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ORIGINAL RESEARCH ARTICLE

The AWAKE-HF Study: Sacubitril/Valsartan Impact on Daily Physical Activity and Sleep in Heart Failure

Raj M. Khandwalla[1] · Daniel Grant[2] · Kade Birkeland[3] · J. Thomas Heywood[4] · Emmanuel Fombu[5,8] · Robert L. Owens[6] · Steven R. Steinhubl[7] · for the AWAKE-H. F. Study Investigators

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Abstract

Background AWAKE-HF evaluated the effect of the initiation of sacubitril/valsartan versus enalapril on activity and sleep using actigraphy in patients who have heart failure with reduced ejection fraction (HFrEF).

Methods In this randomized, double-blind study, patients with HFrEF ($n = 140$) were randomly assigned to sacubitril/valsartan or enalapril for 8 weeks, followed by an 8-week open-label phase with sacubitril/valsartan. Primary endpoint was change from baseline in mean activity counts during the most active 30 min/day at week 8. The key secondary endpoint was change in mean nightly activity counts/minute from baseline to week 8. Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) was an exploratory endpoint.

Results There were no detectable differences between groups in geometric mean ratio of activity counts during the most active 30 min/day at week 8 compared with baseline (0.9456 [sacubitril/valsartan:enalapril]; 95% confidence interval [CI] 0.8863–1.0088; $P = 0.0895$) or in mean change from baseline in activity during sleep (difference: 2.038 counts/min; 95% CI −0.062 to 4.138; $P = 0.0570$). Change from baseline to week 8 in KCCQ-23 was 2.89 for sacubitril/valsartan and 4.19 for enalapril, both nonsignificant.

Conclusions In AWAKE-HF, no detectable differences in activity and sleep were observed when comparing sacubitril/valsartan with enalapril in patients with HFrEF using a wearable biosensor.

Clinical trial registration ClinicalTrials.gov, NCT02970669.

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✉ Raj M. Khandwalla
Raj.Khandwalla@cshs.org

Daniel Grant
daniel.grant@novartis.com

Kade Birkeland
Kade.Birkeland@cshs.org

J. Thomas Heywood
Heywood.James@scrippshealth.org

Emmanuel Fombu
ef374@cornell.edu

Robert L. Owens
rowens@ucsd.edu

Steven R. Steinhubl
steinhub@scripps.edu

[1] Department of Cardiology, Cedars-Sinai Medical Care Foundation, Cedars-Sinai Heart Institute, 8501 Wilshire Ave, Beverly Hills, California 90211, United States

[2] Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, USA

[3] Department of Cardiology, Cedars-Sinai, 127 S San Vicente Blvd a3600, Los Angeles, CA 90048, USA

[4] Division of Cardiovascular Medicine, Scripps Clinic, 10666 N Torrey Pines Rd, San Diego, CA 92037, USA

[5] Previously Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

[6] Division of Pulmonary, Critical Care, and Sleep Medicine, San Diego School of Medicine, University of California, 4520 Executive Drive, San Diego, CA 92121, USA

[7] Digital Medicine, Scripps Research Translational Science Institute, 3344 North Torrey Pines Court, Suite 300, San Diego, CA 92037, USA

[8] Present Address: Locust Walk Partners, 610 W 42nd St., New York, NY 10036, USA

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Key Points

AWAKE-HF evaluated activity and sleep in patients with heart failure with reduced ejection fraction (HFrEF) after the initiation of sacubitril/valsartan treatment.

Physical activity and sleep were evaluated using actigraphy, a wearable biosensor.

Actigraphy can objectively and accurately evaluate 24-h activity.

No differences in activity or sleep were observed with sacubitril/valsartan vs. enalapril.

AWAKE-HF demonstrated the feasibility of using actigraphy to measure outcomes in HFrEF.

1 Introduction

Individuals who have heart failure (HF) with reduced ejection fraction (HFrEF) often experience functional limitations and poor sleep quality [1, 2], which predict an increased rate of both hospitalization and mortality [3–6] and negatively impact health-related quality of life (HRQoL) [1, 2, 7, 8]. The mainstay of HRQoL assessments is patient-reported outcomes (PROs), which have been extensively validated but rely on subjective recall [9, 10].

Actigraphy, which measures activity and sleep patterns with a wearable sensor, can augment PROs and functional assessments by continuously measuring the frequency and intensity of patients' daily physical activity and sleep quantity and quality. Actigraphy can provide insights into the effect of therapies on patients' lives outside the health care setting [11]. Previous studies have successfully used actigraphy to assess fatigue in patients with HF [11] and the impact of nitrates in patients with HF with preserved ejection fraction [12]. There have been no large-scale trials using actigraphy to assess the effect of therapy in patients with HFrEF.

Sacubitril/valsartan is a first-in-class angiotensin-receptor/neprilysin inhibitor [13], indicated to reduce the risk of cardiovascular death and hospitalization for patients with HF with chronic heart failure (New York Heart Association [NYHA] class II–IV) and reduced ejection fraction [14]. In the PARADIGM-HF trial, treatment with sacubitril/valsartan reduced cardiovascular death, overall mortality, and HF-related hospitalizations versus treatment with enalapril [15]. Moreover, in PIONEER-HF, patients treated with sacubitril/valsartan during hospitalization had a greater decline in N-terminal pro b-type natriuretic peptide concentration than those receiving enalapril, suggesting that treatment with sacubitril/valsartan led to less pulmonary congestion [16]. Sacubitril/valsartan also slowed deterioration of HRQoL and improved most physical activity domains measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), with improvements demonstrated over 36 months [17, 18].

We investigated the effect of initiating sacubitril/valsartan on activity and sleep in individuals with HFrEF using a wearable sensor. We hypothesized that, when starting treatment with sacubitril/valsartan, objective measures of sleep and activity would improve when compared with enalapril.

2 Methods

2.1 Oversight

AWAKE-HF (ClinicalTrials.gov, NCT02970669) was designed and conducted by a study steering committee in collaboration with the study sponsor and in accordance with the principles of the Declaration of Helsinki and in line with Good Clinical Practice. Table S1 in the electronic supplementary material (ESM) contains a list of participating centers. The trial was approved by ethics committees, and all patients provided written, informed consent before participation.

2.2 Patients

Ambulatory patients aged 18–80 years with HFrEF were eligible if they experienced NYHA class II or III symptoms, had an ejection fraction $\leq 40\%$, were living in residences where they could move about freely and schedule their activities and sleep, and were candidates for treatment with sacubitril/valsartan according to US prescribing information [14]. Key exclusion criteria were use of continuous positive airway pressure device or similar technology for sleep disorders, ongoing/planned use of either prescription or over-the-counter sleep aids, and hospitalization within 4 weeks before enrollment. For full eligibility criteria, see Table S2 in the ESM.

2.3 Design

AWAKE-HF was a multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study. The 18-week study comprised three phases: a 2-week baseline phase assessing current HF therapy, an 8-week randomized, double-blind phase during which patients were randomly assigned (via interactive response technology) in a 1:1 ratio to sacubitril/valsartan or enalapril treatment, and an 8-week open-label phase during which all patients received

sacubitril/valsartan. Each phase was separated by a 36-h washout period during which study treatment was withheld.

During the double-blind phase, oral sacubitril/valsartan was initiated at 24/26 mg twice daily (BID) (dose level 1) and uptitrated every 2 weeks, as tolerated, to 49/51 mg BID (dose level 2), and then to the target dose of 97/103 mg BID (dose level 3). Oral enalapril was initiated at 2.5 mg BID (dose level 1) and uptitrated every 2 weeks, as tolerated, to 5 mg BID (dose level 2), and then to the target dose of 10 mg BID (dose level 3). To maintain blinding, patients received matching placebo for the alternative treatment. During the open-label phase, all patients initiated sacubitril/valsartan at dose level 2, and uptitrated every 2 weeks to target dose level 3, unless they completed the double-blind phase on dose level 1, in which case they initiated the open-label phase at dose level 1.

2.4 Outcomes measures and assessments

The primary endpoint was change from baseline (week − 1) to the end of the double-blind phase (week 8) in mean activity counts during the most active 30 min/day. The primary endpoint was chosen based on a previous actigraphy study, which found that, in individuals with HFrEF, the most active 30 min/day correlated with patient-reported fatigue [11]. In a separate actigraphy study, more symptomatic patients with HF had reduced activity when awake and increased movement when resting than healthier patients [19]. Therefore, treatment-related increases in activity during active periods may be offset by simultaneous reductions in movement when resting, confounding the assessment of benefit. Activity measurements during the most active 30 min/day allow for assessment of activity patterns during periods of maximal exertion rather than overall activity and may be more likely to reflect symptomatic improvement.

The key secondary endpoint was change from baseline to week 8 in mean activity counts/minute during the patient's nightly sleep period using actigraphy. Other secondary endpoints included change from baseline to sacubitril/valsartan initiation (week 1) and to the beginning and end of the open-label phase (weeks 9 and 16) in mean activity counts during the most active 30 min/day and during sleep.

Exploratory endpoints included change in apnea–hypopnea index (AHI) using a type III portable sleep monitor (AccuSom III, NovaSom, Inc., Glen Burnie, MD, USA), change in mean activity counts during the most active 6 min/day based on actigraphy, and change in KCCQ-23 summary score [20] at weeks 8 and 16 versus baseline.

2.4.1 Actigraphy

Actigraphy data were collected continuously during the 18-week study using an accelerometer (Philips Actiwatch Spectrum; Philips Respironics, Boston, MA, USA) worn on the nondominant wrist. Devices were exchanged and data downloaded five times over five study visits to ensure adequate battery life and guard against data loss. The occurrence and degree of sensor motion was captured in counts per second (0.000175 G-force per activity count) sampled at a rate of 32 Hz and recorded in 30-s epochs. Overall activity was assessed by measurement of counts per minute, and the most active 30 min/day was calculated by summation of the counts collected during the 30 highest scoring minutes of the day. To visualize individual activity, a heat map was generated by sorting daily minutes from most to least active. Daytime activity refers to activity during waking (nonsleep) hours.

Each actigraphy assessment period comprised 7 consecutive days, including weeks—1 (assessment period 1), 1 (assessment period 2), 8 (assessment period 3), 9 (assessment period 4), and 16 (assessment period 5), allowing for continuous actigraphy recording for each 7-day period.

2.4.2 Home Sleep Test

Sleep-disordered breathing was assessed using the AccuSom III, which measures arterial oxygen saturation, pulse rate, respiratory effort, and airflow wave form. To obtain ≥ 6 h of data, home sleep tests could be attempted on up to 3 nights of the patient's choice during the weeks preceding the first, third, and fifth actigraphy assessment periods (weeks—2, 7, and 15, respectively). Actigraphy data recorded during home sleep testing were not included in the outcomes because of the potential for sleep disruption related to the performance of the home sleep test.

2.4.3 Patient-Reported Outcomes

The KCCQ-23 is a validated health status measure comprising 23 items covering physical limitation, clinical symptoms, social function, self-efficacy, and knowledge, and HRQoL [20]. The physical limitation domain is designed to specifically detect clinically significant changes in capacity for physical activity. The scale runs from 0 to 100, with a higher score correlating with better functioning and outcomes. A clinically significant change is defined as a 5-point change on the scale scores [21]. The KCCQ-23 questionnaire was administered using a smartphone (personal or provided by the sponsor) at the end of each study period.

2.4.4 Safety Assessments

Adverse events (AEs) and serious AEs were monitored and recorded; hematology, blood chemistry, and urine values were evaluated; vital signs were measured regularly; and physical examinations were performed.

2.5 Statistical Analysis

Assuming a significance level of 0.05, a sample size of 136 patients would provide 90% power to detect a clinically meaningful difference [11] of 5000 mean activity counts during the most active 30 min (lower counts indicate lack of energy and are associated with reduced activity and lower HRQoL) between groups in the primary endpoint, assuming a standard deviation of 7400 activity counts, a 20% dropout rate, and a 10% rate of nonevaluable data. This sample size provides 93% power to detect a 3.5-point difference between groups in change from baseline to week 8 in mean activity value during sleep, assuming a common standard deviation of 4.9 points, a 20% dropout rate, and a 10% rate of nonevaluable data.

During the double-blind phase, mean change from baseline for each continuous variable was analyzed at each time point using an analysis of covariance model, with treatment and baseline activity as explanatory variables. The least square means (LSMs) of the two treatment groups, LSM difference of the treatment groups, 95% confidence interval (CI), and *P* value based on the fitted linear model are reported. Missing data were imputed using the last observation carried forward.

Before performing the above analysis, tests of normality of the variable, change in mean activity counts collected during the most active 30 min of the patient's day between baseline and week 8, and the log of the variable (log [week 8 value] − log [baseline value]) were performed. If the variable was not normally distributed (based on Shapiro–Wilk test $P < 0.05$) and the lognormal distribution fit better, then the above analysis was performed using log-transformed data. Geometric means were exponentially back-transformed from the LSM; *P* value and treatment comparison by geometric mean ratio (GMR) were evaluated using an analysis of covariance model for a log-scaled response, with treatment group as a class variable and baseline value in logarithmic scale as a continuous covariate.

During the open-label phase, change from baseline (mean of week − 1) for each continuous variable was analyzed at each time point using paired *t* tests for the group randomized to sacubitril/valsartan. The analyses were repeated using the week 8 measurement as baseline for the group randomized to enalapril.

Efficacy was evaluated according to randomized treatment assignment in the full analysis set (all patients who met eligibility criteria). Safety was evaluated according to treatment received in all randomized patients who received one or mor dose of study treatment.

3 Results

Between December 2016 and November 2017, a total of 175 patients were screened at 23 centers in the USA. Following the 2-week baseline phase, 140 patients were randomly assigned to sacubitril/valsartan ($n = 70$) or enalapril ($n = 70$) in the double-blind phase. During the open-label phase, 126 patients received sacubitril/valsartan; 120 patients completed treatment (Fig. 1). Treatment groups were well matched at baseline (Table 1). The mean age of patients was 63 years, 77.1% were men, the median duration of HF was 5.2 years, and 90% of patients had NYHA class II HF. Prior to the study, 82.0% of patients were either on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. During the study period, 78.4% of patients were on concomitant guideline-directed β-blockers, 25.2% were on concomitant mineralocorticoid receptor antagonists, and 57.6% were on loop diuretics. During the randomized portion of the trial, 58.6% of patients in the enalapril arm had reached dose level 3, equivalent to enalapril 20 mg daily, and 53.6% of patients in the sacubitril/valsartan arm had reached dose level 3, equivalent to sacubitril/valsartan 97/103 mg BID. Table 2 lists baseline activity counts and KCCQ-23 scores.

Patients adhered to wearing the actigraphy wrist monitor throughout the study, with a mean time recorded off-wrist of ≤ 1% at each time point (Table S3 in the ESM). Over 20 million minutes of activity data were collected throughout the study. Results are summarized in Fig. 2.

3.1 Overall Activity

To visualize individual activity, heat maps displaying activity from the most active 30-min interval for each patient longitudinally are shown in Fig. 3. These data demonstrate consistency over time in the maximum activity for individual patients.

3.2 Daytime Activity

For the primary endpoint, there was no detectable difference between sacubitril/valsartan and enalapril in device-measured change from baseline to week 8 in mean activity counts during the most active 30 min/day (GMR for sacubitril/valsartan:enalapril 0.9456; 95% CI 0.8863–1.0088; $P = 0.0895$) (Fig. 4a). At week 8, there was no detectable difference from baseline within either the sacubitril/valsartan (GMR 0.98; $P = 0.49$) or enalapril (GMR 1.04; $P = 0.09$) groups. Mean activity counts/minute for the most active 30 min/day, most active 6 min/day, and total activity were similar between groups across all time periods (Fig. 4b).

Exploratory endpoints at week 8 also showed no detectable difference in LSM change from baseline in activity

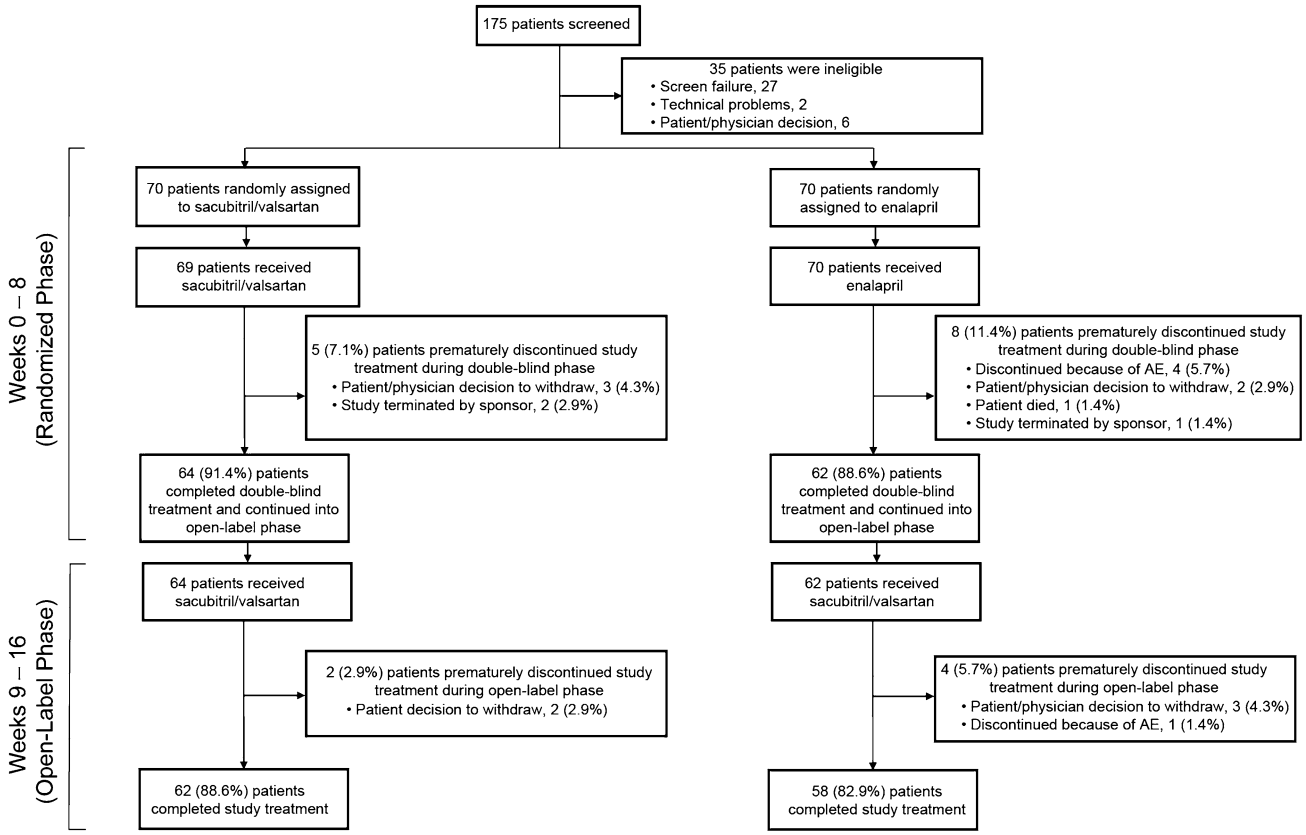


Fig. 1 CONSORT diagram. *AE* adverse event

counts during the most active 30 min/day, most active 6 min/day, and total activity between groups (Table 3).

At the end of the open-label phase, there was no detectable difference in mean activity compared with baseline in either the sacubitril/valsartan group after 16 weeks of treatment (0.2% mean change from baseline; $P=0.9426$) or the enalapril group that switched to sacubitril/valsartan treatment (−1.8% mean change from the start of open-label treatment; $P=0.5158$; Fig. S1 in the ESM). Change from baseline in mean activity counts during the most active 6 min/day was similar.

3.3 Sleep

Mean activity counts during sleep by visit are shown in Fig. 4c. At the end of the double-blind phase, there were no detectable differences in device-measured change from baseline in mean activity counts during sleep for sacubitril/valsartan versus enalapril (LSM change from baseline 2.377 vs. 0.339; 95% CI −0.062 to 4.138; $P=0.0570$; Table 4). At the end of the open-label phase (week 16), mean change from baseline was 1.489 ($P=0.0454$ vs. baseline) in the group that continued sacubitril/valsartan and 1.066 ($P=0.1430$) in the enalapril group after switching to sacubitril/valsartan. Exploratory sleep outcomes as measured by home sleep tests revealed no significant changes in mean AHI 4% scores from baseline to weeks 8 or 16.

3.4 Patient-Reported Outcomes

Overall, the percentage of patients who completed the KCCQ-23 questionnaire was 66% at baseline, 71% during the double-blind phase, and 66% during the open-label phase. Most patients used their own device to complete the questionnaire (baseline, 57%; week 8, 59%; week 16, 58%). Compliance was higher for patients who used their own device (Table S4 in the ESM).

At the end of the double-blind phase, there was no significant change from baseline in KCCQ-23 overall summary score for sacubitril/valsartan versus enalapril (2.89 vs. 4.19; 95% CI −9.97 to 7.38; $P=0.7663$; Fig. 5). At the end of the open-label phase, mean change in KCCQ-23 overall summary score was significantly higher in the sacubitril/valsartan continuation group compared with baseline (8.93; $P=0.005$), whereas there was no significant change in the group that switched to sacubitril/valsartan versus the start of open-label treatment (2.08; $P=0.1433$; Fig. 5).

Table 1 Baseline characteristics (full analysis set)

Characteristic	Sacubitril/valsartan ($n=70$)	Enalapril ($n=70$)
Age (years)	62.3 ± 8.8	64.2 ± 11.6
Sex, male	52 (74.3)	56 (80.0)
Race		
White	48 (68.6)	60 (85.7)
Black	13 (18.6)	8 (11.4)
Asian	4 (5.7)	1 (1.4)
Other	5 (7.1)	1 (1.4)
Systolic blood pressure (mm Hg)	124.0 ± 14.1	128.5 ± 16.6
Heart rate (beats/min)	73.1 ± 8.9	71.4 ± 10.3
Body mass index (kg/m^2)	28.1 ± 3.8	28.7 ± 3.9
Serum creatinine (mg/dL)	1.2 ± 0.5	1.1 ± 0.3
eGFR (mL/min/1.73 m^2)	69.3 ± 24.1	67.5 ± 19.4
NYHA functional class		
II	64 (91.4)	62 (88.6)
III	6 (8.6)	8 (11.4)
Primary heart failure etiology		
Ischemic	48 (68.6)	44 (62.9)
Hypertensive	17 (24.3)	19 (27.1)
Diabetic	6 (8.6)	10 (14.3)
Alcoholic	2 (2.9)	3 (4.3)
Drug-induced (nonchemotherapy)	1 (1.4)	0
Idiopathic other	4 (5.7)	4 (5.7)
Valvular heart disease	3 (4.3)	2 (2.9)
Other	2 (2.9)	0
Prior myocardial infarction	40 (57.1)	36 (51.4)
Prior coronary revascularization	44 (62.9)	41 (58.6)
History of diabetes	30 (42.9)	26 (37.1)
Number of HF hospitalizations in last 12 months	0.7 ± 0.8	0.7 ± 0.7
Most recent ejection fractions	31.1 (7.9)	30.6 (7.7)

Data are *n* (%) or mean ± standard deviation unless otherwise stated

eGFR estimated glomerular filtration rate (based on the Abbreviated Modification of Diet in Renal Disease study equation), *HF* heart failure, *NYHA* New York Heart Association

Physical limitation scores at week 8 were 2.16 and 4.21 for the sacubitril/valsartan and enalapril groups, respectively. This corresponded to a −2.05-point difference ($P=0.6846$) between groups. At week 16, there was an improvement in the KCCQ physical limitation domain in the sacubitril/valsartan continuation group versus baseline (8.94; $P=0.02$), which was not seen in the group that switched to sacubitril/valsartan (−1.54; $P=0.52$ vs. the start of open-label treatment) (Fig. 5).

3.5 Safety

Treatment-emergent AEs were reported in 35 (50.7%) patients in the sacubitril/valsartan group and 44 (62.9%) patients in the enalapril group during the double-blind phase (Table 5). The most common AE (occurring in ≥ 5%) in the sacubitril/valsartan group was dizziness (7.2%). In the enalapril group, the most common AEs were dizziness (17.1%), fatigue (12.9%), diarrhea (8.6%), hypotension (5.7%), and vomiting (5.7%) (Table 5). Only one treatment-related serious AE, HF exacerbation, occurred during the double-blind treatment phase (enalapril group). No angioedema was reported. During the double-blind phase, AEs led to treatment discontinuation in four (5.7%) patients on enalapril and none on sacubitril/valsartan. During the open-label phase, 24 (37.5%) and 28 (45.2%) patients experienced treatment-emergent AEs in the sacubitril/valsartan continuation group and the enalapril switch to sacubitril/valsartan group, respectively. No patients discontinued treatment because of an AE in the continuation group; one patient (0.7%) in the switch group discontinued because of an AE. One patient died during enalapril treatment from a cerebrovascular accident, which was considered unrelated to the study drug.

4 Discussion

Regulatory agencies have increasingly encouraged collection of real-world data (RWD) to understand the effect of medical therapies in the community after approval [22]. Wearable activity monitors that unobtrusively collect objective data on patient movement are an effective tool to obtain RWD [23, 24] and have been used in patients with HFrEF outside the clinical setting [3, 9, 25, 26].

AWAKE-HF collected RWD via wearable activity monitors to compare the early effects of sacubitril/valsartan and enalapril on activity levels in patients with HFrEF and demonstrated that both treatments produced similar effects on activity over 8 weeks as measured by actigraphy. No detectable difference between treatment groups was apparent for the key secondary endpoint, change from baseline to week 8 in mean activity counts/minute during nightly sleep. Mean activity counts at week 8 for most active 30 min, most active 6 min, and total daytime activity were higher in the enalapril group than the sacubitril/valsartan group but did not meet statistical significance.

The two most novel findings of our study are (1) the divergence between actigraphy results and PROs at week 16 and (2) the very high rates of adherence to use of wearable devices by patients to collect RWD.

Interestingly, the exploratory outcome of change in KCCQ over 8 weeks did not result in a significant difference in either treatment group versus baseline, but at 16 weeks

Table 2 Baseline activity counts and Kansas City Cardiomyopathy Questionnaire-23 scores (full analysis set, exploratory outcome)

Treatment	Patients (*N*)	Mean baseline activity/score
Activity counts during most active 30 min of day		
Sacubitril/valsartan	64	25,765.1 ± 7250.6
Enalapril	63	25,147.2 ± 6758.0
Activity counts during most active 6 min of day		
Sacubitril/valsartan	64	6,844.6 ± 1945.6
Enalapril	63	6,858.9 ± 1989.9
Activity counts during daily active period (counts/min)		
Sacubitril/valsartan	66	206.2 ± 79.9
Enalapril	67	190.2 ± 72.9
Activity counts during sleep (counts/min)		
Sacubitril/valsartan	66	16.8 ± 9.5
Enalapril	65	15.3 ± 7.8
AHI 4% (events/h)		
Sacubitril/valsartan	64	15.8 ± 13.1
Enalapril	60	16.5 ± 14.0
KCCQ-23 overall summary scores		
Sacubitril/valsartan	47	63.45 ± 25.2
Enalapril	46	66.79 ± 21.6
Physical limitation scores		
Sacubitril/valsartan	46	68.45 ± 24.52
Enalapril	46	72.72 ± 23.57

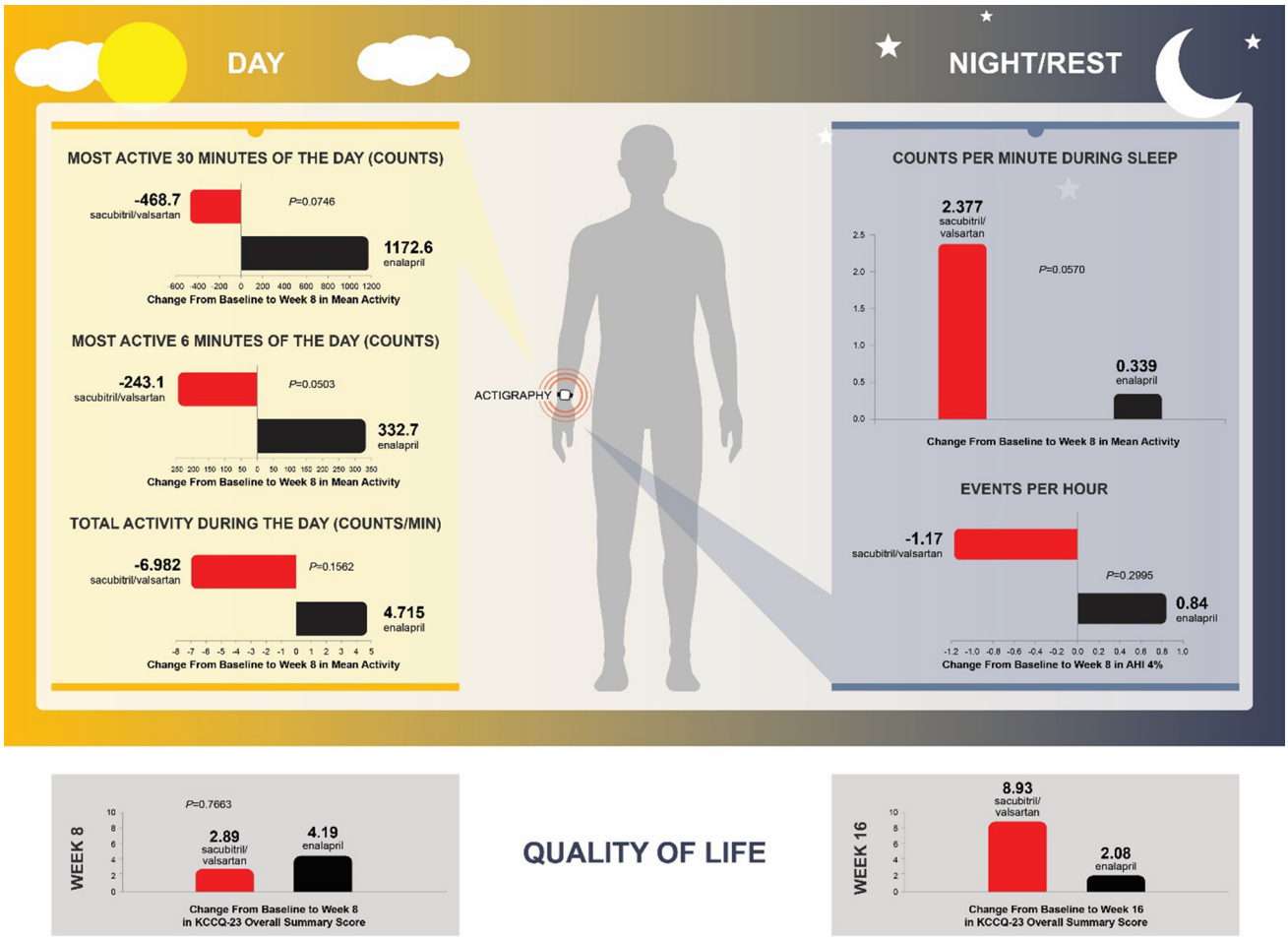
Data are mean ± standard deviation unless otherwise stated

AHI apnea–hypopnea index, *KCCQ-23* Kansas City Cardiomyopathy Questionnaire-23, *SD* standard deviation

there was a statistically significant increase in the KCCQ-23 overall summary score (8.93 points; $P = 0.005$) and the KCCQ physical limitation domain (8.94; $P = 0.02$) compared with baseline for those receiving sacubitril/valsartan during both treatment periods. This could indicate that patient-reported quality of life is independent from activity levels and the two may measure distinct domains. Similar results have been noted when actigraphy and PROs were used to assess the impact of joint replacements on quality of life [27], suggesting that patient perception of capacity for physical activity does not necessarily correspond to objective measurement of physical activity. Also, patients with HF have adapted to a low-activity lifestyle [28], which may be difficult to change. In fact, our data found that baseline activity was a strong predictor of an individual's activity during the study. Finally, improvements in KCCQ, which occurred at 16 weeks but not at 8 weeks, suggest that a longer duration of therapy may be needed for improvement to be reflected in activity levels. These results are consistent with the PARADIGM-HF trial results, which showed significant improvements for sacubitril/valsartan versus enalapril in KCCQ after 4 months of treatment [17].

In the NEAT-HFpEF trial [12] wearable sensors detected a dose-dependent decline in activity in the nitrate arm compared with placebo even though there were no differences in PROs, 6-min walk test results, or pro–brain (B-type) natriuretic peptide levels between groups [12]. Actigraphy may be better at detecting decreases in activity due to medication side effects than increases in activity due to therapeutic effects since an increase in activity requires that the medication have a positive effect on cardiac function and that patients consciously change their behavior and lifestyle. Treatment with sacubitril/valsartan, which has been shown to decrease death and HF hospitalizations in patients with HFrEF [15], may improve cardiac function and alter the trajectory of a patient's HF by preventing functional decline. Over time, patients may be able to maintain or slow decreases in their current activity levels with treatment.

Although AWAKE-HF did not demonstrate a difference in activity levels following treatment with sacubitril/valsartan, it did demonstrate the feasibility of using wearable activity monitors in patients with HFrEF. We collected over 20 million minutes of activity data. Notably, patient adherence and data quality were high: over 99% of patients' physical activity during key measurement weeks (weeks −2, −1, 1, 8, and 16) was collected and analyzed. We believe that, in addition to providing RWD about the effect of initiating sacubitril/valsartan on activity and sleep, our trial design and results will guide future investigators in the use of actigraphy to measure clinical outcomes. For instance, the American



KCCQ indicates Kansas City Cardiomyopathy Questionnaire.
AWAKE-HF was a phase 4, multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study. The 18-week study consisted of a screening period, a 2-week baseline phase, an 8-week randomized treatment phase in which patients received either double-blind enalapril or sacubitril/valsartan, and an 8-week open-label extension phase in which all patients received sacubitril/valsartan. Key actigraphy outcomes included change from baseline in mean activity counts during the most active 30 minutes/day, during the most active 6 minutes of the day, in total activity counts during the day, and in mean activity counts per minute and change in apnea hypopnea index (AHI) ≥4% during the patient's nightly sleep period. The changes from baseline on these measures did not differ substantially between treatment groups. Health-related quality of life was assessed using the KCCQ-23. Percentage of patients that completed the KCCQ-23 questionnaire was 66% at baseline, 71% during the double-blind phase, and 66% during the open-label phase.

Fig. 2 Summary of the AWAKE-HF study

Academy of Sleep Medicine has recommended the use of actigraphy to estimate total sleep time in patients with obstructive sleep apnea when polysomnography is not available [28]. Since our study includes both a home sleep study and actigraphy, it may shed light on the use of actigraphy to screen for potential sleep disorders in patients with HFrEF. Further analyses could provide insight into the effects of sacubitril/valsartan on other measures of daytime and sleep activity beyond the prespecified endpoints.

Several study limitations must also be considered. This was a short-duration study specifically designed to assess the effect of treatment in patients with HFrEF. However, these short-term outcomes may not fully reflect the impact of treatment on patient's activity and sleep in the longer term. In addition, 90% of the patients had NYHA class II symptoms. It is possible that activity in this group was not perceived by the patients to be constrained by a cardiac limit, making it more difficult to detect a treatment effect. While

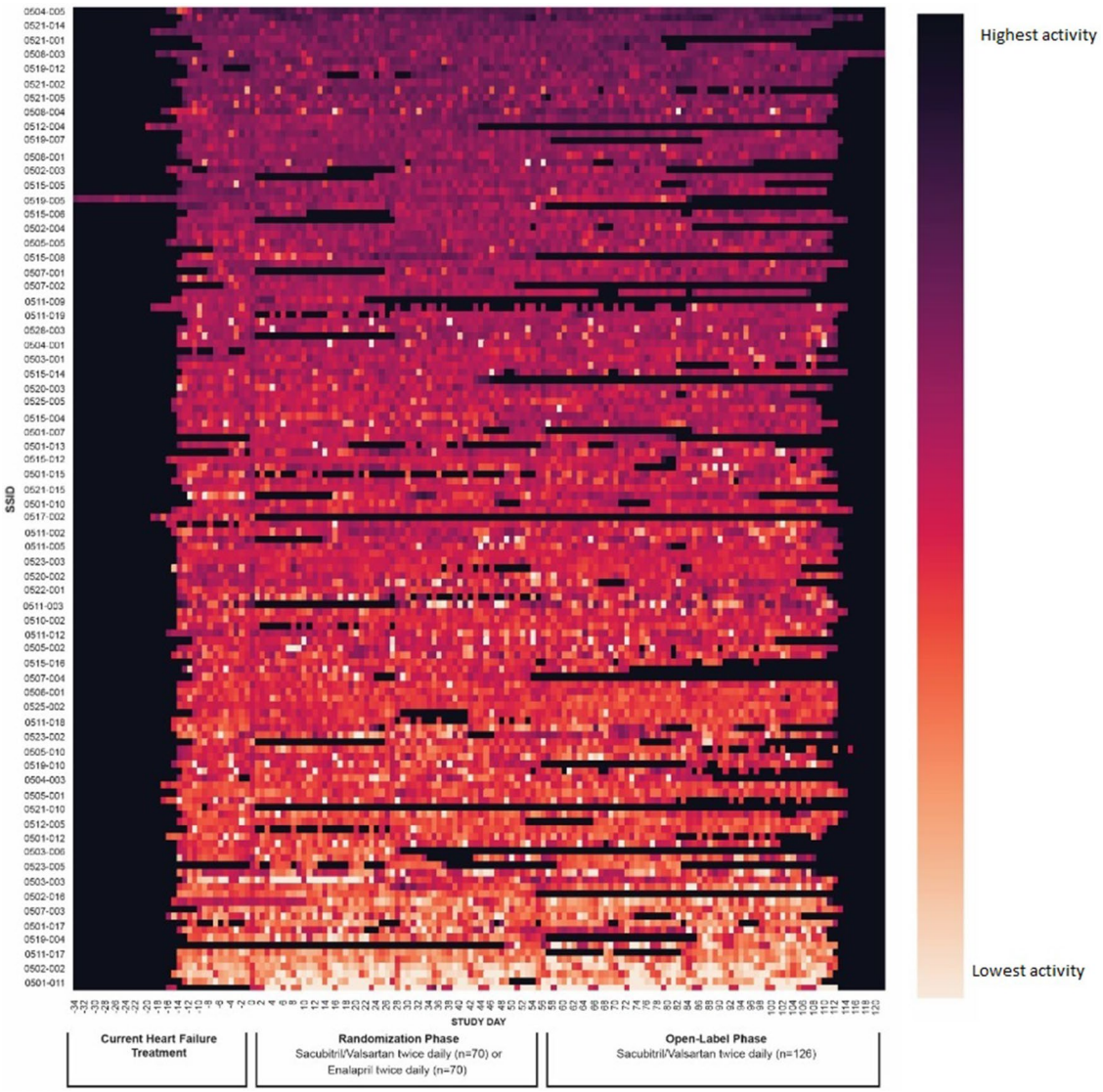


Fig. 3 Heat map of most active 30 min throughout the day, sorted according to average activity for each patient, by study day

the actigraphy device used was a US FDA -cleared class 2 medical device, few studies have used it to study activity in patients with HFrEF [29, 30], and the choice of device may have affected the study results. Our study did not assess activity type or intensity. Finally, the design of our trial with respect to the choice of comparator drug (enalapril) and dosing schedule during the randomized portion was based on the PARADIGM trial. A criticism of the PARADIGM trial design is that the dose of enalapril was not increased as aggressively as the dose of sacubitril/valsartan. The same criticism can be made of our trial.

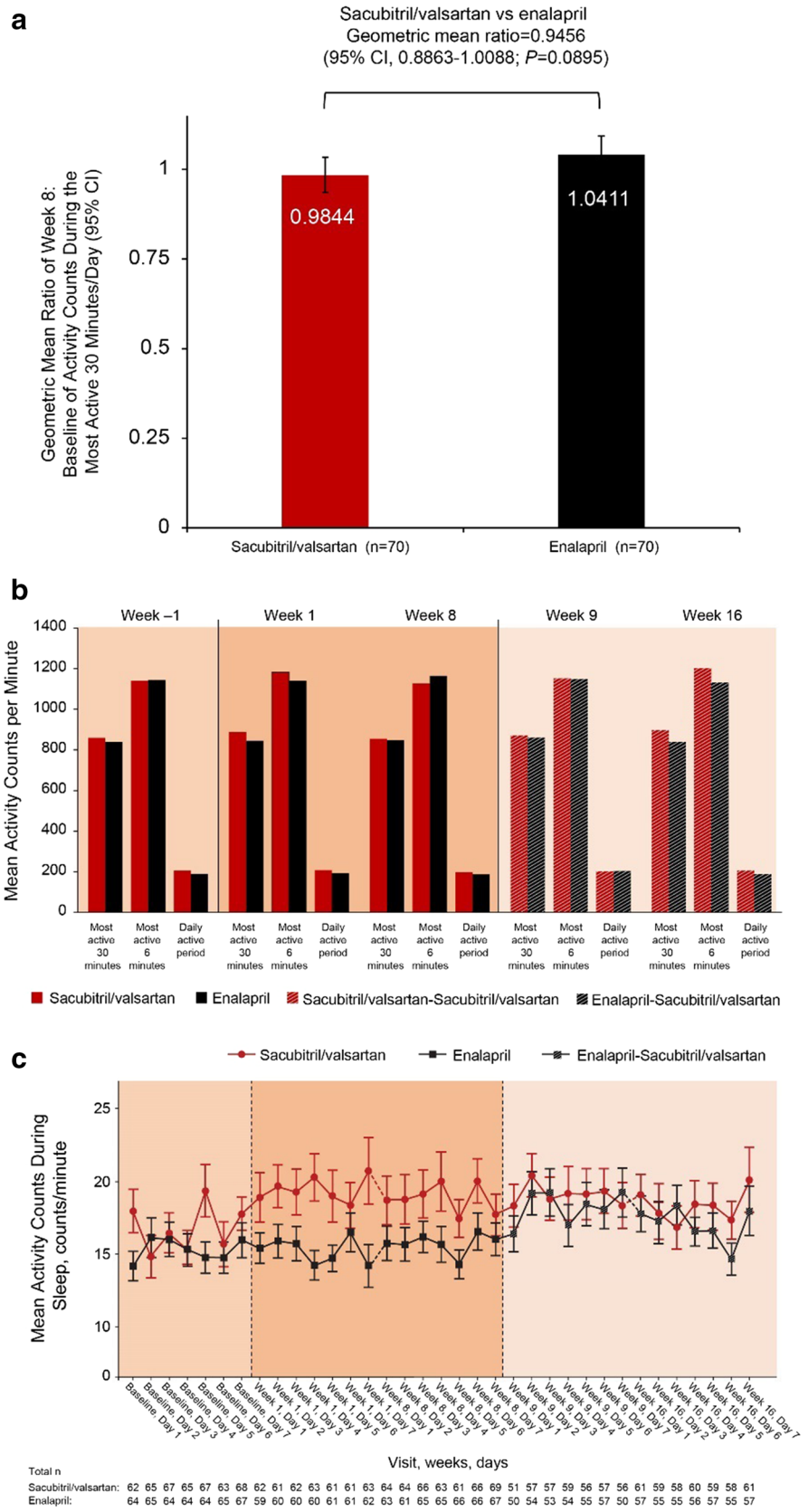


Fig. 4 Activity data. **a** Primary outcome: change from baseline to week 8 (double-blind phase) in mean activity counts during the most active 30 min of the day (GMR, 95% CI). **b** Mean activity counts/minute during the most active 30 min/day (primary and secondary endpoints) and the most active 6 min/day and daily active period (exploratory endpoints). **c** Daily mean activity counts during sleep over the study assessment weeks (secondary endpoint). *CI* confidence interval, *GMR* geometric mean ratio

Table 3 Change in mean activity counts from baseline to 8 weeks based on randomized therapy

Activity	Baseline		8 weeks		LSM change from BL to 8 weeks (SE)		*P* value change with SAC/VAL vs. ENA
	SAC/VAL	ENA	SAC/VAL	ENA	SAC/VAL	ENA	
Most active 30 min[a] (counts)	25,765.1 ± 7250.6	25,147.2 ± 6758.0	25,790.7 ± 7526.9	26,132.2 ± 7863.4	− 468.7 (634.2)	1172.6 (655.0)	0.0746
Most active 6 min (counts)	6844.6 ± 1945.6	6858.9 ± 1989.9	6746.5 ± 1918.6	7158.0 ± 2375.0	− 243.1 (202.6)	332.7 (209.2)	0.0503
Total activity (counts/min)	206.2 ± 79.9	190.2 ± 72.9	199.7 ± 82.3	195.8 ± 74.7	− 6.982 (5.753)	4.715 (5.798)	0.1562

Data are presented as mean ± standard deviation unless otherwise stated

BL baseline, *ENA* enalapril, *LSM* least squares mean, *SAC* sacubitril, *SE* standard error, *VAL* valsartan

[a]Not on a log scale

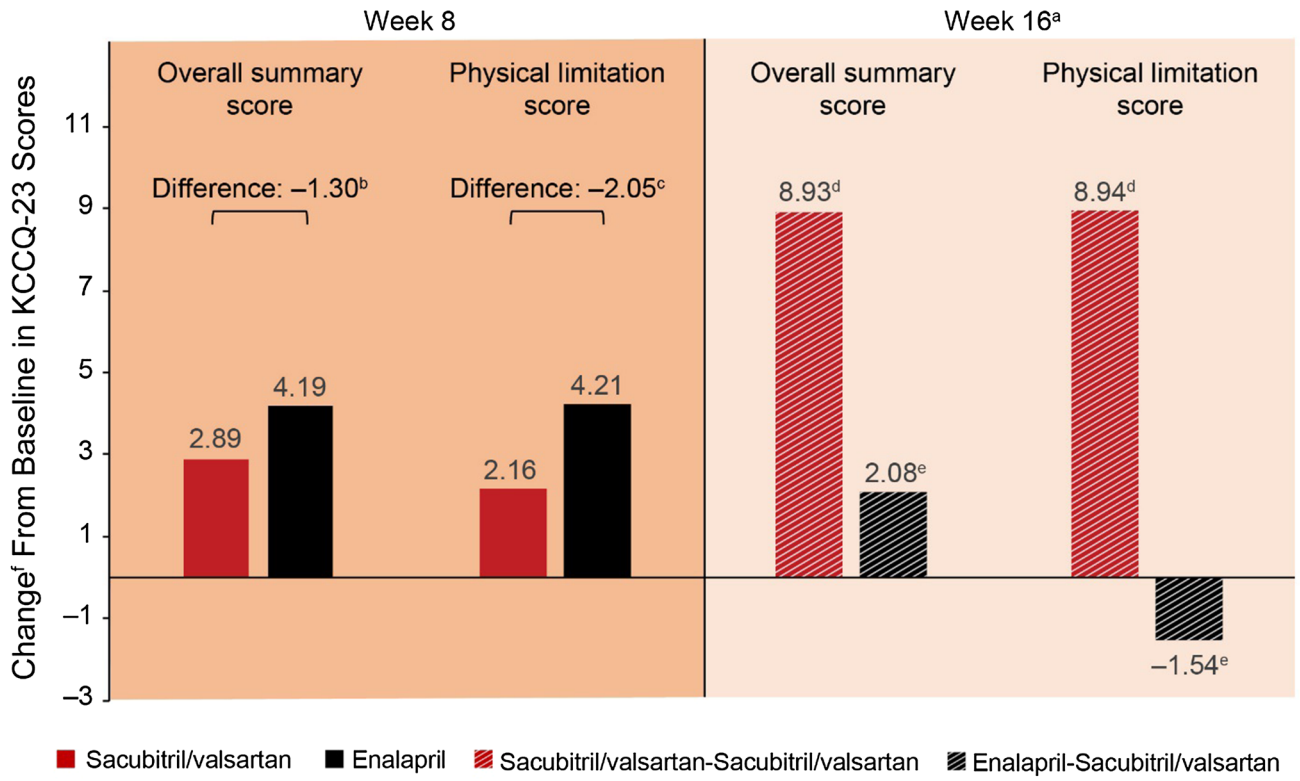
Table 4 Change in activity and sleep parameters from baseline during the randomized treatment period (full analysis set)

Parameter visit	Least squares mean change (SE) from baseline		LSM difference (95% CI)	*P* value
	Sacubitril/valsartan n = 70	Enalapril n = 70		
Mean activity count per minute during sleep				
Week 8	2.377 (0.746)	0.339 (0.752)	2.038 (− 0.062 to 4.138)	0.0570
AHI 4% (events/h)				
Week 8	− 1.17 (1.35)	0.84 (1.38)	− 2.01 (− 5.85 to 1.82)	0.2995

AHI apnea–hypopnea index, *CI* confidence interval, *LSM* least squares mean, *SE* standard error

5 Conclusions

Treatment with sacubitril/valsartan over 8 weeks in individuals with HF demonstrated no detectable differences in activity compared with enalapril assessed using actigraphy. However, treatment with sacubitril/valsartan over 16 weeks resulted in a statistically significant improvement in HRQoL versus baseline, suggesting a divergence between objective and subjective measurements in this population. Wearable devices can collect large amounts of data with a high compliance rate, and further analyses should provide more insight into the future use of actigraphy in clinical trials.



KCCQ indicates Kansas City Cardiomyopathy Questionnaire.
[a]Treatment differences were not evaluated.
[b]P value and treatment comparison evaluated using analysis of covariance; 95% CI, −9.97 to 7.38; *P*=0.7663.
[c]P value and treatment comparison evaluated using analysis of covariance; 95% CI, −12.07 to 7.98; *P*=0.6846.
[d]For sacubitril/valsartan-sacubitril/valsartan, changes at week 16 were calculated compared with baseline.
[e]For enalapril-sacubitril/valsartan, changes at week 16 are calculated compared with the start of the open-label phase.
[f]The week 8 data are based on least squares mean change, while those for week 16 are based on mean change.

Fig. 5 Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ-23) overall summary and physical limitation scores (exploratory endpoint)

Table 5 Treatment-emergent adverse events occurring in ≥5% of patients in either group during the randomized phase (safety set)

Preferred term	Sacubitril/valsartan n=69	Enalapril n=70
Any event	35 (50.7)	44 (62.9)
Dizziness	5 (7.2)	12 (17.1)
Fatigue	1 (1.4)	9 (12.9)
Diarrhea	1 (1.4)	6 (8.6)
Hypotension	1 (1.4)	4 (5.7)
Vomiting	0	4 (5.7)

Data are presented as *n* (%)

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Declarations

Conflict of interest Raj M. Khandwalla has served as a consultant for Novartis Pharmaceuticals Corporation and has received a research grant from General Electric. Kade Birkeland has served as a consultant for Novartis Pharmaceuticals Corporation. J. Thomas Heywood has served as a consultant for Actelion Pharmaceuticals, Medtronic, and Abbott; was a speaker for Actelion Pharmaceuticals, Medtronic, Abbott, Otsuka, and Novartis Pharmaceuticals Corporation; has received grant funding from Medtronic, Abbott, and Impedimed; and has received fellowship grant support from Abbott. Robert L. Owens has received honoraria and travel reimbursements from ResMed, LLC, and Itamar Medical and has served as a consultant for Novartis Pharmaceuticals Corporation. Steven Steinhubl has received financial compensation from Novartis Pharmaceuticals Corporation for serving as an adviser. Emmanuel Fombu was an employee of Novartis Phar-

maceuticals at the time of this study. Daniel Grant is an employee of Novartis Pharmaceuticals.

Ethics approval Not applicable

Consent to participate All participants in the trial signed an informed consent upon enrollment.

Consent for publication All co-authors have consented for publication.

Availability of data and materials Data and materials were made available to the co-investigators.

Code availability Not applicable.

Author Contributions All authors contributed to the conception and design of the study and/or data analysis/interpretation, drafting, and/or critical review of the manuscript, and all provided final approval to submit the manuscript for publication. RMK wrote the first draft of the manuscript, and the other authors, as part of the steering committee, revised subsequent drafts. Medical writing and editing assistance was provided by ApotheCom (Yardley, PA, USA), funded by Novartis Pharmaceuticals Corporation. All authors agree to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A full list of all investigators and institutions involved in the study is provided in Table S1 in the ESM.

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