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# Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure
## A Secondary Analysis of the PARADIGM-HF Trial

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**IMPORTANCE** Health-related quality of life (HRQL) of patients with heart failure is markedly reduced compared with that in patients with other chronic diseases, demonstrating substantial limitations in physical and social activities. In the Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, sacubitril/valsartan improved overall HRQL compared with enalapril, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

**OBJECTIVE** To examine the effects of sacubitril/valsartan on physical and social activities.

**DESIGN, SETTING, AND PARTICIPANTS** The PARADIGM-HF trial was a randomized, double-blind, active treatment–controlled clinical trial performed from December 8, 2009, to March 31, 2014, in 8399 patients with New York Heart Association class II to IV disease and a left ventricular ejection fraction of 40% or less at 1043 centers in 38 countries. Data analysis was performed from August 1, 2017, to December 25, 2017.

**INTERVENTIONS** Sacubitril/valsartan, 200 mg twice daily, or enalapril, 10 mg twice daily.

**MAIN OUTCOMES AND MEASURES** Patients completed HRQL assessments using the KCCQ at randomization, 4-month, 8-month, and annual visits. The effect of sacubitril/valsartan on components of the physical and social limitation sections of the KCCQ at 8 months and longitudinally and related biomarkers and clinical outcomes were studied.

**RESULTS** At baseline, 7618 of 8399 patients (90.7%) (mean [SD] age, 64 [11] years; 5987 [78.6%] male and 1631 [21.4%] female) completed the initial KCCQ assessment. Patients reported the greatest limitations at baseline in jogging and sexual relationships. Patients receiving sacubitril/valsartan had significantly better adjusted change scores in most physical and social activities at 8 months and during 36 months compared with those receiving enalapril. The largest improvement over enalapril was in household chores (adjusted change score difference, 2.35; 95% CI, 1.19-3.50; $P < .001$) and sexual relationships (adjusted change score difference, 2.72; 95% CI, 0.97-4.46; $P = .002$); both persisted through 36 months (overall change score difference, 1.69 [95% CI, 0.78-2.60], $P < .001$; and 2.36 [95% CI, 1.01-3.71], $P = .001$, respectively).

**CONCLUSIONS AND RELEVANCE** In patients with heart failure with reduced ejection fraction, sacubitril/valsartan significantly improved nearly all KCCQ physical and social activities compared with enalapril, with the largest responses in household chores and sexual relationships. In addition to reduced likelihood of cardiovascular death, all-cause mortality, and heart failure hospitalization, sacubitril/valsartan may improve limitations in common activities in these patients.

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Supplemental content

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Health-related quality of life (HRQL) is known to be markedly reduced in patients with heart failure,[1] even compared with HRQL typical of patients with other chronic diseases.[2] The Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which found that sacubitril/valsartan, compared with enalapril, significantly reduced cardiovascular mortality, heart failure-associated hospitalization, and all-cause mortality in patients with heart failure and reduced ejection fraction,[3] also found improvement in overall HRQL in surviving patients, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[4] Despite comparison with an active treatment and that baseline HRQL was measured after an active run-in period with sacubitril/valsartan up to 6 weeks, the magnitude of improvement noted at 8 months after randomization in the PARADIGM-HF trial was comparable to the HRQL improvement observed with cardiac resynchronization therapy.[5]

The KCCQ domains have limited granularity for describing limitations in individual activities that are particularly important to patients with heart failure. Moreover, measures of HRQL are inherently heterogenous, and benefits of specific therapies may affect individual measures differently. In this secondary analysis of the PARADIGM-HF data, we focused on individual physical and social activity items in the KCCQ domains in the PARADIGM-HF trial,[6,7] allowing for a better understanding of the responsiveness of each individual activity to sacubitril/valsartan.

### Key Points

**Question** Compared with enalapril, does sacubitril/valsartan improve specific physical or social activities in patients with heart failure and reduced ejection fraction?

**Findings** In this post hoc secondary analysis of 8399 patients from the Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, limitations in physical and social activities were significantly improved in almost all domains in patients randomized to receive sacubitril/valsartan, compared with enalapril. The largest improvement was seen in limitations of sexual activity.

**Meaning** In addition to improving morbidity and mortality, sacubitril/valsartan may significantly improve limitations in physical and social activities that are common in patients with heart failure, including sexual activities.

## Methods

### Study Population

The PARADIGM-HF trial was a randomized, double-blind, active treatment–controlled, clinical trial performed from performed from December 8, 2009, to March 31, 2014, that enrolled patients 18 years or older who had heart failure and left ventricular ejection fraction (LVEF) of 40% or less, New York Heart Association (NYHA) class II to IV disease, and a serum brain-type natriuretic peptide (BNP) level greater than 150 pg/mL, an N-terminal pro-brain-type natriuretic peptide (NT-proBNP) level greater than 600 pg/mL (to convert BNP and NT-proBNP levels to nanograms per liter, multiply by 1), or a heart failure–associated hospitalization within 12 months before enrollment. The details of this study have been described previously.[3,8] All enrolled patients were placed in a single-blind, active run-in phase during which they were given enalapril, 10 mg twice daily, for 2 weeks, followed by sacubitril/valsartan, uptitrated to 200 mg twice daily during a period of 4 to 6 weeks. Patients who did not develop significant intolerance during the run-in phase were then randomized to enalapril, 10 mg twice daily, or sacubitril/valsartan, 200 mg twice daily, in a 1:1 ratio, double-blinded fashion. All participants provided written informed consent. Data analysis in this secondary analysis was performed from August 1, 2017, to December 25, 2017. The study protocol was approved by the institutional review boards at each site. Our analysis was completed on existing deidentified data of PARADIGM-HF, which did not require separate approval.

### Outcome Measures of Physical and Social Limitation Attributable to Heart Failure

The KCCQ is a widely used, 23-item, self-administered, disease-specific HRQL instrument that has been validated for heart failure.[8,9] It was initially administered during the randomization visit, which served as baseline. It was administered again at 4, 8, 12, 24, and 36 months or until the final visit. The principal HRQL efficacy time point was prespecified at 8 months.

For each of the physical activities contained in the physical limitation domain, patients were asked to respond to the following: "Please indicate how limited you have been by heart failure (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks: dressing yourself; showering or having a bath; walking 100 yd on level ground; doing gardening or housework or carrying groceries; climbing a flight of stairs without stopping; and jogging or hurrying (as if to catch a bus)."

For each of the social activities contained in the social limitation domain, patients were asked the following question, "How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks: hobbies, recreational activities, working or doing household chores, visiting family or friends, and intimate or sexual relationships."

Each of a patient's responses was then scaled from 0 to 100, with 0 indicating extremely or severely limited and 100 indicating not at all limited. Responses of limited for other reasons or did not do the activity were considered to be nonresponses.

### Statistical Analysis

The physical and social activity scores are individual components of the KCCQ domains.[9] Mean values were calculated from patient scores on all physical and social activities. Combined physical and social activity mean scores were then calculated

by averaging the means of these individual activities. Missing values were not accounted for in the primary analysis. Baseline characteristics were stratified into quartiles of combined physical and social activity mean scores using descriptive statistics: means (SDs) and medians (interquartile ranges) for continuous variables, along with the 2-tailed, unpaired *t* test and Mann-Whitney test. For categorical variables, numbers and percentages were used with the $\chi^2$ test. In addition, physical and social activity scores at baseline and 8-month follow-up were calculated. The principal efficacy analysis was the change mean score between baseline and the 8-month follow-up visit.

The change score analyses of sacubitril/valsartan compared with enalapril on changes in the KCCQ physical and social activity scores were performed using multivariable linear regression adjusted for each activity's baseline mean score. In this model, the adjusted change score differences and the 8-month follow-up change scores along with their respective CIs were calculated using the Δ method.[10] Patients who died, did not complete the 8-month KCCQ, or answered "does not apply" were excluded from the primary analysis. The effects of sacubitril/valsartan compared with enalapril on all physical and social activities were measured through the 36-month visit using longitudinal analysis adjusting for respective baseline values. Multivariable linear regression models were performed to determine clinical factors that were independently associated with improvement in the KCCQ combined physical and social activity mean scores. With the multivariable model, we also performed nonlinear combinations of estimators to estimate the ratio of the effect of randomization to sacubitril/valsartan compared with the effect of age.

Spearman correlation was used to estimate the association between physical and social activity change scores and NT-proBNP levels. Landmark analysis after 8 months was performed to associate changes in the KCCQ physical and social activity mean scores with clinical outcomes. We also performed interaction testing between sex and the effect of sacubitril/valsartan on each physical and social activity. A description of characteristics of patients who had missing KCCQ overall summary scores at baseline and 8-month follow-up has been detailed previously.[4] In this analysis, we further analyzed the difference in characteristics between patients who answered "limited for other reasons" to the physical and social activity limitations questions and those who did not. Finally, baseline KCCQ physical and social activity mean scores of patients who answered "limited for other reasons" to the sexual relationships question were compared with those who did not by using descriptive statistics as detailed above.

To perform a sensitivity analysis to address missing data, we assigned a score of 0 to each physical and social activity question at 8-month follow-up if the patient answered the question at baseline but died before the 8-month visit, as was prespecified in the primary analysis plan.[3] We repeated this analysis comparing adjusted change scores in all 10 physical and social activities between the 2 treatment groups. In addition, we performed a responder analysis in which logistic regression was used to assess whether sacubitril/valsartan was significantly associated with a 5-point or greater adjusted change score improvement in combined physical and social activity mean score. Finally, we performed ordinal logistic regression in which we analyzed the odds ratio (OR) of patients moving up the scale on each individual activity (eg, 25 to 50 or 50 to 100).

## Results

At randomization, which served as baseline for KCCQ data collection, 7618 of 8399 patients (90.7%) (mean [SD] age, 64 [11] years; 5987 [78.6%] male and 1631 [21.4%] female) in 38 countries completed the initial KCCQ assessment, as previously described.[4] Patients with the greatest limitations attributable to heart failure in physical and social activities (**Table 1**) were older, more likely to be women, and more likely to have multiple comorbidities, a worse NYHA class, and higher NT-proBNP levels. Of the 781 of 8399 patients (9.3%) who did not complete the baseline KCCQ, 657 (84.1%) did not have a KCCQ form available in the appropriate language; these patients were also younger, more likely to be Asian, and had fewer medical comorbidities. In contrast, patients without KCCQ data at 8 months were older; more likely to have prior heart failure-associated hospitalization, worse LVEF, and lower baseline combined physical and social activity mean scores; and were significantly less likely to be randomized to receive sacubitril/valsartan (343 of 759 patients [45.2%] vs 3453 of 6859 patients [50.3%], $P = .007$).[4] There were no significant differences in baseline characteristics and physical and social activity scores between the treatment groups among patients who had baseline data but were missing 8-month follow-up data (eTable 1 in the Supplement).

At the baseline and 8-month follow-up, the number of patients who answered "limited for other reasons" was much higher for the sexual limitation question (2290 of 7541 [30.4%]) compared with other physical and social activities (81 of 7609 [1.1%] to 638 of 7615 [8.4%]) (eTable 2 in the Supplement). Patients who answered "limited for other reasons" to the sexual limitations question at baseline were older (69 vs 62 years, $P < .001$), were more likely to be women (881 of 2367 [37.2%] vs 759 of 5251 [14.5%], $P < .001$), had a worse NYHA class (mean of 2.3 vs 2.2, $P < .001$), and had higher KCCQ social activity mean scores (72.6 vs 71.3, $P = .04$).

At baseline, jogging and sexual relationships had the lowest mean scores, which suggest the greatest limitations, whereas dressing yourself and showering had the highest mean scores (eTable 3 in the Supplement), which suggest the fewest limitations. The baseline-adjusted change score differences between treatment groups significantly favored the sacubitril/valsartan group in all activities with the exception of dressing yourself, showering, and climbing a flight of stairs (**Table 2** and **Figure 1**). The largest adjusted change score differences were seen in household chores and sexual relationships. Similarly, in longitudinal analyses during the entire study (36 months), sacubitril/valsartan was associated with significantly greater change score differences in all activities except dressing yourself, with the greatest overall treatment group difference in sexual relationships (Table 2).

Table 1. Baseline Characteristics Stratified by Quartiles of Mean Combined Scores of All Physical and Social Activities Among Patients With Baseline KCCQ Data[a]

| Characteristic | Quartile 1 (n = 1983) | Quartile 2 (n = 1988) | Quartile 3 (n = 1811) | Quartile 4 (n = 1836) | *P* Value for Trend |
|---|---|---|---|---|---|
| Scores of combined physical and social activities, mean (SD) [range] | 41.5 (12.6) [14.3-57.5] | 68.6 (5.8) [57.5-77.5] | 84.6 (3.7) [77.5-90] | 96.5 (3.0) [90-100] | NA |
| Baseline age, mean (SD), y | 65.4 (11.2) | 65.0 (11.0) | 63.7 (10.9) | 62.5 (11.3) | <.001 |
| Female sex | 594 (30.0) | 408 (20.5) | 350 (19.3) | 279 (15.2) | <.001 |
| Race/ethnicity | | | | | |
| White | 1594 (80.4) | 1550 (78.0) | 1227 (67.8) | 1097 (59.7) | <.001 |
| Black | 106 (5.3) | 91 (4.6) | 92 (5.1) | 112 (6.1) | |
| Asian | 139 (7.0) | 182 (9.2) | 286 (15.8) | 384 (20.9) | |
| Other | 144 (7.3) | 165 (8.3) | 206 (11.4) | 243 (13.2) | |
| Region | | | | | |
| North America | 175 (8.8) | 163 (8.2) | 122 (6.7) | 140 (7.6) | .01 |
| Latin America | 225 (11.3) | 258 (13.0) | 330 (18.2) | 431 (23.5) | |
| Western Europe and other[b] | 527 (26.6) | 507 (25.5) | 500 (27.6) | 479 (26.1) | |
| Central Europe | 926 (46.7) | 883 (44.4) | 579 (32.0) | 412 (22.4) | |
| Asia Pacific | 130 (6.6) | 177 (8.9) | 280 (15.5) | 374 (20.4) | |
| Baseline medical history | | | | | |
| Hypertension | 1543 (77.8) | 1484 (74.6) | 1265 (69.9) | 1193 (65.0) | <.001 |
| Diabetes | 802 (40.4) | 681 (34.3) | 621 (34.3) | 543 (29.6) | <.001 |
| Atrial fibrillation | 918 (46.3) | 805 (40.5) | 641 (35.4) | 547 (29.8) | <.001 |
| Hospitalization for heart failure | 1351 (68.1) | 1292 (65.0) | 1117 (61.7) | 1051 (57.2) | <.001 |
| Myocardial infarction | 932 (47.0) | 945 (47.5) | 784 (43.3) | 709 (38.6) | <.001 |
| Stroke | 218 (11.0) | 200 (10.1) | 132 (7.3) | 113 (6.2) | <.001 |
| BMI, mean (SD) | 29.5 (6.1) | 28.7 (5.6) | 28.1 (5.2) | 27.4 (4.9) | <.001 |
| NYHA functional class III or IV | 958 (48.3) | 561 (28.2) | 304 (16.8) | 151 (8.2) | <.001 |
| KCCQ overall summary score, mean (SD) | 47.6 (13.2) | 69.7 (8.6) | 83.1 (6.7) | 93.5 (5.4) | <.001 |
| Left ventricle ejection fraction, mean (SD), % | 30.0 (6.1) | 29.8 (6.3) | 29.6 (6.3) | 29.1 (6.1) | <.001 |
| BNP, median (IQR), pg/mL | 268 (158-499) | 250 (158-462) | 242 (152-428) | 238 (144-434) | <.001 |
| NT-proBNP, median (IQR), pg/mL | 1813 (945-3676) | 1641 (930-3364) | 1505 (856-2923) | 1409 (827-2862) | <.001 |
| Randomized to sacubitril/valsartan | 962 (48.5) | 958 (48.2) | 900 (49.7) | 976 (53.2) | .003 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, brain-type natriuretic peptide; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not applicable; NT-proBNP, N-terminal pro–brain-type natriuretic peptide; NYHA, New York Heart Association.

SI conversion factor: To convert BNP and NT-proBNP levels to nanograms per liter, multiply by 1.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] This category includes South Africa and Israel.

As a sensitivity analysis, we assigned a score of 0 to each physical and social activity question at the 8-month follow-up if patients with baseline data died before the visit (194 in the enalapril arm and 163 in the sacubitril/valsartan arm) and excluded patients who did not complete the KCCQ at 8-month follow-up because of a cause other than death (210 in the enalapril arm and 173 in the sacubitril/valsartan arm). The improvement in the sacubitril/valsartan arm vs the enalapril arm was comparable to or greater than that observed in the original analysis in all 10 physical and social activities (Figure 1).

In a multivariable model, several baseline clinical factors were independently associated with worsening limitations on physical and social activities at 8-month follow-up, including older age, female sex, higher body mass index, worse NYHA functional class, higher NT-proBNP level, and higher prevalence of comorbidities (**Table 3**). After adjustment for these factors, randomization to sacubitril/valsartan remained independently associated with improved limitations in the combined physical and social activity score. At baseline, increasing age was inversely related to the KCCQ scores in physical and social activity limitations (β coefficient = −0.20; $P < .001$). The improvement in combined physical and social activity score at the 8-month visit between patients randomized to receive sacubitril/valsartan vs enalapril was comparable to a difference of 9 years of aging (95% CI, 4-13 years) (**Figure 2**). This result remained similar after adjustment for baseline physical and social activity score (9 years; 95% CI, 2-17 years).

In a responder analysis, sacubitril/valsartan was significantly associated with a 5-point or greater improvement in change score difference in combined physical and social activity mean score with adjustment for baseline score at 8-month

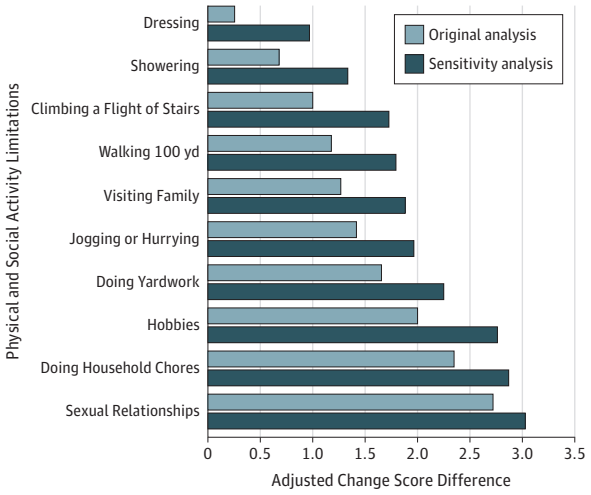
Table 2. Change Score Analysis of KCCQ Physical and Social Activities at 8 Months and Overall, Adjusted for Baseline Mean Score of Each Respective Activity[a]

| KCCQ Physical and Social Activity | 8-mo Change Score, Mean (SE) | | 8-mo Change Score Difference (95% CI) | *P* Value for 8-mo Follow-up | Overall Change Score Difference (95% CI) | *P* Value for Overall Effect |
|---|---|---|---|---|---|---|
| | Enalapril | Sacubitril/ Valsartan | | | | |
| Dressing yourself | −0.67 (0.33) | −0.42 (0.33) | 0.25 (−0.66 to 1.16) | .59 | 0.51 (−0.16 to 1.19) | .14 |
| Showering or having a bath | −0.74 (0.33) | −0.07 (0.33) | 0.68 (−0.24 to 1.59) | .15 | 0.78 (0.07 to 1.48) | .03 |
| Walking 100 yd on level ground | −0.73 (0.38) | 0.45 (0.38) | 1.18 (0.12 to 2.24) | .03 | 1.09 (0.26 to 1.92) | .01 |
| Doing gardening or housework or carrying groceries | −0.15 (0.43) | 1.50 (0.43) | 1.65 (0.46 to 2.84) | .007 | 1.14 (0.20 to 2.08) | .02 |
| Climbing a flight of stairs without stopping | −0.07 (0.44) | 0.94 (0.44) | 1.01 (−0.20 to 2.23) | .10 | 1.39 (0.44 to 2.33) | .004 |
| Jogging or hurrying (as if to catch a bus) | 1.62 (0.49) | 3.04 (0.39) | 1.42 (0.05 to 2.78) | .04 | 1.38 (0.32 to 2.44) | .01 |
| Hobbies, recreational activities | −0.09 (0.44) | 1.91 (0.44) | 2.00 (0.77 to 3.22) | .001 | 1.45 (0.51 to 2.39) | .002 |
| Working or doing household chores | 0.18 (0.42) | 2.53 (0.42) | 2.35 (1.19 to 3.50) | <.001 | 1.69 (0.78 to 2.60) | <.001 |
| Visiting family or friends | −1.38 (0.41) | −0.10 (0.41) | 1.27 (0.15 to 2.40) | .03 | 1.20 (0.36 to 2.05) | .005 |
| Intimate or sexual relationships | −2.34 (0.63) | 0.37 (0.63) | 2.72 (0.97 to 4.46) | .002 | 2.36 (1.01 to 3.71) | .001 |

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.

[a] Each activity's change score was calculated using multivariable linear regression. The overall effect was calculated using longitudinal regression analysis using data collected from 4-, 8-, 12-, 24-, and 36-month follow-up. Positive numbers favor the sacubitril/valsartan group. All analyses were adjusted for baseline mean score of each respective activity.

Figure 1. Change Score Differences Between Enalapril and Sacubitril/Valsartan at 8-Month Follow-up, Adjusted for Respective Baseline Mean Score




Positive values indicate greater improvement with sacubitril/valsartan than with enalapril. Results are given for the original analysis and the sensitivity analysis in which a score of 0 was assigned for each physical and social activity question at 8-month follow-up if the patient answered the question at baseline but died before the 8-month visit. *P* values for change score at 8-month follow-up are given in Table 2.

follow-up (OR, 1.12; 95% CI, 1.00-1.24; *P* = .04). Sacubitril/valsartan was also significantly associated with improved activities of walking 100 yd on level ground (OR, 1.13; 95% CI, 1.03-1.24; *P* = .01), gardening (OR, 1.17; 95% CI, 1.07-1.28; *P* = .001), jogging (OR, 1.12; 95% CI, 1.02-1.24; *P* = .02), hobbies (OR, 1.16; 95% CI, 1.05-1.28; *P* = .002), household chores (OR, 1.20; 95% CI, 1.09-1.32; *P* < .001), and sexual relationships (OR, 1.18; 95% CI, 1.05-1.33; *P* = .005) (eTable 4 in the Supplement).

Among a subset of patients who had NT-proBNP data available at 8-month follow-up (n = 1722), changes in NT-proBNP levels correlated weakly with improvements in physical and social activity limitations (Spearman ρ = −0.096; *P* < .001). In a landmark analysis, improvement in combined physical and social activity during 8 months was associated with reduced risk of the primary composite end point (cardiovascular death or first heart failure hospitalization; hazard ratio, 0.79; 95% CI, 0.70-0.90). There was no significant interaction between sex and the effect of sacubitril/valsartan on any of the physical and social activities.

## Discussion

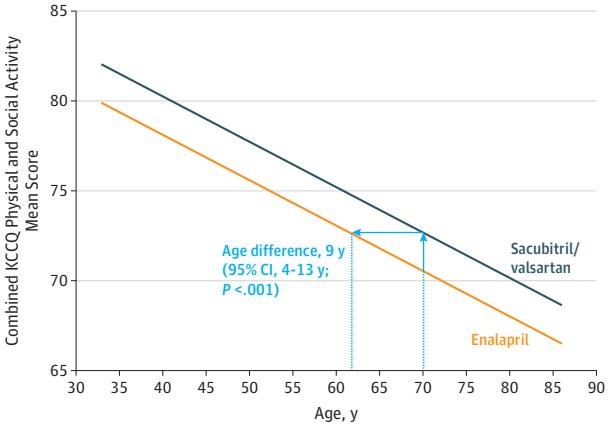
In this large population of patients with heart failure and reduced ejection fraction, patients reported significant baseline physical and social impairments. The greatest limitations were seen in activities of jogging and sexual relationships. Compared with patients receiving enalapril at the prespecified principal efficacy time point of 8 months, patients randomized to receive sacubitril/valsartan had greater change score differences in most of the KCCQ physical and social activities, with the greatest adjusted change score difference seen in limitations of sexual relationships. These findings persisted through 36 months, with all activities except for dressing significantly improving with sacubitril/valsartan. The overall difference in change score for physical and social

Table 3. Multivariable Linear Regression Model Demonstrating Baseline Clinical Factors That Were Independently Associated With 8-Month Change Scores of Combined Scores of All Physical and Social Activities

| Baseline Clinical Factor | β (95% CI) | *z* Score |
|---|---|---|
| Baseline mean scores of combined physical and social activities | −0.36 (−0.38 to −0.34) | 35.5 |
| Baseline body mass index | −0.23 (−0.31 to −0.15) | 5.8 |
| Baseline NYHA functional class | −2.42 (−3.24 to −1.61) | 5.8 |
| White race | −2.68 (−3.64 to −1.72) | 5.5 |
| History of myocardial infarction | −1.90 (−2.71 to −1.08) | 4.6 |
| History of atrial fibrillation | −1.59 (−2.46 to −0.72) | 3.6 |
| Female sex | −1.73 (−2.69 to −0.76) | 3.5 |
| History of diabetes mellitus | −1.39 (−2.22 to −0.55) | 3.3 |
| Baseline log NT-proBNP | −0.70 (−1.12 to −0.27) | 3.2 |
| Baseline age | −0.06 (−0.10 to −0.02) | 3.0 |
| Randomization to sacubitril/valsartan | 1.08 (0.31 to 1.85) | 2.7 |
| Prior heart failure hospitalization | −1.04 (−1.85 to −0.23) | 2.5 |
| History of stroke | −1.73 (−3.11 to −0.35) | 2.5 |

Abbreviations: NT-proBNP, N-terminal pro–brain-type natriuretic peptide; NYHA, New York Heart Association.

Figure 2. Unadjusted Age Equivalency Analysis of Kansas City Cardiomyopathy Questionnaire (KCCQ) Physical and Social Activity Mean Score at 8-Month Follow-up Comparing Sacubitril/Valsartan and Enalapril




limitations in patients treated with sacubitril/valsartan was comparable to a difference of approximately 9 years in aging.

Our results complement the findings by Lewis et al,[4] who found that sacubitril/valsartan, compared with enalapril, improved the overall HRQL of surviving patients. A deeper understanding of the responsiveness of each individual KCCQ activity item allows us to inform patients and clinicians on expectations with treatment. Previous studies have reported that the degree of impairment in physical activities attributable to heart failure is similar to that in patients undergoing hemodialysis,[2] whereas in social activities it is similar to that in patients with depression.[11] However, despite the mortality benefits seen in many of the guideline-directed medical therapies, improving HRQL remains an elusive target in heart failure. β-Blockers do not significantly improve HRQL,[12] and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated mixed results in early trials,[13] although many of these neutral HRQL studies were conducted before the use of rigorous methods and heart failure–specific HRQL instruments, such as the KCCQ and Minnesota Living With Heart Failure Questionnaire. Moreover, therapies may have differential effects on various domains of quality of life that may result in a neutral overall change score. Regardless, the sacubitril/valsartan combination is one of the few heart failure therapies that definitively and significantly improves morbidity and mortality as well as physical and social activity limitations.

Although the benefit observed in patients randomized to sacubitril/valsartan was statistically significant, the magnitude of the changes, less than the 5 points on the KCCQ, which some researchers have argued correspond with meaningful changes in an individual patient, may be considered to be small.[14] Nevertheless, we found that improvement in physical and social limitations was well correlated with hemodynamic improvement, as evidenced by reduction in NT-proBNP levels, and was related to subsequent mortality and heart failure outcomes in a landmark analysis. Moreover, in a model that incorporated age and treatment effect, randomization to receive sacubitril/valsartan was comparable to a difference of approximately 9 years in aging, a finding that may have intrinsic meaning to patients. In a responder analysis, sacubitril/valsartan significantly, although modestly, increased the odds of achieving a 5-point or greater improvement in change score difference in the combined physical and social activity mean score at 8-month follow-up. Moreover, sacubitril/valsartan was significantly associated with patients moving up the point scale across several individual activities: walking 100 yd, gardening, jogging, hobbies, household chores, and sexual relationships. These findings may inform clinicians and patients about the benefits that they might expect with treatment.

Among the 10 physical and social activities described in this study, sexual relationships consistently rated as the activity with the largest magnitude of improvement with sacubitril/valsartan. Despite the American Heart Association recommendations stating that sexual activity is reasonable for patients with compensated and/or mild (NYHA class I or II) heart failure,[15] approximately 50% of patients with heart failure report abstaining from sexual activity.[16] Compared with other social and physical activity variables, 30% of the patients in the study answered "limited for other reasons," consistent with prior low response rates seen in a previous study.[17] Of note, these patients had significantly higher baseline social domain scores. Unfortunately, the PARADIGM-HF trial did not document marital or partner status, and partner availability may have influenced the patient's answers. We do not have evidence that sacubitril/valsartan has any direct effect on sexual function, and this finding may be a surrogate for overall well-being. The PARADIGM-HF trial did not collect erectile dysfunction data, and few patients reported taking erectile dysfunction medication. However, neutral endopeptidase inhibition has been proposed as a potential mechanism to treat female sexual arousal disorder and enhanced genital blood flow responses to pelvic nerve stimulation in a female rabbit model.[18,19]

Of note, the patients in the PARADIGM-HF trial did not complete their baseline KCCQ until randomization. At that

point, both treatment groups had received sacubitril/valsartan for a median of 4 weeks (up to 6 weeks). The therapeutic effect of sacubitril/valsartan has been established to be rapid, with significant treatment effects observed within 4 weeks of randomization.[20] This finding may in part be responsible for KCCQ scores at baseline in the PARADIGM-HF trial being better than those in contemporaneous heart failure trials, such as the Systolic Heart Failure Treatment With the $I_f$ Inhibitor Ivabradine Trial (SHIFT) (ivabradine),[10] Heart Failure–A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) (exercise training),[21] and Surgical Treatment for Ischemic Heart Failure (STICH) (coronary artery bypass graft surgery).[11] The elevated baseline level likely limited the potential improvement, resulting in a potential underestimation of the magnitude of the treatment effect. Furthermore, a chance baseline imbalance, with patients in the sacubitril/valsartan arm having significantly higher mean scores for several of the physical and social activities, may have also contributed to a blunted treatment effect.

### Limitations

Several additional limitations should be noted. As with many HRQL analyses, our results were influenced by missing data. However, given that the patients without KCCQ data at 8 months were sicker, had worse HRQL at baseline, and were more likely randomized to the enalapril group, the impact of missing data, if any, likely biased the comparison toward the null. Moreover, the increased rate of death in the enalapril arm compared with the sacubitril/valsartan arm likely increased the scores in the enalapril arm because of survivor bias. Our HRQL evaluation was limited to study sites at which validated language versions of the KCCQ were available. Finally, the KCCQ was developed as a comprehensive evaluation of HRQL; thus, caution should be used in interpreting the results from individual items.

## Conclusions

In patients with heart failure and reduced ejection fraction, sacubitril/valsartan significantly improved physical and social activity limitations compared with enalapril, with the largest response seen in sexual relationships. In addition to reduced likelihood of cardiovascular death, all-cause mortality, and heart failure–associated hospitalization, sacubitril/valsartan may improve limitations in physical and social activities that are important to patients with heart failure.


### ARTICLE INFORMATION

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**Author Contributions:** Drs Solomon and Chandra had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Chandra, Lewis, Claggett, Packer, Zile, Swedberg, Shi, Lefkowitz, Katova, Solomon.
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## CORRECTION

**Error in Figure Data:** In the Original Investigation titled "Long-term Thromboembolic Risk in Patients with Postoperative Atrial Fibrillation After Coronary Artery Bypass Graft Surgery and Patients with Nonvalvular Atrial Fibrillation,"[1] published online on March 28, 2018, there were errors in the hazard ratios and 95% CIs presented in Figure 3. The correct values for the odds of a thromboembolic event after oral anticoagulant therapy for patients with nonvalvular atrial fibrillation were 0.59 (95% CI, 0.51-0.68), for the odds of death after oral anticoagulant therapy for patients with postoperative atrial fibrillation, 1.09 (95% CI, 0.82-1.43), and for patients with nonvalvular atrial fibrillation, 0.51 (95% CI, 0.47-0.55).

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**Error in End Matter:** The Original Investigation titled "Association of Methylation Signals With Incident Coronary Heart Disease in an Epigenome-Wide Assessment of Circulating Tumor Necrosis Factor α,"[1] published online on April 4, 2018, omitted a list of multiple first and senior authors from the end matter. It should have noted that Drs Agha, Colicino, Do, Lahti, Ligthart, Marioni, Marzi, Mendelson, Tanaka, and Wielscher were first authors; Ms Baccarelli and Drs Bandinelli, Deary, Dehghan, Eriksson, Herder, Jarvelin, and Levy were senior authors; Dr Aslibekyan was overall first author; and Dr Arnett was overall senior author. The article has been corrected online.

1. Aslibekyan S, Agha G, Colicino E, et al. Association of methylation signals with incident coronary heart disease in an epigenome-wide assessment of circulating tumor necrosis factor α [published online April 4, 2018]. *JAMA Cardiol*. 2018. doi:10.1001/jamacardio.2018.0510