OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction

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ABSTRACT

Aims

OUTSTEP-HF compared the effect of sacubitril/valsartan versus enalapril on six-minute walk test (6MWT) distance, non-sedentary daytime physical activity and heart failure (HF) symptoms in patients with HF with reduced ejection fraction (HFrEF).

Methods and results

Ambulatory patients (N=621) with stable symptomatic HFrEF were randomised 1:1 to sacubitril/valsartan (N=310) or enalapril (N=311). Changes in physical activity and mean daily non-sedentary daytime activity from baseline to Week 12 were measured using 6MWT and a wrist-worn accelerometer device, respectively. After 12 weeks, 6MWT improved by 35.09 m with sacubitril/valsartan (97.5% CI: 27.85, 42.32) and by 26.11 m with enalapril (97.5% CI: 18.78, 33.43); however, there was no significant difference between groups (LSM treatment difference: 8.98 m [97.5% CI: -1.31, 19.27]; $p=0.0503$). Mean daily non-sedentary daytime activity decreased by 27 minutes with sacubitril/valsartan and by 21 minutes with enalapril (LSM treatment difference: -6 minutes [97.5% CI: -25.7, 13.4], $p=0.4769$) after 12 weeks. 6MWT improved by ≥ 30 m in 51% of patients in sacubitril/valsartan group versus 44% of patients treated with enalapril (OR [95% CI]: 1.251 [0.895, 1.748]). At Week 4, non-sedentary daytime activity increased by $\geq 10\%$ in 58% of patients treated with sacubitril/valsartan versus 64% with enalapril; 58% treated with sacubitril/valsartan reported improved HF symptoms as assessed by patient global assessment versus 43% with enalapril. However, these differences did not persist at Week 12.

Conclusion

After 12 weeks of treatment, there was no significant benefit of sacubitril/valsartan on either 6MWT or in daytime physical activity measured by actigraphy compared with enalapril.

(ClinicalTrials.gov number, NCT02900378).

KEYWORDS: accelerometer; exercise; heart failure; physical activity; six-minute walk test; sacubitril/valsartan.

OUTSTEP-HF: Randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction

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Abstract: Allowed - 250 words (current – 250)

One-sentence Summary

OUTSTEP-HF is the largest study in patients with heart failure and reduced ejection fraction that measured physical activity using six-minute walking test (6MWT) and accelerometry, and found that there was no significant benefit of sacubitril/valsartan treatment on physical activity compared with enalapril.

INTRODUCTION

Heart failure (HF) is a rapidly growing public health issue affecting about 26 million people globally and is associated with high morbidity and mortality.(1, 2) Limitations in daily physical and social activities are the cardinal features of HF, and are associated with poor prognosis.(3, 4) A modest 10-minute increase in physical activity (PA) or a 5% increase in exercise capacity in HF patients would have beneficial effects on mortality and hospitalisation risk.(5, 6) Based on clinical evidence, regular PA and exercise have been identified as important therapeutic goals in patients with HF to improve quality of life (QoL), and to reduce the risk of HF hospitalisation and mortality.(2, 7-9)

Sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) is indicated for the treatment of HF with reduced ejection fraction (HFrEF), following its demonstration of superiority over the angiotensin converting enzyme inhibitor (ACEI) enalapril in terms of mortality and morbidity in the pivotal PARADIGM-HF trial.(10) Additional analyses from PARADIGM-HF and a real-world observational study (CHAMP-HF) suggest that sacubitril/valsartan had a significant beneficial effect on QoL as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).(10, 11) Physical and social activity are major determinants of the KCCQ-assessed QoL. Although studies with evidence-based therapies for chronic HF, such as ACEIs, angiotensin II receptor blockers (ARBs) or cardiac resynchronisation therapy (CRT), (2, 12, 13) have shown improved exercise capacity, there is a limited evidence on effects of sacubitril/valsartan on PA.(14, 15)

Accelerometers provide objective and continuous assessment of PA during patients' daily life over long periods and therefore may reflect the true effect of a therapy on PA.(16) This study

used six-minute walk test (6MWT) and accelerometry to evaluate the effect of sacubitril/valsartan versus enalapril on PA.

METHODS

Study design and participants

Study design has been published previously.⁽¹⁷⁾ Briefly, this was a randomised, double-blind, actively controlled, prospective study (OUTSTEP-HF, ClinicalTrials.gov number, NCT02900378) over 14 weeks (initial 2 weeks of screening and baseline assessments, followed by a 12-week double-blind treatment period), conducted at 120 sites, across 19 European countries (**Supplementary material, Figure S1**). Study included ambulatory patients aged ≥ 18 years with a diagnosis of HF (New York Heart Association [NYHA] class II-IV), with reduced left-ventricular ejection fraction (LVEF) $\leq 40\%$ and plasma N-terminal pro b-type natriuretic peptide (NT-proBNP) level of ≥ 300 pg/mL or BNP ≥ 100 pg/mL. The complete list of study inclusion and exclusion criteria is shown in **Supplementary material, Table S1**.

Treatment

Patients were randomised 1:1 to sacubitril/valsartan or enalapril. Treatment with sacubitril/valsartan or enalapril was initiated at a specific dose level according to the pre-study ACEI/ARB dose and up-titrated to target dose (sacubitril/valsartan: 97/103 mg twice daily [bid] or enalapril 10 mg bid) in accordance with the European summary of product characteristics (SmPC) (**Supplementary material, Table S2**). Patients were required to continue their background HF medicines except for ACEIs or ARBs (discontinued 36 hours prior to initiation of the study drugs).

Outcomes

The co-primary endpoints were – change from baseline in exercise capacity and mean daily non-sedentary daytime activity, measured by 6MWT and accelerometry, respectively. The importance of 6MWT was increased from a secondary endpoint to a co-primary endpoint along with the actigraphy-based endpoint after recruitment was complete but before database lock and unblinding.(17) As the 6MWT was already accounted for when calculating the initial sample size while planning the study, the change in endpoints did not affect either the study sample size or the remaining of the trial conduct.(17)

Secondary outcomes were – the proportion of patients showing ≥ 30 m improvement (in 6MWT), $\geq 10\%$ increase in non-sedentary daytime PA, mean daily light and moderate-to-vigorous non-sedentary daytime PA and total weekly time spent in light non-sedentary daytime PA. Secondary outcomes also included the proportion of patients with improved symptoms of HF, as assessed by patient global assessment (PGA), and changes from baseline on M6min (an accelerometry-based measure of the peak six minutes of daytime PA) in sacubitril/valsartan-treated versus enalapril-treated patients. Other secondary variables are described in

Supplementary material, *Table S3*.

Exploratory efficacy endpoints included short-term changes from baseline of patients' mental and physical functioning as assessed by the Twelve-Item Short-Form Health Survey (SF-12), and change from baseline of patients' health status as assessed by the patients self-reported EuroQoL five-dimension questionnaire (EQ-5D) in sacubitril/valsartan versus enalapril-treated patients at Weeks 4, 8 and 12.

OUTSTEP-HF was conducted in accordance with the ethical principles of the Declaration of Helsinki, following review of the study protocol and all amendments by the

Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each centre. All participants provided written informed consent prior to enrolment.

Efficacy assessments

6MWT is a validated endpoint to clinically assess patients' PA in HF studies.(18) Patients walked down a long corridor at their own pace and covered as much distance as possible within 6 minutes. At the end of the 6-minute duration, the distance walked was calculated and recorded along with any symptoms at Week 0, Week 4, Week 8 and Week 12.

Accelerometry is a non-invasive method for monitoring PA. Patients were instructed to wear the accelerometer (MotionWatch8®, Camntech, Cambridge, UK) (19, 20) wristband continuously during the study. Assessment of PA was performed during the entire duration of the study (from Week -2 to Week 12) using a continuously wrist-worn accelerometry device on non-dominant wrist. Device non-wear time was defined as 120 minutes or more of continuous zero activity. Daily non-sedentary daytime activity measurements were considered valid with at least 10 hours of activity recordings in a day, and at least 7 available days for each period. Data from Week -2 to Week 0 were used to define the baseline average minutes spent per day in daytime non-sedentary PA for individual patients.

M6min is an accelerometry-based measure of the peak 6 minutes of PA and was calculated over bi-weekly epochs. This parameter is derived from validated algorithms of the MotionWatch8® software that was used to pre-process accelerometry data.(21)

PGA is a self-reported tool that evaluated the patients' subjective rating of their disease activity. The PGA responses correlate with functional capacity assessed by means of the 6MWT.(22) Patients marked the functioning or response to an intervention at the time of PGA reporting on a numerical scale of 1 (much improved) to 7 (much worse), as described previously,

at Weeks 4, 8 and 12. Exploratory assessments included SF-12 and the EQ-5D-5L questionnaires at baseline and at Weeks 4, 8 and 12, to provide insights into the actual impact of the therapy, including safety and efficacy aspects that influence QoL.(23)

Safety assessments

Safety assessments consisted of performing regular evaluation of vital signs, physical examination and local laboratory haematology, blood chemistry, and urine samples to monitor for adverse events (AEs) and serious adverse events (SAEs).

Statistical analysis

Detailed statistical considerations are published elsewhere.(17) Details of dataset used to analyse outcomes measured are given in **Supplementary material, Table S4**. A sample size of 259 patients per treatment group was estimated based on the assumption that a difference of at least 20 minutes between groups in non-sedentary PA/day from a baseline value of 200–230 minute/day of activity could be clinically relevant. Similarly, for the 6MWT, for a between-treatment difference of 35 m, 224 patients in each treatment arm were needed to be recruited. In order to account for dropout patients, the study planned to recruit 600 patients.(17)

The co-primary efficacy analysis, change from baseline to end of study (EOS) in 6MWT comparing between treatments was carried out using an analysis of covariance model, adjusting for treatment and baseline NYHA class (NYHA II vs III/IV) and the 6MWT baseline value as covariates. During the study, patients with an AE/SAE (non-HF related) during/around the 6MWT, that could impact the performance of the 6MWT were blindly excluded. These patients were considered as outliers (sacubitril/valsartan n=12; enalapril n=8) in the double-blind period; hence, statistical analysis plan was amended prior to database closure, and 6MWT primary variable analysis was performed for the full analysis set (FAS population subset) excluding

patients who had a non-HF-related AE/SAE during/around the 6MWT performance. A sensitivity analyses was performed including patients in the FAS, per protocol (PP) and PP subset without AE/SAE (non-HF related) during/around 6MWT. For 6MWT efficacy variable, no imputation of missing data was performed. The two-sided 97.5% confidence interval (CI) and p-values were reported at $\alpha=0.025$ considering the two co-primary endpoints and using Bonferroni correction for multiple comparisons.

The co-primary efficacy analysis, change from baseline to EOS in mean daily non-sedentary daytime activity was carried out similarly adjusting daily non-sedentary daytime activity baseline value as covariate in FAS population with multiple imputations (MI) for missing variables. A sensitivity analysis was also carried out by last observation carried forward (LOCF) imputation method. The key secondary variable, proportion of patients with increased level of non-sedentary daytime PA at EOS compared to baseline, was analysed by applying a logistic regression model with treatment and baseline NYHA class as fixed factors, and the baseline value as covariate, and the odds ratio (OR, 95% CI) was given. All other secondary variables were analysed descriptively using statistics for continuous and categorical data.

Methodology for handling of missing data/censoring/discontinuations for analysis of primary and secondary outcomes has been described earlier.(17) For patients with missing baseline non-sedentary daytime activity, a fully conditional specification using the “proc MI” SAS procedure was used for the multiple imputation with 5 imputations. A conservative approach was used in imputing missing data. For example, for increased level of non-sedentary daytime physical activity, missing Week 12 values of patients due to hospitalisation or death was substituted by worst possible value for the variable (= No).

RESULTS

Of the 764 patients screened, 621 were randomised; however, two patients did not receive at least one dose of the study medication and were excluded from the study, resulting in 619 patients (309 in the sacubitril/valsartan group and 310 in the enalapril group) considered in the safety population. In total, 570 patients completed the study (**Figure 1**). The FAS included 604 patients, and FAS subset excluding patients who had a non-HF-related AE/SAE during/around the 6MWT performance included 584.

At baseline, both treatment arms were well matched across all analysis subsets. **Table 1** shows the baseline characteristics of the safety population. The mean $\pm$ SD values of 6MWT at the baseline were 364.72 ± 06.86 m in the sacubitril/valsartan group and 371.18 ± 105.13 m in the enalapril group. The mean $\pm$ SD age of the overall population was 66.9 ± 10.7 years (59.9% were aged ≥ 65 years), four-fifths of patients were men and 96.45% were Caucasian. Primary aetiology of HF was mainly ischaemic (56.7%) (**Supplementary material, Table S5**). At the EOS, 66.7% of patients in sacubitril/valsartan and 80% in enalapril group achieved the highest drug dose of 200 mg and 10 mg bid, respectively.

Efficacy – primary endpoints

After 12 weeks of treatment, both sacubitril/valsartan and enalapril treatments improved 6MWT distance from baseline (**Supplementary material, Figure S2**). In the modified FAS population, there was a non-significant trend towards greater distance walked on 6MWT after 12 weeks in the sacubitril/valsartan group compared with the enalapril group (treatment difference = 8.98 m; 97.5% CI $-1.31, 19.27$, $p=0.0503$) (**Figure 2A**). The 6MWT assessment data were missing in 2.76% ($n=8$) and 6.46% ($n=19$) of patients in sacubitril/valsartan and enalapril groups, respectively, after 12 weeks. The sensitivity analysis performed in the per-protocol population

set, without patients who had an AE/SAE (non-HF related) during/around the 6MWT performance, confirmed this trend, with a treatment difference of 8.61 m (95% CI -0.61, 17.82, $p=0.0670$).

There were no statistically significant differences in least squares means (LSM) for daily non-sedentary daytime activity, as calculated by the MotionWatch8[®] accelerometer device, after 12 weeks of treatment between the patients receiving sacubitril/valsartan and enalapril (treatment difference of -6.14 minutes [97.5% CI -25.70, 13.41, $p=0.4769$] for the FAS population with multiple imputation) (**Figure 2B**). In total, 88 patients (43 in sacubitril/valsartan and 45 in enalapril group) had missing values for the baseline visit (14.6% of the patients).

Efficacy – key secondary endpoints

The 6MWT improved by ≥ 30 m in 51% of patients in the sacubitril/valsartan group versus 44% of patients treated with enalapril (OR [95% CI]: 1.251 [0.895, 1.748]) after 12 weeks of treatment (**Supplementary material, Figure S3**). A similar trend was observed for proportion of patients with improved performance (≥ 30 m) in the FAS subset with baseline 6MWT distance ≤ 300 m (54.7% in sacubitril/valsartan vs 46.0% in enalapril; OR [5% CI] 1.280 [0.644, 2.544]) and 6MWT distance between 100–450 m (53.0% vs 45.5%, respectively; OR [95% CI] 1.260 [0.865, 1.834]) (**Supplementary material, Table S6**). However, these results did not reach statistical significance. Change from baseline in 6MWT after 4 or 8 weeks in patients receiving sacubitril/valsartan versus enalapril showed no statistically significant difference (**Supplementary material, Table S6**).

The proportion of patients with increased levels ($\geq 10\%$ increase) of non-sedentary daytime PA was higher in patients receiving sacubitril/valsartan versus enalapril after 1, 2 and 4 weeks of treatment: 27.5% versus 17.9%, 27.5% versus 17.6%, and 19.9% versus 13.6%,

respectively. However, at the EOS there were no differences in the proportion of patients who showed increased levels ($\geq 10\%$ increase) of non-sedentary daytime PA between the treatment arms (**Supplementary material, Figure S4**).

Accordingly, mean change from baseline in daily light non-sedentary daytime PA was higher in patients receiving sacubitril/valsartan versus enalapril during first weeks of treatment (**Supplementary material, Figure S5**). There were no differences in M6min in patients receiving sacubitril/valsartan versus enalapril.

At 4 weeks, the proportion of patients with improved symptoms as measured by PGA was higher in patients receiving sacubitril/valsartan versus enalapril treatment (58.3% vs 43.4%). No significant differences were observed at later time points (**Supplementary material, Figure S6**).

At 12 weeks, improvements from baseline on patients' mental and physical functioning, as assessed by SF-12, and improvements from baseline on patients' health status as assessed by the EQ-5D and EQ-VAS, were similar between treatment groups (**Supplementary material, Table S7**).

Safety

At least one treatment-emergent AE (TEAE) was reported in 330 patients (**Table 2**). Suspected drug-related TEAEs were in accordance with the SmPC of sacubitril/valsartan. The incidence of TEAEs leading to discontinuation of study treatment was low and similar between both treatment groups ($n=26$, 4.2%). In total, 47 patients (7.6%) had at least one treatment-emergent serious AE (TSAE). The overall incidence of TSAEs was slightly lower in the sacubitril/valsartan compared to enalapril group (6.2% vs 9.0%). Among the TSAEs, the most

commonly affected primary organ system class was cardiac disorders (3.2% in the sacubitril/valsartan vs 4.8% in the enalapril group), mainly HF and atrial fibrillation.

In total, five patients died during the treatment period and all deaths were considered unrelated to the study drug. There was a higher frequency of all-cause deaths in enalapril group compared to sacubitril/valsartan (n=4, [1.3%] vs n=1, [0.3%]). The most common TEAEs resulting in death were cardiac disorders that occurred in four patients.

DISCUSSION

Increasing PA and exercise capacity in patients with HF is an important therapy goal. Therefore, evaluating the effect of sacubitril/valsartan versus enalapril in terms of improving the PA of patients with chronic HF would be of clinical significance. To our knowledge, OUTSTEP-HF is the largest HF randomised clinical trial to date employing a state-of-the-art accelerometry-based approach along with the 6MWT to evaluate the effects of sacubitril/valsartan compared to enalapril on daily PA in patients with HFrEF.

After 12 weeks, both sacubitril/valsartan and enalapril improved 6MWT with a modest, but non-significant, trend towards longer distance walked in six minutes in patients receiving sacubitril/valsartan versus enalapril (LSM treatment difference: 8.98 m, [97.5% CI: -1.31, 19.27]; p=0.0503). A change of approximately 30 to 35 m for the 6MWT is considered clinically meaningful in patients with HF.(24, 25) In OUTSTEP-HF, treatment with sacubitril/valsartan improved the mean 6MWT by 35 m (97.5% CI: 27.85, 42.32) versus 26 m with enalapril (97.5% CI: 18.78, 33.43). In addition, numerically higher proportion of patients had a ≥ 30 m improvement after sacubitril/valsartan treatment versus those treated with enalapril (51.4% vs 43.9%), after 12 weeks of treatment (OR [95% CI]: 1.251 [0.895, 1.748]). These findings were in

agreement with a small case-series report (n=5) and a pilot study (n=58) in patients with HFrEF that showed short-term (1 month) improvement of 6MWT with sacubitril/valsartan.(14, 15)

Moreover, findings from studies comparing the effect of renin–angiotensin–aldosterone system (RAAS) inhibitors on exercise capacity in patients with HFrEF did not show difference in 6MWT between the treatment arms. In a randomised clinical trial (N=116) comparing the ACEI (enalapril) with ARB (losartan) 12-week therapy, there was no difference in 6MWT in patients with HFrEF (NYHA II-IV, EF <45%).(26) A recent trial, LIFE, assessed the physical functioning in addition to mobility-related outcomes in older adults receiving ACEI or ARB, with no difference in physical performance battery between the treatment arms.(27) While, studies comparing different RAAS inhibitors did not show a difference in exercise capacity, studies comparing RAAS with placebo are inconclusive.(28-30) In a study evaluating the changes in 6MWT in people aged ≥ 65 years with functional impairment, ACEIs did not improve exercise training versus placebo (-8.6 m [95% CI: $-30.1, 12.9$], $p=0.43$). (28) In contrast, another study in 407 elderly (mean age 69 years) individuals, reported that ACEI (n=40) and ARB (n=32) increased 6MWT versus placebo (n=235).(29) A recent meta-analysis of clinical trials in elderly subjects (499) without HF showed that ACEI does not significantly improve walk distance.(30)

Studies in patients with HFrEF have demonstrated the benefits of sacubitril/valsartan in reducing mortality and morbidity associated with HF(10, 31) and greater reduction in NT-proBNP concentration than with enalapril as early as week 1.(32) The lack of statistically significant improvement in 6MWT (and physical activity) with sacubitril/valsartan versus enalapril observed in OUTSTEP-HF seems to be discordant with improved clinical outcomes in these studies. However, following sacubitril/valsartan initiation, the mean 6MWT

improved by 35 m, a change considered clinically meaningful in patients with HF.(24, 25) Additionally, a decrease in adverse events regarding cardiac failure and CV death supports a benefit for patients treated with sacubitril/valsartan. In addition, evidence for benefits on improved 6MWT with other therapies approved for HFrEF is limited and inconclusive.(26, 27, 33, 34) In general, 6MWT does not deteriorate upon pharmacological intervention; however, improvement in 6MWT in response to pharmacotherapies is heterogeneous and is associated with some degree of discordance with changes in other measures/endpoints (such as LVEF improvement).(33) This heterogeneity and discordance could be due to multiple factors. While 6MWT is a useful surrogate to assess improved exercise capacity in response to a pharmacological intervention, it may not be as sensitive to detect differences between interventions. Severity of HF, ‘ceiling effect’ on 6MWT, the environment and the involvement of the person conducting test, motivation of the participants, and prior learning among others may also influence the results of 6MWT assessment.(33)

In OUTSTEP-HF study, no statistically significant differences in daily non-sedentary daytime activity after 12 weeks of treatment in patients receiving sacubitril/valsartan versus enalapril were observed. The PA even decreased during the study, building on the findings from previous trial using accelerometry.(35) A plausible explanation for this could be largely sedentary lifestyle, the lack of motivation and/or the burden of comorbidities in patients with HF. In addition, more than one-third of patients with HF have anergia and nearly half have a largely sedentary lifestyle due in part to low self-efficacy (belief in one’s own competencies).(36, 37) However, the mean change from baseline in light non-sedentary daytime PA was higher in patients receiving sacubitril/valsartan versus enalapril at early stages of treatment. It is likely that this initial improvement in non-sedentary physical activity may have been partly due to rapid and

early reduction of NT-proBNP and troponin levels (myocardial wall stress and injury reduction) and HF symptoms with sacubitril/valsartan treatment.(38, 39) In addition, expectation of improved physical activity due to participation in an interventional trial that aimed to assess changes in routine, voluntary physical activity, despite the study being blinded to treatment, may also have resulted in early improvement seen in non-sedentary daytime PA. However, these improvements were transient and were not sustained until EOS, possibly owing to anergia, low self-efficacy in patients with HFrEF and/or lack of behavioural modification to engage in a more active lifestyle.(36, 37)

Limitations

Findings from previous studies suggest that accelerometry may not be a sensitive measure of changes in PA based on treatment optimization.(40) The study was designed to determine improvements in voluntary PA attributable to amelioration of HF symptoms. However, improvement in PA is dependent on behavioural modification to engage in a more active lifestyle (36) and it is likely that some patients accustomed to a largely sedentary lifestyle may not increase their PA despite improvements in their symptoms. In contrast to improvements in 6MWT from baseline observed in both sacubitril/valsartan and enalapril arms, non-sedentary daytime PA showed a decrease from baseline in both the treatment arms supporting the assumption that concomitant behavioural changes are also needed for improving PA. In 6MWT, the Borg scale is used for assessment of dyspnoea and fatigue. However, Borg scale was not used in this study. Interventions to increase motivation or that actively help patients to become more active (e.g. rehabilitation programmes) are needed to change behaviour. In addition, levels of PA could also be influenced by confounding factors such as LVEF, age and comorbidities such as diabetes mellitus, peripheral artery diseases, chronic obstructive airway disease or degenerative

diseases. OUTSTEP-HF trial was designed to evaluate the short-term effects (12 weeks) of sacubitril/valsartan on physical activity. Further studies are needed to determine whether long-term treatment with sacubitril/valsartan affects sub-maximal exercise capacity and physical activity in patients with HFrEF. In addition, the effect of sacubitril/valsartan on surrogate markers of efficacy (NT-proBNP levels) or on functional capacity (NYHA class) and HF-specific QoL instruments (KCCQ) were not evaluated. Also, a higher proportion of patients treated with sacubitril/valsartan reported improvement in symptoms as per PGA.

Conclusion

After 12 weeks of treatment, there was no significant benefit of sacubitril/valsartan in either 6MWT or in daytime physical activity measured by actigraphy compared with enalapril. However, patients treated with sacubitril/valsartan showed an increase in non-sedentary daily activity as measured by an accelerometer and in PGA early after randomisation

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Conflicts of interest

PF is an employee of Novartis Pharma AG; RH was working with Novartis Pharma AG during the conduct of this study. MP has received speaker honorarium, consultancy from Astra Zeneca, Novartis, and Servier. JCC has received unrestricted research grants from Novartis and consultancy and honoraria from Novartis. RD has served as statistical consultant for Novartis Pharma AG during the conduct of this study. TJ has received reimbursement for consultation from Novartis. FE has received personal fees from Novartis, CVRx, Pfizer, Medtronic, MSD, Bayer, and Resmed, non-financial support from Novartis, personal fees and grant from Boehringer Ingelheim and Servier.

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Legends

Figure 1: Flow chart of the study population

Screening failures were related to ineligibility to meet inclusion criteria. The FAS population subset without AE/SAE comprised all patients of the FAS who did not have an AE/SAE (non-HF related) during/around the 6MWT performance. The following 20 AEs/SAEs were blindly excluded: knee injury (5 patients), intermittent claudication (2 patients), skin necrosis, spinal pain, gout flare up, Achilles tendinitis, COPD exacerbation, ventricular tachycardia, psychosis, toe injury, worsening of knee arthrosis, leg injury, diarrhoea, sinus bradycardia, and bronchitis.

*FAS population subset without AE/SAE (non-HF related) during/around the 6MWT performance.

6MWT, 6-minute walking test; AE, adverse event; COPD, chronic obstructive respiratory disease; FAS, full analysis set; HF, heart failure

Figure 2: Summary of results of the primary endpoints: (A) 6-minute walking test (B) daily non-sedentary daytime activity

Differences of least square means

Estimate (SE) [97.5% CI]*: 8.98 (4.58) [−1.31, 19.27]	Estimate (SE) [97.5% CI]*: −6.14 (8.61) [−25.70, 13.41]
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** Adjustment for multiplicity; error bars represent 97.5% CI*

(A) FAS population subset without AE/SAE (non-HF-related) during/around the 6MWT; (B) FAS population with multiple imputation

For 6MWT, data were missing in 2.76% (n=8) and 6.46% (n=19) patients in sacubitril/valsartan and enalapril groups, respectively. For daily non-sedentary daytime activity, 85 patients (43 in sacubitril/valsartan and 45 in enalapril group) of 581 had missing values for the baseline visit (14.6% of the patients).

6MWT, 6-minute walking test; AE, adverse event; CI, confidence interval; FAS, full analysis set; HF, heart failure; MI, multiple imputations; SAE, serious adverse event; SE, standard error

Table 1

Baseline and disease characteristics of patients

Parameters	Sacubitril/valsartan (N=309)*	Enalapril (N=310)*
Age (years), mean (SD)	67.16 (11.04)	66.62 (10.45)
Male, n (%)	238 (77.02)	249 (80.32)
BMI (kg/m ²), mean (SD)	29.30 (4.72)	29.33 (4.67)
Smoking history, n (%)		
Current	49 (15.86)	46 (14.84)
Former	137 (44.34)	143 (46.13)
Cardiovascular medical history, n (%)	296 (95.79)	290 (93.55)
Hypertension	213 (68.93)	203 (65.48)
Dyslipidaemia/hyperlipidaemia	197 (63.75)	184 (59.35)
Myocardial infarction	137 (44.34)	145 (46.77)
Atrial fibrillation	147 (47.57)	122 (39.35)
Stable coronary artery disease	138 (44.66)	129 (41.61)
Uncomplicated diabetes	73 (23.62)	93 (30.00)
Complicated diabetes	23 (7.44)	24 (7.74)
Prior ischaemic stroke	22 (7.12)	25 (8.06)
Peripheral arterial disease	22 (7.12)	20 (6.45)
Supraventricular tachycardia	16 (5.18)	9 (2.90)
Prior transient ischaemic attack	9 (2.91)	14 (4.52)
Deep vein thrombosis	10 (3.24)	10 (3.23)
Pulmonary embolism	10 (3.24)	7 (2.26)
Prior haemorrhagic stroke	1 (0.32)	2 (0.65)

Parameters	Sacubitril/valsartan (N=309)*	Enalapril (N=310)*
NYHA class at screening visit, n (%)		
II	161 (52.10)	162 (52.26)
III	146 (47.25)	146 (47.10)
IV	2 (0.65)	2 (0.65)
SBP at screening visit (mmHg), mean (SD)	126.32 (16.45)	126.07 (15.84)
DBP at screening visit (mmHg), mean (SD)	76.09 (10.13)	76.02 (10.42)
Pulse rate at screening visit (beats/min), mean (SD)	70.81 (12.91)	70.22 (11.59)
Primary aetiology of heart failure, n (%)		
Ischaemic	177 (57.28)	174 (56.13)
Non-ischaemic	132 (42.72)	136 (43.87)
Daily non-sedentary daytime activity (minutes), mean (SD)	511.00 (127.02)	504.43 (129.88)
M6min (peak six minutes of physical activity) (activity counts), mean (SD)	189.16 (67.56)	182.34 (60.42)
Prior medication for heart failure, n (%)		
ACEi/ARB inhibitors	302 (97.7%)	301 (97.1%)
Beta-blockers	280 (90.6%)	287 (92.6%)
Diuretics	240 (77.7%)	234 (75.5%)
MRA	199 (64.4%)	215 (69.4%)

*Among the 621 randomised patients, two (one in each treatment group) were excluded from the study since they did not receive at least one dose of study drug. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation

Table 2

Safety results: Incidence of TEAEs by preferred term – n (% of patients) (>1% incidence in any group)

Dose level	Sacubitril/valsartan (N=309)	Enalapril (N=310)
Number of patients with at least one TEAE	177 (57.28%)	153 (49.35%)
Number of TEAEs	402	320
Hypotension	43 (13.92%)	20 (6.45%)
Hyperkalaemia	22 (7.12%)	11 (3.55%)
Dizziness	17 (5.50%)	10 (3.23%)
Cardiac failure	11 (3.56%)	17 (5.48%)
Cough	10 (3.24%)	10 (3.23%)
Dyspnoea	10 (3.24%)	10 (3.23%)
Atrial fibrillation	8 (2.59%)	4 (1.29%)
Back pain	6 (1.94%)	9 (2.90%)
Fatigue	6 (1.94%)	6 (1.94%)
Blood creatinine increased	6 (1.94%)	5 (1.61%)
Bronchitis	6 (1.94%)	2 (0.65%)
Renal failure	6 (1.94%)	0 (0.0%)
Oedema peripheral	5 (1.62%)	3 (0.97%)
Chest pain	5 (1.62%)	0 (0.0%)
Blood potassium increased	4 (1.29%)	4 (1.29%)

AEs by preferred terms are presented in descending order of frequency in sacubitril/valsartan group. AEs, adverse events; TEAE, treatment-emergent adverse events

Sacubitril/Valsartan	289	284	280	283
Enalapril	292	283	278	277