investigate whether or not there is heterogeneity of treatment response with sacubitril/valsartan, whereby certain patient-specific clinical

characteristics are associated with a larger health status treatment benefit.

Methods

To better identify patients whose health status may be more likely to improve than others, we used data from CHAMP-HF—an ongoing, observational registry of 140 US clinics that enrolled 5026 outpatients with chronic HFrEF.⁴ Health status was measured using the KCCQ-12 Overall Summary Scale (KCCQ-OS), an extensively validated, disease-specific patient-reported outcome measure that ranges from 0 to 100 (higher scores are better) and where a ≥ 20 -point improvement has been established as a very large improvement in patients' health status.^{3,5}

We used the previously reported cohort of 508 patients newly initiated on sacubitril/valsartan, in whom 104 (20.5%) experienced a ≥ 20 -point change in KCCQ score within 3 months.³ Because those with a baseline score > 80 were not eligible to improve by ≥ 20 points, we excluded 174 patients, leaving a final analytic cohort of 334 patients. To compare the clinical characteristics of those who markedly improved with those who did not, we used hierarchical

multivariable logistic regression, with site as a random effect to account for clustering of patients at the same site. Thirteen patient-level characteristics were considered, including sociodemographic (age, sex, race, and household income), clinical (chronic obstructive lung disease, chronic kidney disease, diabetes mellitus, depression, and number of hospitalizations within the past 12 months), haemodynamic (systolic blood pressure), and medication [angiotensin-converting enzyme/angiotensin receptor blocker (ACE/ARB) and loop diuretic] characteristics, as well as baseline KCCQ-12 score. Non-linear associations for continuous variables were assessed. Calculated odds ratios (ORs) reflect the odds of any predictor being associated with a very large improvement in the KCCQ-OS.

Results

The median (25th and 75th percentiles) patient follow-up between enrolment and post-angiotensin receptor neprilysin inhibitor KCCQ-12 was 61 (33–136) days. A total of 104/334 (31.1%) of patients achieved the primary endpoint. *Table S1* and *Table 1* present the characteristics of those who did and did not experience a very large KCCQ-OS improvement,

Table 1 Patient predictors associated with very large health status benefit with angiotensin receptor neprilysin inhibitor

Patient characteristics ^a	KCCQ-OS improvement		KCCQ-OS ≥ 20 -point improvement	
	<20 points <i>n</i> = 230	≥ 20 points <i>n</i> = 104	Univariable ^b OR (CI)	Multivariable ^c OR (CI)
Age (+5 year increase)	63.5 (13.1)	63.1 (13.0)	0.99 (0.91–1.08)	—
Female	31.7% (73)	34.6% (36)	1.13 (0.68–1.89)	—
White race	73.5% (169)	75.0% (78)	1.04 (0.55–1.99)	—
Total household income < \$25 000	38.3% (88)	31.7% (33)	0.78 (0.43–1.42)	—
Systolic BP (+5 mmHg increase)	120.1 (17.5)	119.3 (16.0)	0.99 (0.92–1.07)	—
Number of HF hospitalizations within prior 12 months (reference is '0')				
0	59.1% (136)	51.0% (53)	—	—
1	25.7% (59)	26.9% (28)	1.12 (0.59–2.15)	—
≥ 2	15.2% (35)	22.1% (23)	1.67 (0.95–2.93)	—
Depression	32.2% (74)	28.8% (30)	0.79 (0.49–1.29)	—
Asthma/bronchitis/COPD	30.0% (69)	37.5% (39)	1.35 (0.81–2.25)	—
Chronic kidney disease	19.1% (44)	24.0% (25)	1.26 (0.71–2.23)	—
Diabetes	44.8% (103)	51.9% (54)	1.39 (0.83–2.34)	—
KCCQ-12 Overall Summary Score ^d (per 5-point increase up to 60)	58.5 (16.2)	44.3 (18.1)	0.86 (0.79–0.93)	0.86 (0.79–0.93)
KCCQ-12 Overall Summary Score ^d (per 5-point increase above 60)			0.61 (0.45–0.82)	0.61 (0.45–0.82)
ACE-I/ARB in 2 weeks prior to ARNI	39.1% (90)	27.9% (29)	0.66 (0.42–1.05)	—
Loop diuretic at time of ARNI initiation	73.9% (170)	83.7% (87)	1.68 (0.88–3.20)	—

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GEE, generalized estimating equation; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary.

^aContinuous variables are shown as mean (standard deviation). Categorical variables are shown as per cent (frequency). Values are from the time of ARNI initiation.

^bUnivariable odds ratios with 95% confidence intervals are derived from logistic regression models, where each variable serves as the only predictor. Models use GEEs to account for correlation among patients at each site.

^cMultivariable modelling used forward selection to identify important predictors. Significance level to enter and stay were both $P = 0.05$. As KCCQ-OS was the only variable selected, the estimates are the same as the univariable.

^dKCCQ-OS was fit as a two-part piece-wise linear spline with the knot at 60, to accommodate a non-linear relationship with the outcome.

as well as the univariate and multivariable-adjusted ORs of a very large improvement, respectively. Following multivariable adjustment, the only patient characteristic associated with very large health status improvements was worse baseline health status. The higher the score, the less likely patients were to attain a very large benefit from sacubitril/valsartan—with a non-linear relationship—such that those with a KCCQ-12 score of 0–60 points had an OR = 0.86/5-point higher score (CI 0.79, 0.93) and those with a KCCQ-12 score of 60–80 points had an OR = 0.61/5-point higher score (0.45–0.82). No other patient characteristics were associated with very large health status improvements ($P > 0.05$).

Conclusions

Although all patients may derive a survival or hospitalization benefit from sacubitril/valsartan, we sought to identify patient characteristics associated with a very large, early health status treatment response. We found that only poorer baseline health status was associated with such improvement. In fact, the worse the health status, the greater the observed treatment benefit. This suggests that it is not possible to readily identify patients who are more likely to derive a very large health status benefit from sacubitril/valsartan and that a trial of therapy—particularly in those with worse symptoms, function and quality of life—and assessing treatment response is likely to be the best prospective strategy. Notably, there was no significant difference in health status outcomes by heart failure aetiology (ischaemic vs. non-ischaemic). Our study should be interpreted with the understanding that our model was developed to predict patient characteristics associated with large health status improvement and not meant to estimate causal treatment effects. We also cannot exclude regression to the mean, as we only studied patients initiated on sacubitril/valsartan, and we recognize that those with worse health status may be more likely to demonstrate regression to the mean. Interestingly, patients previously on ACE/ARB were less likely to experience a very large health status benefit; while these findings were not statistically significant, the mechanism remains unclear. To that end, further studies in larger patient cohorts will be needed to extend and validate our findings and to determine whether patients' health status improvements are sustained over a period of prolonged clinical follow-up.

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Conflict of interest

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Supporting information

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

Table S1. Baseline patient characteristics.

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