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ORIGINAL RESEARCH ARTICLE

Association between sacubitril/valsartan initiation and real-world health status trajectories over 18 months in heart failure with reduced ejection fraction

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Abstract

Aims Improving the health status (symptoms, function, and quality of life) of patients with heart failure with reduced ejection fraction (HFrEF) is a primary treatment goal. Angiotensin receptor neprilysin inhibitors (ARNI) improve short-term health status in clinical practice, but the sustainability of these improvements is unknown.

Methods and results In CHAMP-HF, a multicentre observational study of outpatients with HFrEF, patients initiated on ARNI were propensity score matched 1:2 to patients not using ARNI with Cox regression modelling time to ARNI initiation, adjusted for sociodemographic and clinical variables, medical history, medications, and baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Repeated measures models for the overall KCCQ score and each domain compared the health status trajectories of patients initiated on ARNI vs. not. Among 3930 participants, 746 (19.0%) began ARNI, of whom 576 were matched to 1152 non-ARNI patients. Prior to matching, participants initiated on ARNI were younger, non-Hispanic, had lower EFs, more commonly had a history of ventricular arrhythmia, were less likely to be taking an ACEI/ARB, and more likely to be treated with beta-blockers and mineralocorticoid receptor antagonists. There were no differences after matching. In the matched cohort, participants initiated on ARNI experienced improved health status by 3 months that persisted through 12 months [KCCQ Overall Summary Score (OSS) = 73.4 vs. 70.8; $P < 0.001$], with the largest benefit observed in the KCCQ Quality of Life domain (68.7 vs. 64.7; $P < 0.001$). Similar health status benefits were noted through 18 months (KCCQ-OSS = 73.9 vs. 71.3; $P < 0.001$). A responder analysis showed that 12 patients would need to be initiated on ARNI for one to experience at least a large improvement (≥10 points) in health status benefit at 12 months.

Conclusions In outpatient practice, ARNI therapy was associated with improved health status by 3 months and continued to 18 months after initiating therapy.

Introduction

Improving health status—symptoms, function, and quality of life—in patients with heart failure with reduced ejection fraction (HFrEF) is a primary goal of treatment.[1] In addition to being important to patients and providers, health status is associated with subsequent mortality, hospitalization, and healthcare-associated cost in HFrEF.[2–5] The Prospective Comparison of ARNI with ACEI to Determine the Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial compared sacubitril/valsartan with enalapril in the treatment of patients with HFrEF.[6] Patients taking sacubitril/

valsartan not only had improved survival and lower hospitalization rates but also had significantly less deterioration in health status from baseline to 8 months as compared with patients taking enalapril.[6] While other heart failure therapies have also shown reduced mortality in clinical trials, health status improvement with sacubitril/valsartan was a novel finding compared with trials of earlier drugs.

Although there have been a number of randomized controlled trials establishing the efficacy of sacubitril/valsartan, the effectiveness in diverse clinical populations is less clear. Given that the health status improvement was a novel finding and that trial populations, practice settings, and delivery of care differ from real-world clinical care, supplementing clinical trial data with real-world experiences can support the effectiveness, as opposed to the efficacy, of new treatments in clinical practice.[7,8]

In early real-world evidence from CHAnge the Management of Patients with Heart Failure (CHAMP-HF), sacubitril/valsartan was associated with improvements in health status as early as 2 months following initiation of the medication[9]; however, whether these benefits are sustained is unknown. In this study, we aimed to determine whether real-world early improvements in health status following initiation of sacubitril/valsartan were sustained through 1 year.

Methods

Study design

CHAMP-HF is a US-based multicentre, prospective registry of outpatients with HFrEF that serially documented patients' disease-specific health status and carefully measured changes in patients' medical treatment.[10] Briefly, consecutive patients with chronic HFrEF [left ventricular ejection fraction (LVEF) $\leq$ 40%] who were treated with $\geq$1 HFrEF pharmacotherapy were enrolled at 140 outpatient centres across the USA. Patients who were under 18 years of age, currently enrolled or planning to participate in a clinical trial, receiving

Figure 1 Consort diagram.
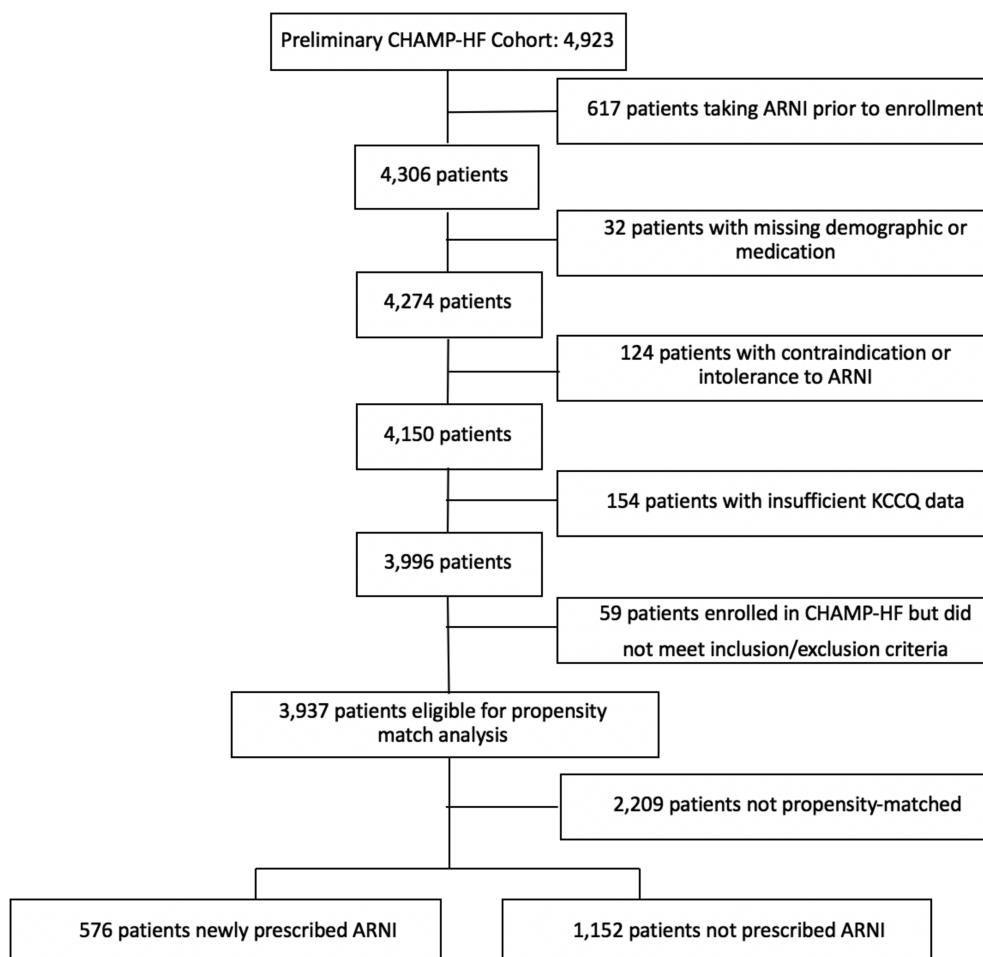
comfort care measures or hospice care, diagnosed with end-stage cardiomyopathy with planned heart transplant or left ventricular assist device implantation, and undergoing dialysis were excluded. Study coordinators recruited patients for the registry during the course of routine outpatient visits. To be included in this analysis, patients had to have completed a baseline and at least one follow-up KCCQ, could not be taking an ARNI prior to enrolment, and could not have a documented contraindication or intolerance to ARNI (*Figure 1*). Clinical data were captured in an electronic case report form at baseline and 1, 3, 6, 12, 18, and 24 months. Patient-reported data were collected at the same time intervals in person at baseline and in person or by telephone interviews at follow-up. All study participants provided written informed consent, and each study centre obtained site-specific institutional review board approval. Novartis Pharmaceuticals Corporation (East Hanover, NJ) sponsored CHAMP-HF, and Duke Clinical Research Institute (Durham, NC) served as the data analytic centre.

Data collection and defining angiotensin receptor neprilysin inhibitors use

Each site collected baseline patient sociodemographic and clinical data, medical and device therapies, and administered the KCCQ at enrolment and 3, 6, 9, and 12 months as well as at 18 and 24 months after enrolment. Patient data were serially collected through in-person interviews at enrolment and by in-person or phone interviews during follow-up. A patient was considered to be a new ARNI start if they began ARNI therapy on or after the enrolment date.

Study outcomes

The primary outcome for this study was patients' health status over time as measured by the KCCQ-12 Overall Summary (KCCQ-OS) score. The secondary outcomes were patients' KCCQ domain scores—physical limitation, symptom frequency, quality of life, and social limitation—over time. The KCCQ-OS and domain scores ranges from 0 to 100 with higher scores associated with fewer symptoms, less functional limitations, and better quality of life.[11] We considered a 5-point change in score on the KCCQ as a clinically meaningful change in health status based on previously published data, and large and very large clinical changes are associated with changes of 10 and 20 points, respectively.[12,13]

Statistical analysis

Kaplan–Meier plots were created to describe the unadjusted initiation or discontinuation of ARNI treatment. Because patients who start ARNI may be different from patients who do not, our primary analysis evaluates outcomes within a matched cohort of new ARNI users and non-ARNI patients. This matching algorithm has been described previously.[9] Briefly, patients initiated on ARNI were matched 1:2 to patients not started on ARNI using time-dependent propensity scores for ARNI initiation derived from Cox proportional hazard models. These models were used to calculate a propensity score (for each patient and at each value of ARNI start time) that reflects their probability of starting an ARNI at that time. For these models, all predictors (except sociodemographic variables) were allowed to change over time. Models included sociodemographics (age, sex, race, Hispanic ethnicity, household income, and employment status), and clinical factors (body mass index, systolic blood pressure, heart rate, and LVEF), medical history (atrial fibrillation, ventricular tachycardia/ventricular fibrillation, cardiac resynchronization therapy, chronic obstructive pulmonary disease, coronary artery disease, diabetes, depression or anxiety, hypertension, ischaemic heart failure, current smoker, prior HF hospitalizations, and chronic kidney disease), medications (beta-blocker, mineralocorticoid receptor antagonist, loop diuretic, hydralazine, digoxin, and ivabradine), and baseline KCCQ Symptom Frequency and Quality of Life scores. Continuous variables were assessed for the linearity of their relationship with the outcome using restricted cubic splines, and these terms were included, when necessary, to accommodate nonlinearity. Multi-level variables were converted to binary variables (white vs. nonwhite, income <$50 K vs. ≥$50 K, and employed full-time or part-time vs. not working for any reason).

For covariates in the propensity model, missing values were imputed using single imputation with full conditional specification. Patients had to be either on or off ACEi/ARB for 2 weeks prior to the assigned match day to reduce biasing the differences in KCCQ scores simply due to a change in ACEi/ARB just prior to matching, which led to seven patients being excluded. Covariate balance before and after matching was assessed using standardized differences, with >10% being considered clinically relevant. Median (interquartile ranges) time from matching to last KCCQ score result for both the ARNI and non-ARNI groups was calculated.

A restricted cubic spline was used to assess the difference in slopes between ARNI and no-ARNI patients. Outcomes were assessed by five repeated measures regression models: one for the KCCQ-OS and one for each KCCQ domain score. A patient-specific random effect was included in each repeated-measures analysis, as well as a fixed effect for treatment (ARNI) and a fixed effect for time (since match). As patients can report they are limited in their physical function or social function for reasons other than HF, there was some missing data for individual KCCQ domain scores (2.1% for physical limitations and 1.3% for social limitations). If a patient had a missing value for a given KCCQ domain

score in the matched set, the mean imputed value for that variable was used. The least square means for the estimated KCCQ scores were calculated from the restricted cubic spline mixed model with 0, 3, 6, 9, 12, and 18 months after matching estimated. Figures displaying the adjusted estimated mean KCCQ score and confidence limits over time are presented.

As mean KCCQ scores represent a population average effect, we also examined the distribution of individual patient change in KCCQ scores to illustrate the proportion of patients with clinically important changes in health status. The proportion of patients (n; %) across categories of KCCQ change [worse to moderate improvement (change <10 points), large improvement (change ≥10 to <20 points), and very large improvement (change ≥20 points)] were calculated.

All estimates were reported using 95% confidence intervals, and a P-value ≤ 0.05 was considered statistically significant. All analyses were performed using SAS software (version 14.3, SAS Institute, Cary, NC). Analyses were performed independently by the Duke Clinical Research Institute, and the lead author takes responsibility for guiding data analysis and interpretation.

Results

A total of 4923 patients from 140 sites were enrolled in CHAMP-HF. Over 18 months of follow-up, 18% (722/3937) of participants were initiated on ARNI (Supporting Information, Figure S1). There were 18% (143/792) of patients who were receiving ARNI therapy that discontinued treatment within a year of starting ARNI (Supporting Information, Figure S2), but these patients were retained in the analysis to maintain the intention to treat perspective of this study. After excluding patients who were prescribed ARNI prior to enrolment (n = 617), who had a contraindication or intolerance to ARNI (n = 124), with missing demographic or medication data (n = 32), with missing KCCQ data (n = 154), or who did not meet the CHAMP eligibility criteria (n = 59), 3937 patients were eligible for propensity matching, of whom 746 (18.9%) of these were initiated on an ARNI. Prior to matching, patients initiated on ARNI were more likely to be younger, non-Hispanic, have lower ejection fraction and a history of ventricular arrhythmia, and were less likely to be taking an ACEi or ARB, but were more likely to be on beta-blocker and mineralocorticoid receptor antagonist (Table 1). We were able to match 576 ARNI patients to 1152 patients not initiated on ARNI (Figure 1). Matching was well-balanced for sociodemographic and clinical characteristics, medical history, medications, and baseline KCCQ scores with the exception of the Symptom Frequency and Quality of Life domains (standardized differences = 11.6% and 12.4%, respectively; Table 1), resulting in the retention

of these scores in the multivariate models. The median time from matching to final KCCQ score was 16.5 months (IQR: 8.6, 22.3) in the ARNI cohort and 15.7 months (IQR: 7.4, 21.8) in the non-ARNI cohort, and the proportion of deaths were equal between the two groups.

Patients initiated on ARNI experienced improved health status compared with patients not on ARNI by 3 months, and these differences persisted to 12 months (P < 0.001; Figure 2). Estimated KCCQ-OS scores at 12 months were 73.4 (95% CI 72.1–74.7) with ARNI vs. 70.8 (95% CI 69.9–71.8) without ARNI. While the largest benefit of ARNI was observed in the KCCQ Quality of Life domain (P < 0.001), there were also statistically significant differences observed in the symptom frequency (P = 0.02) and social limitation (P = 0.007) domains (Figure 3). There was not a statistically significant difference in the physical limitation domains between the ARNI and non-ARNI cohorts (P = 0.16). These health status benefits noted at 12 months remained unchanged through 18 months of follow-up (Supporting Information, Figures S3 and S4).

To facilitate the interpretation of the mean differences KCCQ-OS scores, patients were categorized by the magnitude of health status improvement and the proportion of patients in each category were calculated: those experiencing worse to moderately improved health status (KCCQ scores <10 points), large (10 to <20 points), and very large health status (≥20 points) improvement. Overall, 35.8% of patients initiated on ARNI (vs. 27.5% of patients not initiated on ARNI) had at least a large improvement in their health status over a median of ~10 months, P = 0.001 (Table 2) with most of these patients experiencing a very large improvement in their health status (20.3% treated with ARNI vs. 14.7% comparison patients). This corresponds to a number needed to treat of 12, meaning that 12 patients would need to be initiated on ARNI for one to experience at least a large improvement (≥10 points) in health status benefit. A 5-point responder analysis has been provided in Supporting Information, Appendix S1.

Discussion

In this large, outpatient, observational registry of patients with HFrEF, we found that patients prescribed ARNI experienced both early and sustained improvements in disease-specific health status as measured by the KCCQ. A similar pattern of improvement was seen for all KCCQ domains, except for the physical limitation domain. While the mean improvement in KCCQ was less than the 5-point difference considered to be clinically significant, using a population average is not the best method to assess health status as the mean difference does not reflect the experiences of individual patients. We therefore performed a responder analysis

Table 1 Comparison of baseline patient characteristics before and after matching

Description	Pre-match			Post-match		
	ARNI	No ARNI	Standardized difference (%)	ARNI	No ARNI	Standardized difference (%)
N	746	3184		576	1152	
Sociodemographic						
Age	63.4 (13.0)	67.3 (12.3)	30.4	64.7 (13.2)	65.7 (12.5)	8.2
Female	29% (217)	29% (923)	0.2	30% (173)	27% (310)	6.9
White race	75% (559)	74% (2348)	2.7	76% (437)	74% (854)	4.0
Hispanic	11% (83)	20% (652)	25.9	12% (67)	12% (133)	0.3
Low income (<$25 K)	38% (285)	42% (1326)	7.0	37% (214)	39% (454)	4.6
Working FT/PT	26% (195)	20% (640)	14.4	25% (143)	24% (279)	1.4
Clinical measures						
BMI	31.3 (7.3)	30.1 (7.2)	15.7	31.0 (7.4)	30.4 (7.4)	9.1
Systolic BP	119.9 (17.1)	122.0 (17.8)	11.5	121.1 (18.1)	119.8 (17.8)	7.4
Heart rate	74.0 (12.7)	74.0 (12.5)	0.0	74.4 (12.9)	73.9 (12.7)	3.8
LVEF	27.8 (7.8)	30.2 (7.7)	30.9	30.1 (7.0)	30.0 (9.0)	2.0
Medical history						
History AF/flutter	36% (271)	36% (1150)	0.4	38% (218)	38% (441)	0.9
History VT/VF	25% (183)	18% (568)	16.4	26% (149)	24% (276)	4.4
CRT	9% (67)	6% (204)	9.7	11% (61)	10% (113)	2.6
Lung disease	27% (202)	33% (1036)	12.0	29% (169)	29% (331)	1.3
CAD	61% (458)	66% (2101)	9.6	63% (361)	66% (765)	7.8
Diabetes	42% (310)	42% (1342)	1.2	44% (253)	39% (455)	9.0
Depression or anxiety	34% (250)	36% (1133)	4.4	36% (206)	36% (420)	1.4
Hypertension	83% (617)	85% (2716)	7.1	83% (480)	83% (958)	0.5
Ischaemic HF	38% (281)	41% (1303)	6.7	39% (224)	42% (488)	7.1
Current smoker	21% (159)	20% (633)	3.5	22% (125)	21% (244)	1.3
Prior HF hospitalization	38% (280)	37% (1172)	1.5	41% (235)	45% (515)	7.9
CKD	19% (143)	22% (691)	6.3	20% (113)	21% (240)	3.0
Medications						
ACEi/ARB	65% (487)	79% (2529)	32.0	49% (284)	49% (568)	0.0
Beta-blocker	96% (719)	90% (2853)	26.8	97% (556)	97% (1116)	1.9
MRA	47% (347)	32% (1024)	29.7	47% (270)	44% (505)	6.1
Loop diuretic	72% (537)	63% (1991)	20.2	73% (418)	70% (812)	4.6
Hydralazine	4% (29)	6% (185)	9.0	5% (27)	3% (40)	6.1
Digoxin	18% (134)	13% (413)	13.8	17% (99)	15% (178)	4.7
Ivabradine	1% (11)	1% (32)	4.2	1% (6)	2% (20)	5.9
KCCQ scores						
Overall score	64.1 (23.6)	65.0 (23.6)	3.5	66.9 (23.2)	69.2 (23.3)	9.9
Symptom frequency	68.4 (25.6)	69.9 (25.0)	6.1	70.6 (25.4)	73.5 (24.5)	11.6
QOL	56.8 (28.6)	58.5 (28.1)	6.0	59.1 (27.7)	62.6 (27.3)	12.4
Social limitations	65.9 (29.1)	67.7 (29.1)	6.3	69.8 (28.1)	72.2 (28.3)	8.6
Physical limitations	65.1 (26.0)	63.8 (27.5)	5.1	67.7 (26.5)	68.3 (26.8)	2.0

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; QOL, quality of life; VF, ventricular fibrillation; VT, ventricular tachycardia.

that showed that patients initiated on ARNI were significantly more likely to experience a large or very large improvement in health status compared with patients who were not initiated on an ARNI.

Our findings substantially extend the findings from both the clinical trial data from PARADIGM-HF as well as the findings from a prior CHAMP-HF analysis.[6,9,14,15] In PARADIGM-HF, patients randomized to ARNI experienced greater preservation of their health status over 8 months.[14] Not only can health status improvement in the setting of a clinical trial be independent of treatment, due to increased contact with the healthcare system and optimization of medical management, but the baseline KCCQ assessment in PARADIGM-HF was collected after the run-in phase, where

patients were already on maximal ARNI doses.[16,17] It is important, however, to supplement clinical trial data with real-world ARNI experiences because follow-up and intensification of medical therapy are variable. To this end, a prior study from the CHAMP-HF registry showed that initiation of ARNI was associated with early improvements in health status at 2 months.[9] With this current study, we extend these prior findings by showing that early improvements in disease-specific health status associated with ARNI treatment persist to 18 months in a real-world setting.

Improving health-related quality of life is important to both patients and physicians. For patients with heart failure, their quality of life is often considered by them to be as important as their longevity, and for physicians, improving

Figure 2 KCCQ Overall Summary Score health status trajectory in patients initiated on ARNI vs. not for 12 months following initiation, $P < 0.001$.
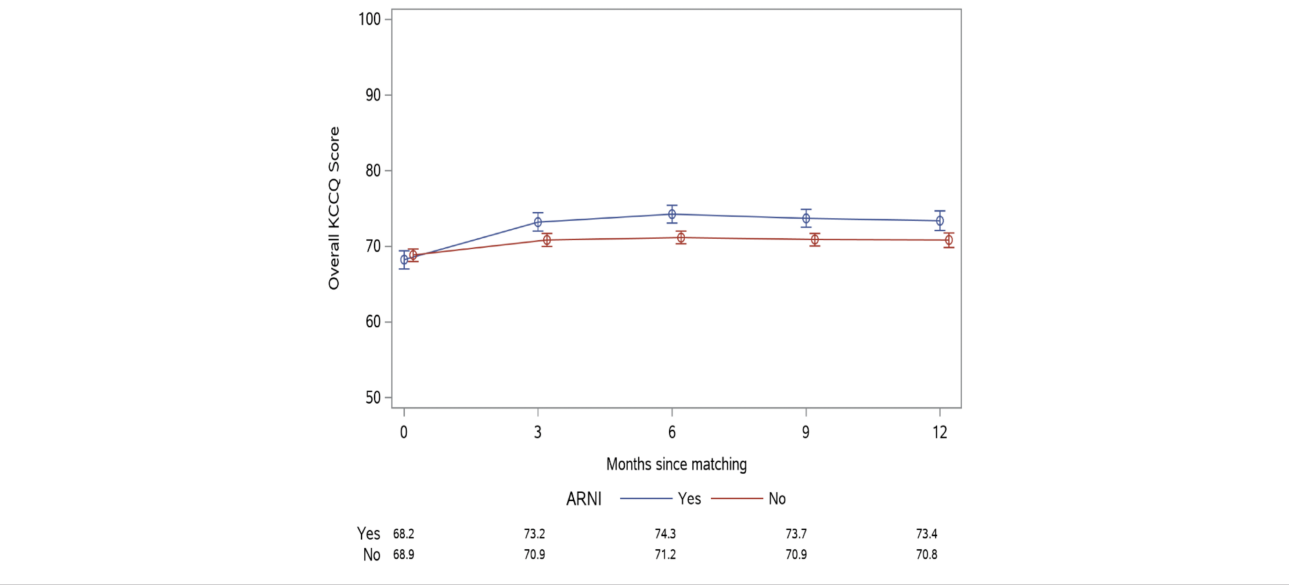

Figure 3 KCCQ domain health status trajectories in patients initiated on ARNI vs. not for 12 months following initiation. (A) Physical limitation score ($P = 0.16$), (B) symptom frequency score ($P = 0.02$), (C) quality of life score ($P < 0.001$), and (D) social limitation score ($P = 0.007$).
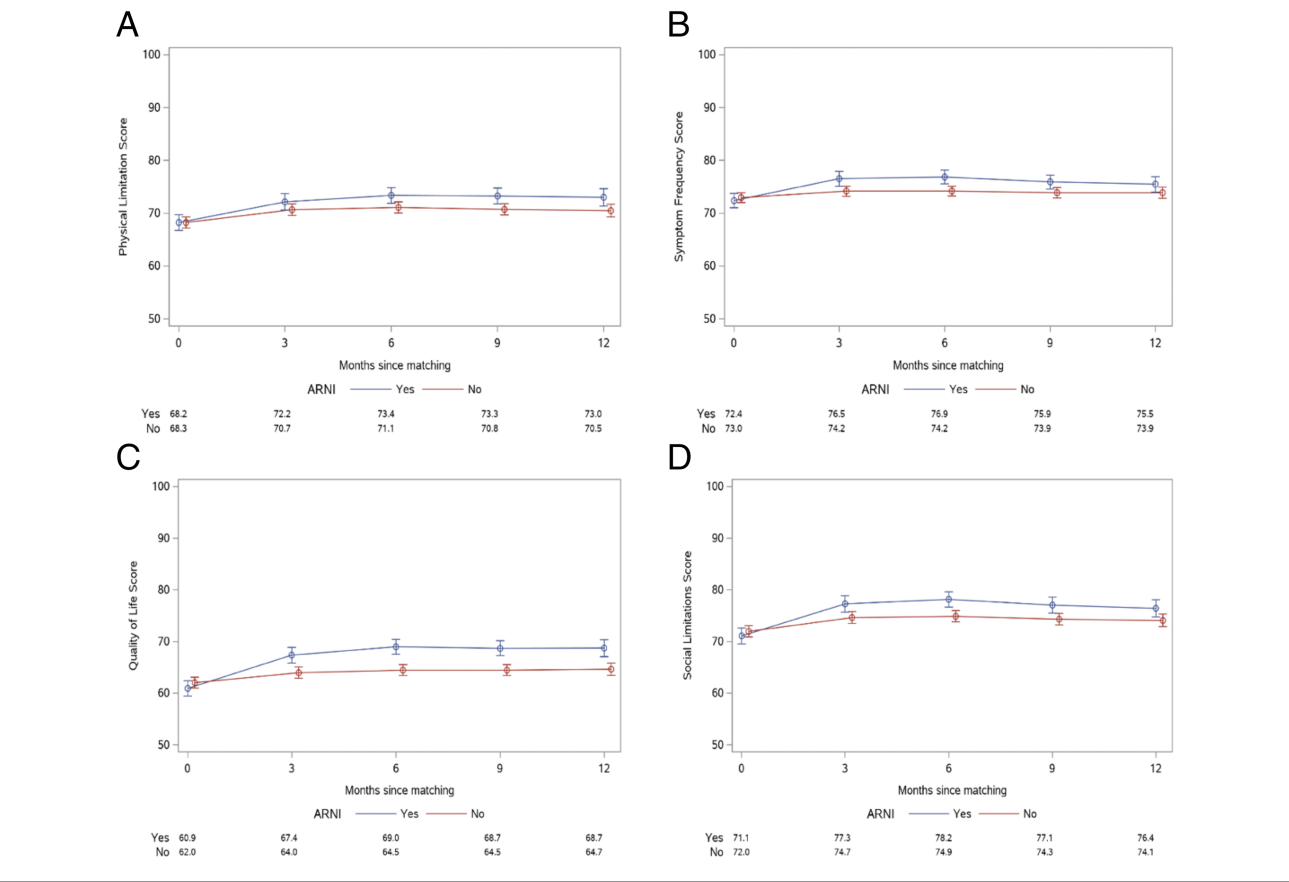
Table 2 Change in KCCQ Overall Summary Score

Change in KCCQ score	ARNI (n = 576)	No ARNI (n = 1152)	P-value
No change, moderate improvement, or lower scores compared with baseline (<10 points)	370 (64.2%)	835 (72.5%)	0.001
Large improvement (≥10 to <20 points)	89 (15.5%)	148 (12.8%)	
Very large improvement (≥20 points)	117 (20.3%)	169 (14.7%)	
Median follow-up (IQR, in months)	10.7 (6.9, 11.7)	10.3 (6.0, 11.6)	

patients' health status is a principal goal of heart failure management.[18,19] Despite this, few HF pharmacologic therapies have been shown to improve symptoms, function, and quality of life. While dapagliflozin has been shown in the clinical trial setting to improve quality of life for patients with HFrEF, there is not real-world evidence available, to date, supporting its effectiveness in improving patients' health status.[20] On the other hand, evidence from CHAMP-HF has shown that treatment with ARNI results in early and sustained improvement in disease-specific health status in a real-world setting. This can help inform patients and clinicians on expectations with initiating ARNI therapy and can be used in patient-centred decision-making discussions regarding management.

Although physical limitations improved to a greater extent among the ARNI cohort as compared with the non-ARNI cohort, this did not reach statistical significance at 12 months. While Khariton *et al*. showed that there is an early improvement in physical limitations at ~2 months following initiation of ARNI therapy,[4] there are several possible factors that explain our results. First, there is increased heterogeneity of the cohort over the time period from 2 to 12 months. Second, the patients who discontinued ARNI during the study period were retained in the ARNI cohort for the analysis; it is possible that this dissipated the early improvements in physical limitations. Lastly, early benefits seen in functional limitations may stagnate over time. Despite a non-statistically significant improvement in physical limitations, overall health status was significantly improved in the ARNI cohort over the 12 month time period.

Our findings should be interpreted in the context of the following potential limitations. First as CHAMP-HF is an observational registry, we cannot exclude bias from unmeasured confounders despite propensity matching. In addition, it is possible the health status benefit observed with ARNI was placebo effect, although the duration and stability of benefit with ARNI makes this less likely. Second, it is worth noting that while patients treated and not treated with ARNI were well matched at baseline, the addition of ARNI includes both an ARB and neprilysin inhibitor. With the addition of both medications, this study cannot distinguish whether patients would have benefited from the addition of an ACEi or ARB alone; nevertheless, the patients initiated on ARNI experienced sustained and significant improvements in health status. Third, the CHAMP-HF registry includes a broad

distribution of outpatient practices, participation of clinical practice sites, physicians, and patients were voluntary, and our results may not be generalizable to patients and clinics that differ from CHAMP-HF, including those in other countries or in other heart failure settings besides outpatient care. Fourth, due to missingness of some laboratory data, we were unable to match for measures such as B-type natriuretic peptide levels. Lastly, despite the propensity match including KCCQ scores, the KCCQ scores in the non-ARNI group were slightly higher at baseline compared with the ARNI group which could have inflated the results of the responder analysis as lower scores have been shown to be stronger predictors of large health status benefits with ARNI.[21]

Conclusions

In real-world clinical practice, the health status benefits associated with ARNI therapy occur within 3 months and persists up to 18 months after initiating therapy. These real-world data can help support the clinical effectiveness for patient reported outcome measures of ARNI in the outpatient management of patients with HFrEF and can be used to assist physicians in making patient-centred decisions regarding management.

Conflict of interest

Funding

Supporting information

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

Figure S1. Rate of patient initiation on ARNI.
Figure S2. Rate of patient discontinuation of ARNI.
Figure S3. KCCQ Overall Summary Score Health Status Trajectory in Patients Initiated on ARNI vs Not Through 18-months Following Initiation.
Figure S4. KCCQ Domain Health Status Trajectories in Patients Initiated on ARNI vs Not Through 18-months Following Initiation.
Appendix S1. 5-point Responder Analysis.

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