Journal of the American Heart Association

ORIGINAL RESEARCH

Effects of Sacubitril/Valsartan on Serum Lipids in Heart Failure With Preserved Ejection Fraction

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BACKGROUND: Dyslipidemia is common in heart failure with preserved ejection fraction. Sacubitril/valsartan improves glycemic control and augments natriuretic peptide signaling, providing mechanisms by which sacubitril/valsartan may affect serum lipids. However, empiric data on these effects are lacking.

METHODS AND RESULTS: We analyzed 4774 participants from PARAGON-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in Heart Failure With Preserved Ejection Fraction) with available screening lipids. During follow-up visits, we analyzed the treatment effect on lipid levels and assessed for interaction by baseline lipid levels. At the 16-week visit, we adjusted these treatment effects for the change in several biomarkers (including hemoglobin A_{1c} and urinary cyclic guanosine monophosphate/creatinine [a biomarker of natriuretic peptide activation]). The average age was 73±8 years, 52% were women, 43% had diabetes mellitus, and 64% were on statin therapy. Compared with valsartan, sacubitril/valsartan reduced triglycerides –5.0% (95% CI, –6.6% to –3.5%), increased high-density lipoprotein cholesterol +2.6% (95% CI, +1.7% to +3.4%), and increased low-density lipoprotein cholesterol +1.7% (95% CI, +0.4% to +3.0%). Sacubitril/valsartan reduced triglycerides most among those with elevated baseline levels (triglycerides≥200 mg/dL) (*P*-interaction<0.001), and at 16 weeks by –13.0% (95% CI, –18.1% to –7.6%), or –29.9 (95% CI, –44.3 to –15.5) mg/dL, in this group. Adjusting for the change in urinary cyclic guanosine monophosphate/creatinine significantly attenuated treatment effects on triglycerides and high-density lipoprotein cholesterol, but not low-density lipoprotein cholesterol, while adjusting for other biomarkers did not significantly alter the treatment effects.

CONCLUSIONS: Sacubitril/valsartan significantly reduces triglycerides compared with valsartan, an effect that was nearly threefold stronger in those with elevated baseline triglycerides. Modest increases in high-density lipoprotein cholesterol and low-density lipoprotein cholesterol cholesterol were also observed with therapy. The underlying mechanism(s) of changes in high-density lipoprotein cholesterol and triglycerides are related to sacubitril/valsartan's effects on natriuretic peptide activity.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01920711.

Key Words: heart failure with preserved ejection fraction ■ lipids ■ metabolism ■ sacubitril/valsartan

Dyslipidemia is common in patients with heart failure with preserved ejection fraction (HFpEF).[1,2] The relevance of metabolic risk and cardiac lipotoxicity to heart failure pathophysiology, including diastolic dysfunction, has been recognized.[3–7] Lipid levels are complexly regulated but influenced by several pathways affected by neprilysin, a ubiquitous endopeptidase responsible for the breakdown of many vasoactive peptides. Pathways relevant to both neprilysin inhibition and lipid metabolism include insulin

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022069.

This work was presented at the American College of Cardiology Scientific Sessions, May 15 to 17, 2021.

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with heart failure with preserved ejection fraction, sacubitril/valsartan significantly reduced triglycerides compared with valsartan, an effect that was substantially stronger in those with elevated baseline triglycerides (13% or 30 mg/dL), while modest increases in low-density lipoprotein and high-density lipoprotein were also observed.

What Are the Clinical Implications?

- Neprilysin inhibition may be part of the therapeutic armamentarium in decreasing triglycerides, though further research is needed to define the clinical benefits.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
NP	natriuretic peptide
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PARAGON-HF	Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in Heart Failure With Preserved Ejection Fraction
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial

and sympathetic and natriuretic peptide (NP) activity.[8] NPs, for example, have potent effects on lipolysis and lipid oxidation through cyclic guanosine monophosphate (cGMP)-mediated, hormone-sensitive lipase activation.[9]

Sacubitril/valsartan is an angiotensin receptor/neprilysin inhibitor and therefore may significantly alter lipid levels through these common pathways,[8,10] though empiric data are limited.[10] We explored these effects in the PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blocker] Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial. We further sought to assess candidate pathways relevant to lipid changes induced by sacubitril/valsartan.

METHODS

In accordance with the terms of the study contract, data from this publication will not be made publicly available.

PARAGON-HF Study Population

The design and primary results of the PARAGON-HF study have been described previously.[2,8] Briefly, PARAGON-HF was an international, randomized, double-blind, actively controlled, event-driven trial comparing the efficacy and safety of sacubitril/valsartan with valsartan in patients with HFpEF. PARAGON-HF included 4796 validly randomized patients with signs and symptoms of heart failure (New York Heart Association class II–IV), left ventricular ejection fraction (EF) ≥45%, increased plasma concentrations of NT-proBNP (N-terminal pro-B-type natriuretic peptide), evidence of structural heart disease, and diuretic therapy within 30 days. All patients entered sequential single-blind run-in periods before randomization to ensure that both treatments were tolerated at half the target doses. The study was approved by institutional review boards at individual study sites, and all patients signed written informed consent.

Key exclusion criteria included prior left ventricular EF <40%, estimated glomerular filtration rates <30 mL/min per 1.73 m^2, and systolic blood pressure <110 or ≥180 mm Hg. Detailed exclusion criteria are listed elsewhere.[8]

PARAGON-HF Laboratory Measurements

Prespecified lipid measurements were performed through a central laboratory at screening, during run-in, at randomization, weeks 16, 48, and then annually. Participants were asked to fast for at least 8 hours before each of these scheduled laboratory evaluations, though sample collection still occurred if participants were nonfasting.[2] Cholesterol and triglyceride levels were measured with the Roche Boehringer Mannheim Diagnostics assay by enzymatic in vitro methodology.[10] Cholesterol and triglyceride values were converted from millimoles per liter to milligrams per deciliter by multiplying by 38.67 and 88.57, respectively. We considered the screening values for baseline measurements given lipid changes with therapy during the run-in period. Triglyceride values were categorized using the National Lipid Association classification scheme: normal (<150 mg/dL), borderline (150–199 mg/dL), and elevated (≥200 mg/dL).[11] A total of 22 participants with missing lipids at baseline were excluded.

Candidate Variables Related to Treatment Effect on Serum Lipids

Among a subgroup of participants with available data, we also assessed whether the treatment effect on serum lipids was related to the treatment effect on candidate variables. These potentially explanatory variables included systolic blood pressure, estimated glomerular filtration rate, hemoglobin A_{1c}, weight, New York Heart Association class, NT-proBNP, thiazide diuretics, and nonselective beta-blockers. These blood pressure medications were specifically assessed since sacubitril/valsartan reduces blood pressure[12] and therefore may reduce related medication use; additionally, these medications may worsen serum lipids. Because urinary cGMP-to-creatinine ratio was not available at the screening visit, we analyzed its change from randomization to 16 weeks in a smaller subset of participants with available data (N=1136). cGMP is a secondary messenger associated with NP activity.[13]

Statistical Analysis

Baseline (screening) characteristics grouped by treatment arm are described using mean±SD and median and 25th to 75th percentiles or percentages as appropriate for the levels of measurement and distributions of the variables. Treatment groups were compared using *t* tests for continuous variables (or Wilcoxon rank-sum test for nonparametric comparisons) and chi-squared tests (or Fisher's exact test when appropriate) for categorical variables.

Since lipid levels were right skewed, we assessed the between-group difference in lipid levels adjusting for baseline lipid values using quantile regression to estimate median changes. Similarly, we used linear regression to assess the relative treatment effect using post-baseline, log-transformed lipid values as the outcome variable and baseline, log-transformed lipid levels as the exposure variable. Overall changes were assessed in a mixed-effects longitudinal analysis model. Interaction terms between treatment and baseline lipid level, sex, EF, and visit were tested.[14,15]

To understand potential variables underlying the treatment effect of sacubitril/valsartan on lipids, we also adjusted for baseline and 16-week change in several candidate variables. The relationship between 16-week change in serum lipids with change in urinary cGMP/creatinine was further explored using continuous splines, adjusting for their respective baseline values; 2 knots were used after confirming linearity. Finally, we analyzed initiation of specific antihyperlipidemic treatments during follow-up by treatment arm.

Analyses were performed using STATA version 14 (StataCorp, College Station, TX), and a two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The screening characteristics of the 4774 participants meeting study inclusion criteria stratified by treatment arm are shown in Table 1. The average age was 73±8 years, 52% were women, average body mass index was 30.2±5.0, and 43% had diabetes mellitus. The median (25th–75th percentile) number of drinks of alcohol per day was 1 (0–3). The predominant lipid treatment was statin therapy (64%), while other antihyperlipidemic treatments were infrequently employed. The median (25th–75th percentile) triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were 123 (89–168), 49 (40–60), and 97 (73–124) mg/dL, respectively. Normal, borderline, and elevated triglycerides were observed in 66.7%, 17.6%, and 15.7%, respectively. No significant differences between treatment groups were observed at the screening visit.

Effect of Treatment on Lipid Levels

The treatment effect on serum lipids throughout follow-up is depicted in Figure 1. Overall, sacubitril/valsartan reduced triglycerides –5.0% (95% CI, –6.6% to –3.5%; *P*<0.001), increased HDL-C + 2.6% (95% CI, +1.7% to +3.4%; *P*<0.001), and increased LDL-C + 1.7% (95% CI, +0.4% to +3.0%; *P*=0.012). The mean postrandomization values by treatment arm are also displayed in Table S1. These lipid effects were consistent by sex, EF, and visit (*P*-interaction >0.05 for all comparisons). However, sacubitril/valsartan reduced triglycerides significantly more in participants with higher baseline levels (*P*-interaction <0.001) (Table 2 and Figure 2). At the 16-week visit, sacubitril/valsartan reduced triglycerides –2.5% (95% CI, –4.7% to –0.1%), –3.0% (95% CI, –7.5% to +1.6%), and –13.0% (95% CI, –18.1% to –7.6%) among those with normal, borderline, and elevated baseline triglycerides (Table 3). Corresponding median changes in triglyceride level were –3.0 (95% CI, –5.5 to –0.4), –6.7 (95% CI, –15.2 to +1.7), and –29.9 (95% CI, –44.3 to –15.5) mg/dL. Treatment effects by baseline triglyceride group were consistent over time.

Potential Explanatory Variables Related to Treatment Effect on Lipid Change

To understand potentially relevant pathways underlying the effect of sacubitril/valsartan on serum lipids,

Table 1. Baseline Clinical Characteristics at Screening by Treatment Arm

	Valsartan	Sacubitril/Valsartan
	N=2378	N=2396
Age, y	72.8±8.5	72.7±8.3
Women, n (%)	1235 (51.9)	1236 (51.6)
White race, n (%)	1934 (81.3)	1954 (81.6)
NYHA, n (%)		
II	1700 (71.5)	1737 (72.5)
III	663 (27.9)	644 (26.9)
IV	15 (0.6)	15 (0.6)
Geographic region, n (%)		
Asia-Pacific or other	388 (16.3)	371 (15.5)
Central Europe	857 (36.0)	852 (35.6)
Latin America	179 (7.5)	190 (7.9)
North America	268 (11.3)	286 (11.9)
Western Europe	686 (28.8)	697 (29.1)
KCCQ-OSS	69±19	67±20
Alcohol, drinks/d*	1 (0–2)	1 (0–3)
Physical characteristics		
Systolic blood pressure, mm Hg	136±15	136±16
Diastolic blood pressure, mm Hg	76±11	77±11
Body mass index, kg/m^2	30.2±5.1	30.2±4.9
Heart rate, beats/min	70±14	70±14
Comorbidities, n (%)		
Hypertension	2269 (95.4)	2294 (95.7)
Hospitalization for HF	1166 (49.0)	1127 (47.0)
Atrial fibrillation or flutter	769 (32.5)	770 (32.2)
Diabetes mellitus	1011 (42.5)	1044 (43.6)
Myocardial infarction	517 (21.7)	560 (23.4)
Stroke	242 (10.2)	266 (11.1)
Current smoker	170 (7.2)	179 (7.5)
Medication use, n (%)		
ACEI and/or ARB	2058 (86.5)	2065 (86.2)
Any beta-blocker	1893 (79.6)	1923 (80.3)
Nonselective beta-blocker	332 (14.0)	323 (13.5)
Calcium channel blocker	818 (34.4)	824 (34.4)
Loop diuretic	1855 (78.0)	1828 (76.3)
Thiazide diuretic	298 (12.5)	311 (13.0)
Mineralocorticoid antagonist	667 (28.0)	621 (25.9)
Insulin	313 (13.2)	336 (14.0)
Oral diabetic medication	713 (30.0)	694 (29.0)
Statin	1516 (63.8)	1507 (62.9)
Fibrates	65 (2.7)	82 (3.4)
Ezetimibe	64 (2.7)	58 (2.4)
Omega-3 fatty acids	61 (2.6)	62 (2.6)
Bile acid sequestrants	1 (0.0)	5 (0.2)
Niacin	3 (0.1)	3 (0.1)

(*Continued*)

Table 1. Continued

	Valsartan	Sacubitril/Valsartan
	N=2378	N=2396
Laboratory testing		
Estimated glomerular filtration rate, mL/min per 1.73 m^2	64±20	64±19
Hemoglobin A_{1c}, %	6.5±1.3	6.5±1.3
Hemoglobin, mg/dL	13.3±1.5	13.4±1.5
NT-proBNP, pg/mL*	914 (453, 1623)	902 (475, 1598)
Triglycerides, mg/dL*	124 (89, 168)	118 (89, 168)
HDL-C, mg/dL*	49 (41, 60)	49 (40, 60)
LDL-C, mg/dL*	94 (73, 124)	97 (73, 124)
Ejection fraction	57±8	58±8

No statistically significant difference (P>0.05) between groups for all shown variables.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Presented as median (25th, 75th percentile) since values are skewed.

we simultaneously adjusted lipid treatment effect estimates for the change in several candidate variables (Tables 4 and 5). The values of these candidate variables at the screening visit and the 16-week visit are shown in Table S2. Adjusting for 16-week change in hemoglobin A_{1c}, systolic blood pressure, estimated glomerular filtration rate, weight, nonselective beta-blocker, thiazide diuretic, New York Heart Association class, and NT-proBNP minimally affected the treatment estimate among the 4506 participants with available data (Table 4). We performed similar analyses in a smaller subset of participants with available urinary cGMP data (N=1136), and differences between those with and without these data are shown in Table S3. Adjusting for the change in urinary cGMP/creatinine substantially attenuated and statistically eliminated the treatment effects of sacubitril/valsartan on triglycerides (P=0.13) and HDL-C (P=0.94) but not LDL-C (P<0.001) (Table 5). Spline analyses combining both treatment arms confirmed the linear relationship between change in urinary cGMP/creatinine with change in triglycerides and HDL-C (P<0.001 for both comparisons), but not with LDL-c (P=0.24) (Figure 3). The relationships between change in lipids with change in urinary cGMP/creatinine were not significantly different by treatment arm (Figure S1; P-interaction >0.20 for all comparisons).

Initiation of Lipid Therapies During Follow-Up

Initiation of lipid lowering therapy (bile acid sequestrants, ezetimibe, fibrates, omega-3 fatty acids, niacin, proprotein convertase subtilisin/kexin type 9 inhibitor and statin) at any point during follow-up is shown in Table 6 by treatment arm. There were no significant differences in the implementation of lipid-lowering therapies by treatment arm. Aside from initiation of statins (occurring in 21.5% of all participants), initiation of other therapies including ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and omega-3 fatty acids was low during the trial (<2%).

DISCUSSION

In PARAGON-HF, sacubitril/valsartan compared with valsartan decreased serum triglycerides by 5.0% and increased HDL-C and LDL-C by 2.6% and 1.7%, respectively. However, the sacubitril/valsartan treatment effect was nearly 3-fold higher among those with elevated triglycerides, decreasing triglycerides by 13.0% among those subjects, corresponding to a median reduction of 30 mg/dL at 16 weeks. Among candidate pathways tested, the treatment effects on triglycerides and HDL-C were strongly related to sacubitril/valsartan's effects on NP activity through cGMP, and independent of its effects on glycemic control. Our analyses provide insight into the therapeutic effect of sacubitril/valsartan on serum lipids and the relevance of the natriuretic peptide pathway to effects on triglycerides and HDL-C.

The effect of sacubitril/valsartan compared with valsartan on lipids was most marked in the changes of serum triglycerides. Sacubitril inhibits neprilysin, an enzyme expressed in a wide variety of tissues including adipocytes, and is responsible for the breakdown of a number of vasoactive peptides such as NPs, bradykinin, and glucagon-like peptide 1.[8,16] There are several potential mechanisms by which inhibition of neprilysin might lead to reduction in triglycerides. NPs,

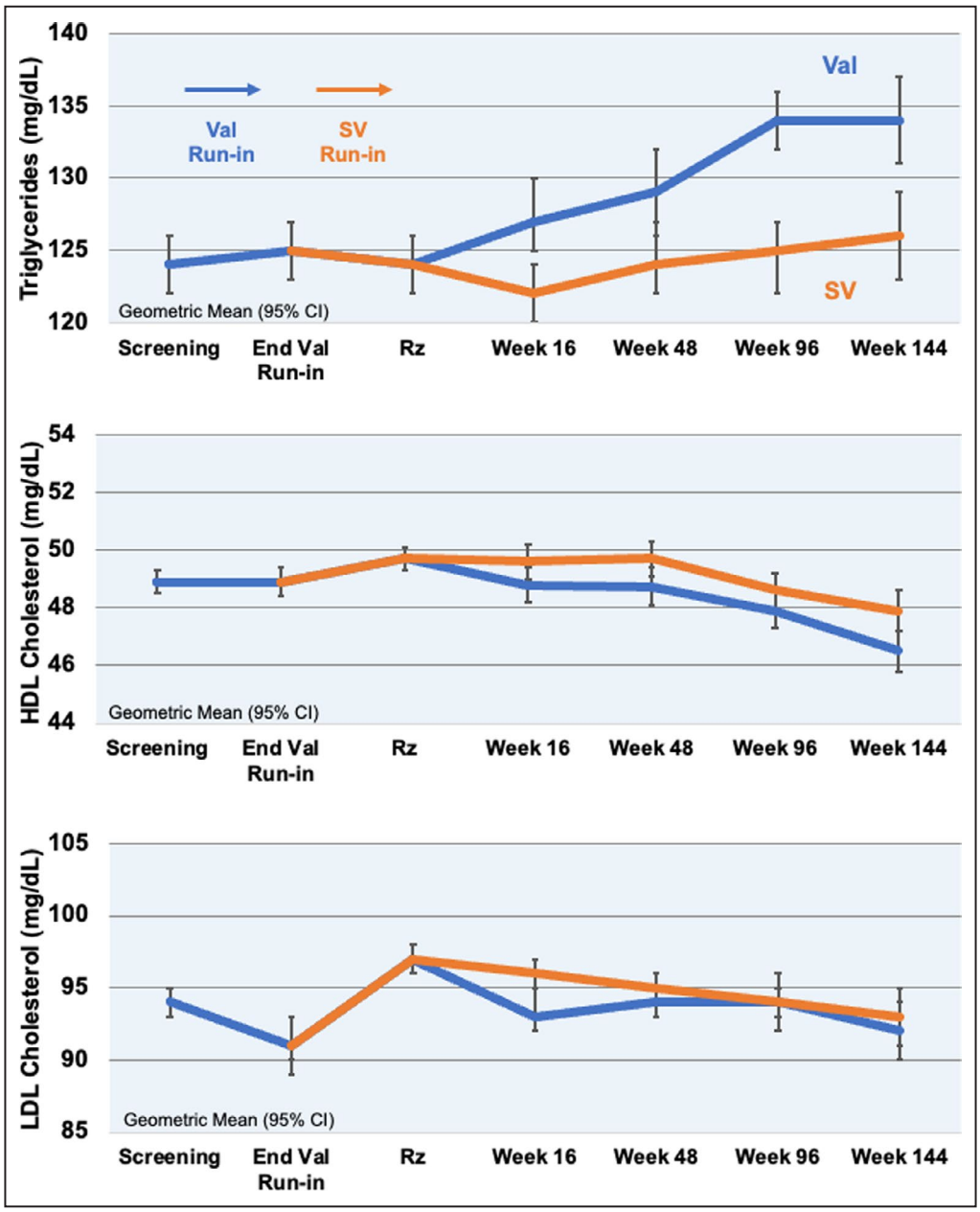

Figure 1. Serum lipid levels over time by treatment arm.
The effect of study drug on unadjusted geometric mean of serum lipid levels is shown over study visits where serum lipid level was prespecified to be collected (truncated after the week 144 visit) with 95% CIs delineated. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; Rz, randomization; SV, sacubitril/valsartan; and Val, valsartan.

which are increased by neprilysin inhibition, potently stimulate lipolysis and lipid oxidation, with concordant effects on mitochondrial biogenesis.[9,17,18] While NPs increase both local abdominal, subcutaneous lipolysis and circulating free fatty acids,[19] sacubitril/valsartan only augments local lipolysis without effect on free fatty acid concentrations, which may relate to the degree to which sacubitril/valsartan affects NP levels compared with direct infusions of NPs.[9,20] While speculative, this may suggest increased fatty acid oxidation not captured by measurements of systemic metabolism such as indirect calorimetry.[20] In addition, NPs also promote "browning" of white fat and increase the uptake of triglycerides from plasma-rich lipoproteins.[18,21,22] Brown fat plays a critical role in energy dissipation and nonshivering thermogenesis.[21] Our analysis showing the relevance of the cGMP pathway to several lipid changes observed is

Table 2. Valsartan-Adjusted Change in Serum Lipids During Follow-Up by Treatment Arm

	Treatment Effect of Sacubitril/Valsartan vs Valsartan		Treatment Effect of Sacubitril/Valsartan vs Valsartan		
	Median (95% CI) Change in Lipid Level From Baseline (mg/dL)	*P* Value	Ratio (95% CI) of Lipid Level from Baseline	*P* Value	Overall Screening Lipid* Treatment Interaction *P* Value
Triglycerides					<0.001
16 wk	−4.4 (−7.5 to −1.3)	0.005	−4.3% (−6.2% to −2.4%)	<0.001	
48 wk	−5.9 (−9.3, −2.5)	0.001	−4.3% (−6.3% to −2.2%)	<0.001	
96 wk	−6.1 (−10.5 to −1.8)	0.006	−6.5% (−8.7% to −4.4%)	<0.001	
144 wk	−4.9 (−10.0 to +0.2)	0.06	−5.7% (−8.2% to −3.0%)	<0.001	
Overall			−5.0% (−6.6% to −3.5%)	<0.001	
HDL-C					0.086
16 wk	+0.9 (+0.3 to +1.4)	0.001	+2.3% (+1.3% to +3.4%)	<0.001	
48 wk	+1.2 (+0.6 to +1.8)	<0.001	+2.6% (+1.6% to +3.7%)	<0.001	
96 wk	+1.1 (+0.5 to +1.7)	<0.001	+2.2% (+0.9% to +3.5%)	0.001	
144 wk	+1.9 (+1.2 to +2.6)	<0.001	+3.6% (+2.2% to +5.1%)	<0.001	
Overall			+2.6% (+1.7% to +3.4%)	<0.001	
LDL-C					0.99
16 wk	+3.1 (+1.7 to +4.5)	<0.001	+2.8% (+1.3% to +4.4%)	<0.001	
48 wk	+2.3 (+0.8 to +3.9)	0.003	+1.7% (+0.0% to +3.4%)	0.042	
96 wk	+0.4 (−1.4 to +2.2)	0.65	+0.8% (−1.0% to +2.7%)	0.39	
144 wk	+1.2 (−1.1 to +3.5)	0.32	+1.2% (−1.9% to +3.6%)	0.33	
Overall			+1.7% (+0.4% to +3.0%)	0.012	

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.
*Longitudinal model.

most consistent with the biological plausibility of NPs mediating these effects.[23] Other pathways contributing to the effects observed may include glucagon-like peptide 1 (though the greatest metabolic effects are typically observed in the postprandial state),[24] while contributions from bradykinin, which attenuates lipolysis, seem unlikely.[25]

Adjustment for urinary cGMP significantly attenuated and statistically eliminated the relationship between sacubitril/valsartan and both triglycerides and HDL-C, but not LDL-C. This may either underscore the common pathobiology of triglycerides and HDL-C as components of the metabolic syndrome, or it may signify that only triglycerides and HDL-C changes observed with treatment are related to NPs. In fact, while NPs positively relate to HDL-C and inversely to triglycerides (consistent with our findings of the treatment effects with sacubitril/valsartan), NPs and cGMP levels inversely relate to LDL-C (potentially mediated by modulation of proprotein convertase subtilisin/kexin type 9 expression).[23,26,27] Moreover, clinical trials of a plant-based polyphenol (anthocynanin) that increases plasma cGMP also increases HDL-C and decreases LDL-C,[28,29] which may relate to modulation of cellular cholesterol efflux.[29] Therefore, the small increase in LDL-C with sacubitril/valsartan is unlikely to be related to NP activity.[22]

The effects of sacubitril/valsartan on lipids have been studied in heart failure with reduced EF. Specifically, in a diabetic substudy of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, a randomized trial of sacubitril/valsartan versus enalapril, sacubitril/valsartan increased HDL-C to a smaller degree than shown here.[10] While the overall treatment effect on triglycerides was not statistically significant in this heart failure with reduced EF study, sacubitril/valsartan significantly reduced triglycerides at year 2, with similar trends noted at other visits. It is noteworthy that the comparators in these trials are different (enalapril and valsartan); the comparator arm in PARAGON-HF (valsartan) allowed us to isolate the direct contribution of neprilysin inhibition. Additionally, the greater metabolic phenotype in HFpEF compared with heart failure with reduced EF may also underlie the differences observed in these trials.[3,30,31]

Among the treatment-associated lipid changes, sacubitril/valsartan most robustly affected triglycerides (particularly those with elevated [≥200 mg/dL] levels), reducing triglycerides by 13.0% and a median of 30 mg/dL at 16-weeks. For comparison, treatment of

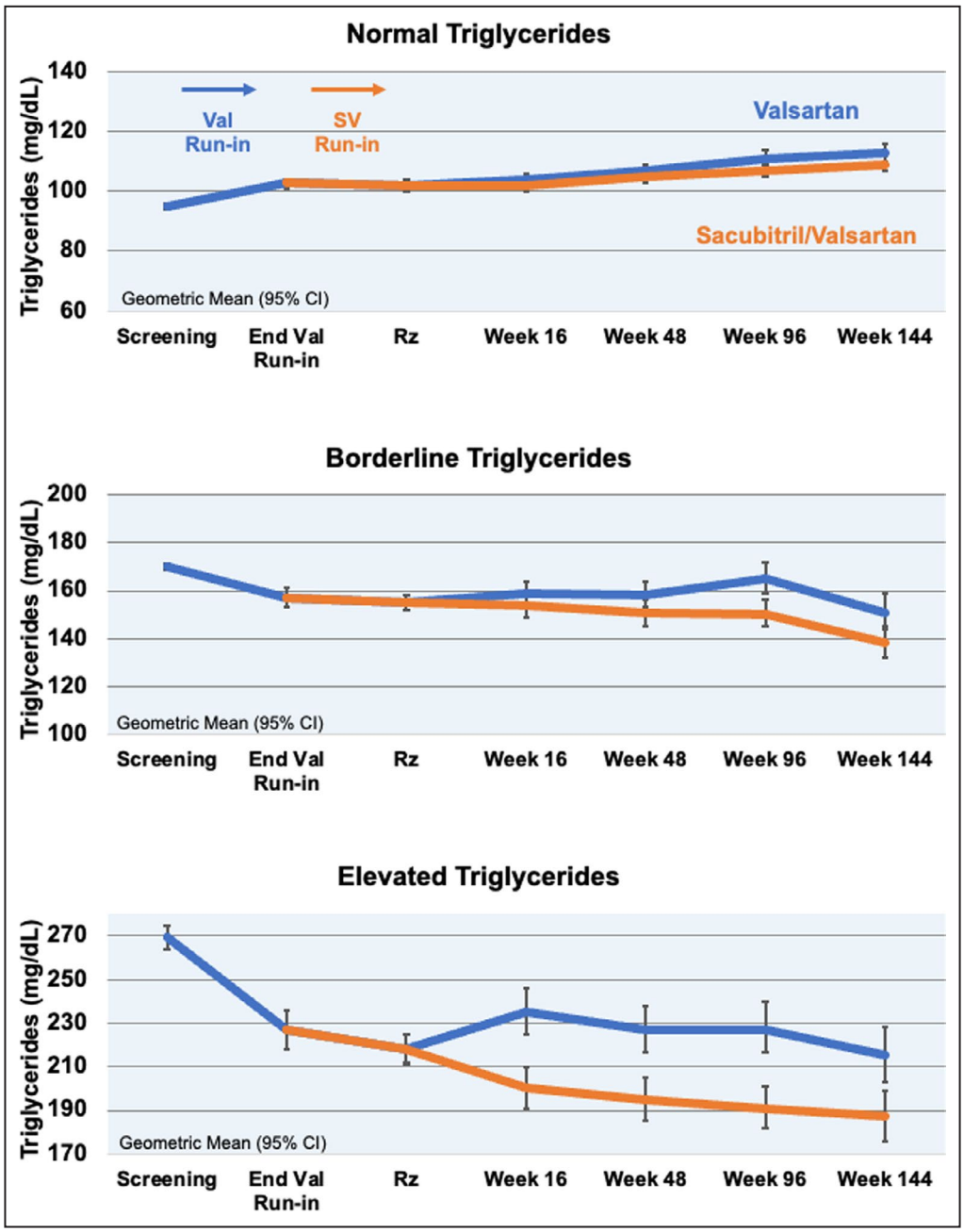

Figure 2. Serum triglyceride levels over time by baseline clinical triglyceride group and treatment arm.

The effect of study drug on the unadjusted geometric mean of serum triglyceride levels by clinical groups is shown over study visits where serum triglyceride level was prespecified to be collected (truncated after the week 144 visit) with 95% CIs delineated. Clinical groups included normal (<150 mg/dL), borderline (150–199 mg/dL), and elevated (≥200 mg/dL) triglycerides. Rz indicates randomization; SV, sacubitril/valsartan; and Val, valsartan.

participants with triglycerides 200 to 499 mg/dL with icosapent ethyl at 2 and 4 g/d reduced triglycerides by 10.1% and 21.5%, respectively, at 12 weeks compared with placebo.[32] Similar to our findings, treatment with icosapent ethyl was even more efficacious at higher baseline triglyceride levels. The control arm comparison in these studies clarifies that these treatment effects which are heightened in participants with the highest baseline levels are not solely related to regression to the mean.

Table 3. Valsartan-Adjusted Change in Serum Triglycerides by Baseline Triglyceride Group and Treatment Arm

Baseline Serum Lipid Group	Treatment Effect of Sacubitril/Valsartan vs Valsartan		Treatment Effect of Sacubitril/Valsartan vs Valsartan	
	Median (95% CI) Change in Triglyceride Level (mg/dL)	*P* Value	16-week Ratio (95% CI) of Triglyceride Level	*P* Value
Week 16 visit				
Triglycerides<150 mg/dL	−3.0 (−5.5 to −0.4)	0.024	−2.5% (−4.7% to −0.1%)	0.04
150 mg/dL≤Triglycerides<200 mg/dL	−6.7 (−15.2 to +1.7)	0.12	−3.0% (−7.5% to +1.6%)	0.20
Triglycerides≥200 mg/dL	−29.9 (−44.3 to −15.5)	<0.001	−13.0% (−18.1% to −7.6%)	<0.001
Week 48 visit				
Triglycerides<150 mg/dL	−1.8 (−5.0 to +1.5)	0.29	−2.8% (−4.6% to +0.3%)	0.081
150 mg/dL≤Triglycerides<200 mg/dL	−8.9 (−16.8 to −0.9)	0.029	−4.3% (−8.9% to +0.6%)	0.087
Triglycerides≥200 mg/dL	−26.6 (−43.4 to −9.8)	0.002	−12.4% (−18.2% to −6.8%)	<0.001
Week 96 visit				
Triglycerides<150 mg/dL	−3.5 (−7.0 to −0.1)	0.044	−4.0% (−6.5% to −1.5%)	0.002
150 mg/dL≤Triglycerides<200 mg/dL	−8.9 (−20.0 to +2.3)	0.12	−8.8% (−13.4% to −3.6%)	0.001
Triglycerides≥200 mg/dL	−28.6 (−49.8 to −7.4)	0.008	−13.2% (−20.0% to −8.0%)	<0.001
Week 144 visit				
Triglycerides<150 mg/dL	−4.4 (−8.3 to −0.5)	0.026	−3.7% (−6.7% to −0.6%)	0.021
150 mg/dL≤Triglycerides<200 mg/dL	−13.3 (−27.2 to +0.6)	0.062	−8.8% (−14.8% to −2.2%)	0.009
Triglycerides≥200 mg/dL	−23.2 (−45.0 to −1.5)	0.036	−10.3% (−17.9% to −2.9%)	0.007

As PARAGON-HF included an active comparator (valsartan), the placebo-adjusted effects of sacubitril/valsartan on serum lipids are unknown. However, a randomized, placebo-controlled trial of valsartan in hypertensive participants demonstrated a neutral treatment effect on triglycerides and HDL-C and a decrease in LDL-C.[33] Uncontrolled studies of valsartan in other clinical settings generally demonstrate similar lipid effects.[34,35] Therefore, some of the lipid changes with valsartan in PARAGON-HF may reflect natural progression in HFpEF, though a placebo-controlled assessment would be required to be definitive.

There may be several clinical implications of the lipid changes observed with sacubitril/valsartan treatment. While changes in lipid values are overall modest, sacubitril/valsartan had a greater effect in triglyceride reduction among those with elevated triglycerides. The utility of triglyceride lowering through sacubitril/valsartan in more general populations, who are at elevated risk for atherosclerotic cardiovascular disease without significant competing risks (as in patients with HFpEF), may be of interest. This, of course, presumes that triglyceride reduction itself affords cardiovascular risk reduction, which has not been clearly established.[36] It will also be important to note the contributions to this risk by the modest increases in HDL-C and LDL-C. Additionally, dedicated study of the utility of triglyceride reduction to mitigate cardiac remodeling/dysfunction and worsening HF may be warranted,[6,37] as our evaluation was limited in PARAGON-HF since participants had largely controlled triglycerides levels.

We also investigated whether treatment arm influenced subsequent initiation of lipid-lowering therapies. The lack of treatment arm differences in LDL-C lowering therapy initiation is concordant with the small, early increase in LDL-C observed with sacubitril/valsartan that appears to wane over time. This finding also clarifies that the triglyceride-lowering effect of sacubitril/valsartan was not attributable to greater relevant medication initiation, such as statins. The lack of increased rates of antitriglyceride treatment initiation in the valsartan arm likely reflects only the recent publication of the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), which also included patients with HF.[38] Regardless of treatment arm, these findings reflect the overall low use and initiation of nonstatin therapies in HFpEF. As more lipid treatment evidence accumulates in populations that include heart failure,[38–40] our results provide a contemporary survey of its use in HFpEF.

There are some limitations. The specific inclusion/exclusion criteria in PARAGON-HF may limit generalizability to a broad HFpEF population. In addition, comprehensive lipid (and hormonal) phenotyping could be helpful to understand specific pathways involved in

Table 4. Relationship of Candidate Variables to Treatment Effect on Lipid Change at the 16-Week Visit

	Treatment Effect of Sacubitril/Valsartan vs Valsartan on 16-Week Ratio (95% CI) of Lipid Level
	N=4506
Unadjusted treatment effect on triglycerides	−4.3% (−6.2% to −2.4%)
Adjusted for change in hemoglobin A_{1c}	−4.0% (−5.9% to −2.1%)
Adjusted for change in systolic blood pressure	−4.5% (−6.4% to −2.5%)
Adjusted for change in estimated glomerular filtration rate	−3.9% (−5.8% to −2.0%)
Adjusted for change in weight	−4.3% (−6.2% to −2.4%)
Adjusted for change in nonselective beta-blocker	−4.3% (−6.2% to −2.3%)
Adjusted for change in thiazide diuretic	−4.3% (−6.2% to −2.3%)
Adjusted for change in New York Heart Association class	−4.0% (−6.0% to −1.9%)
Adjusted for change in NT-proBNP*	−4.5% (−7.9% to −3.0%)
Unadjusted treatment effect on HDL-C	+2.3% (+1.3% to +3.3%)
Adjusted for change in hemoglobin A_{1c}	+2.2% (+1.2% to +3.3%)
Adjusted for change in systolic blood pressure	+2.7% (+1.7% to +3.8%)
Adjusted for change in estimated glomerular filtration rate	+2.1% (+1.1% to +3.2%)
Adjusted for change in weight	+2.3% (+1.3% to +3.3%)
Adjusted for change in nonselective beta-blocker	+2.3% (+1.2% to +3.4%)
Adjusted for change in thiazide diuretic	+2.3% (+1.3% to +3.4%)
Adjusted for change in New York Heart Association class	+2.2% (+1.1% to +3.3%)
Adjusted for change in NT-proBNP*	+2.2% (+0.9% to +3.5%)
Unadjusted treatment effect on LDL-C	+2.7% (+1.2% to +4.3%)
Adjusted for change in hemoglobin A_{1c}	+2.8% (+1.2% to +4.4%)
Adjusted for change in systolic blood pressure	+3.1% (+1.6% to +4.7%)
Adjusted for change in estimated glomerular filtration rate	+2.7% (+1.2% to +4.3%)
Adjusted for change in weight	+2.7% (+1.2% to +4.3%)
Adjusted for change in nonselective beta-blocker	+2.7% (+1.2% to +4.3%)
Adjusted for change in thiazide diuretic	+2.7% (+1.2% to +4.3%)
Adjusted for change in New York Heart Association class	+2.6% (+1.0% to 4.2%)
Adjusted for change in NT-proBNP*	+2.4% (+0.5% to +4.4%)

HDL indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Analyses adjusted for screening and 16-week parameter value.
*Data shown for 4506 participants with complete baseline and 16-week data for all variables aside from NT-proBNP, which is available in 3153 participants at these time points.

lipid effects. Strengths of our study include the large sample size, comprehensive determination of lipids and related therapies during follow-up at numerous visits, and mechanistic analyses to understand the potential pathways related to lipid changes with sacubitril/valsartan.

Table 5. Influence of Urinary cGMP Underlying Treatment Effect on Lipid Change at the 16-Week Visit

	Treatment Effect of Sacubitril/Valsartan vs Valsartan on 16-week Ratio (95% CI) of Lipid Level*
	N=1136
Unadjusted treatment effect on triglycerides	−4.5% (−7.9% to −1.0%), *P*=0.014
Adjusted for change in urinary cGMP/creatinine	+3.6% (−1.0% to +8.2%), *P*=0.13
Unadjusted treatment effect on HDL-C	+2.1% (+0.3% to +4.0%), *P*=0.023
Adjusted for change in urinary cGMP/creatinine	−0.0% (−2.3% to +2.2%), *P*=0.94
Unadjusted treatment effect on LDL-C	+5.8% (+3.1% to +8.5%), *P*<0.001
Adjusted for change in urinary cGMP/creatinine	+8.4% (+5.0% to +11.9%), *P*<0.001

cGMP indicates cyclic guanosine monophosphate HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.
Data shown for 1136 participants with complete randomization and 16-week urinary cGMP/creatinine values.
*Adjusted for randomization and 16-week parameter value.

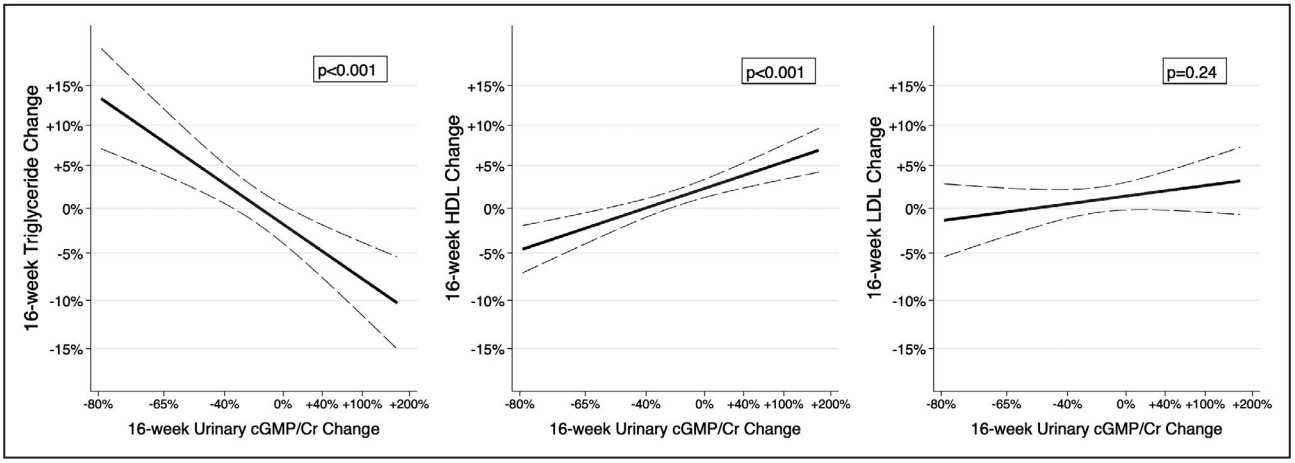

Figure 3. Relationship between 16-week changes in serum lipids and urinary cGMP.
Splines analyses depicting the relationship between change in lipids with change in urinary cGMP/creatinine at the 16-week visit combining both treatment arms, adjusted for their corresponding baseline values. *P* value shown for linear trend, and dashed lines indicate 95% confidence intervals. cGMP indicates cyclic guanosine monophosphate; Cr, creatinine; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Table 6. Lipid Related Therapy Initiation During Follow-Up by Treatment Arm

	Valsartan (n, %) N=2378	Sacubitril/Valsartan (n, %) N=2396	*P* Value
Bile acid sequestrants	7 (0.3)	5 (0.2)	0.55
Ezetimibe	49 (2.1)	43 (1.8)	0.50
Fibrates	37 (1.6)	36 (1.5)	0.88
Omega-3 fatty acids	19 (0.8)	21 (0.9)	0.77
Niacin	2 (0.1)	3 (0.1)	0.66
PCSK9 inhibitor	5 (0.2)	3 (0.1)	0.47
Statin	520 (21.9)	505 (21.1)	0.51

PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

In summary, sacubitril/valsartan compared with valsartan decreased serum triglycerides and increased HDL-C and LDL-C to a lesser degree. However, sacubitril/valsartan robustly decreased triglycerides among those with elevated triglycerides. The treatment effects on triglycerides and HDL-C were related to sacubitril/valsartan's effects on NP activity and independent of its effects on hemoglobin A_{1c}.

ARTICLE INFORMATION

Received April 16, 2021; accepted May 5, 2021.

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Sources of Funding

PARAGON-HF was funded by Novartis.

Disclosures

Dr Selvaraj receives research support from the Doris Duke Charitable Foundation (Physician Scientist Fellowship Award 2020061), the Measey Foundation, Institute for Translational Medicine and Therapeutics (Junior Investigator Preliminary/Feasibility Grant Program and Translational Bio-Imaging Center awards), and the American Society of Nuclear Cardiology (Institute for the Advancement of Nuclear Cardiology award). Dr Claggett has received consultancy fees from Boehringer Ingelheim, Gilead, AOBiome, and Corvia. Dr Packer is a consultant for Amgen, AstraZeneca, Bayer Boehringer Ingelheim, Cardiorentis, Saiichi Sankyo, Gilead, NovoNordisk, Novartis, Relypsa, Sanofi, Teva, Takeda, and ZS Pharma. Dr Zannad reports receiving fees for serving on a steering committee from Janssen, Bayer, Boston Scientific, CVRx, and Boehringer Ingelheim; consulting fees from Amgen, Vifor Pharma–Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, and Merck; and consulting fees and fees for serving on a steering committee from AstraZeneca; and serving as founder of cardiorenal and CVCT. Dr Anand reports receiving fees for serving on a steering committee from AstraZeneca, ARCA Biopharma, Amgen, and LivaNova; fees for serving as chair of a data and safety monitoring board from Boston Scientific; fees for serving on an end point committee from Boehringer Ingelheim; and fees for serving on an advisory board from Zensun. Dr Pieske reports receiving fees for serving on a steering committee, fees for serving on an advisory board, and lecture fees from Bayer HealthCare Pharmaceuticals and MSD; lecture fees from AstraZeneca; fees for serving on an advisory board and lecture fees from Bristol-Myers Squibb; fees for serving on an advisory board from Daiichi Sankyo; and lecture fees and honoraria from Medscape. Drs Zhao, Lefkowitz, and Shi are salaried employees of Novartis. Dr McMurray has served as an executive committee member and co–principal investigator of ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) and co–principal investigator of the PARADIGM-HF and PARAGON-HF trials; and his employer, Glasgow University, has been paid by Novartis for his time spent in these roles. Dr Solomon has received research grants from Actelion; Alnylam; Amgen; AstraZeneca; Bellerophon;

Bayer; BMS; Celladon; Cytokinetics; Eidos; Gilead; GSK; Ionis; Lilly; Mesoblast; MyoKardia; National Institutes of Health/National Heart, Lung, and Blood Institute; Neurotronik; Novartis; NovoNordisk; Respicardia; Sanofi Pasteur; and Theracos; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, and American Regent.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FIGURE LEGENDS

Figure S1:

Title: ***Relationship between 16-week Changes in Serum Lipids and Urinary cGMP by Treatment Arm***

Caption: Splines analyses depicting the relationship between change in lipids with change in urinary cGMP/creatinine at the 16-week visit, adjusted for their corresponding baseline values, shown by treatment arm. P-value shown for linear trend, and dashed lines indicate 95% confidence intervals. cGMP, cyclic guanosine monophosphate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE S1. Unadjusted Cumulative Mean Post-Randomization Values of Serum Lipids by Treatment Arm

Time Point	Valsartan N=2378 (mean ± standard deviation)	Sacubitril/Valsartan N=2396 (mean ± standard deviation)	P-value
Triglycerides (mg/dL)	148.0 ± 77.9	138.5 ± 65.7	<0.001
HDL cholesterol (mg/dL)	50.0 ± 14.3	51.0 ± 14.4	0.02
LDL cholesterol (mg/dL)	99.5 ± 33.7	101.6 ± 35.1	0.048

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
These data include all post-randomization visits, including visits when lipid collection was not pre-specified.

TABLE S2. Candidate Variable Values at Screening and the 16-week Visit by Treatment Arm

Candidate Variable	Time Point	Valsartan	Sacubitril/Valsartan	P-value
Hemoglobin A1c (%)	Screening visit (N=4,763)	6.5 ± 1.3	6.5 ± 1.3	0.29
	16-week visit (N=4,550)	6.5 ± 1.3	6.5 ± 1.3	0.67
Systolic blood pressure (mmHg)	Screening visit (N=4,774)	136.0 ± 14.8	136.2 ± 15.8	0.53
	16-week visit (N=4,610)	134.5 ± 17.1	130.1 ± 17.3	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	Screening visit (N=4,774)	64.0 ± 19.8	63.8 ± 19.2	0.69
	16-week visit (N=4,572)	61.3 ± 19.9	62.6 ± 19.5	0.031
Weight (kg)	Screening visit (N=4,773)	83.1 ± 17.5	82.9 ± 16.9	0.6
	16-week visit (N=4,601)	83.7 ± 17.7	83.5 ± 17.1	0.67
Non-selective beta-blocker (n, %)	Screening visit (N=4,774)	332 (14.0%)	323 (13.5%)	0.63
	16-week visit (N=4,612)	313 (13.7%)	309 (13.3%)	0.73
Thiazide diuretic (n, %)	Screening visit (N=4,774)	298 (12.5%)	311 (13.0%)	0.64
	16-week visit (N=4,612)	278 (12.1%)	284 (12.2%)	0.92
NT-proBNP (pg/mL)*	Screening visit (N=4,739)	914 [453, 1623]	902 [475, 1598]	0.59
	16-week visit (N=3,228)	762.0 [385, 1435]	585.0 [288, 1206]	<0.001
New York Heart Association Class II	Screening visit (N=4,774)	1700 (71.5%)	1737 (72.5%)	0.44
	16-week visit (N=4,649)	1709 (73.9%)	1731 (74.1%)	0.91
Urinary cGMP / creatinine**	Randomization visit (N=1,189)	115 [81, 156]	111 [81 , 149]	0.22
	16-week visit (N=1,173)	66 [50 , 92]	118 [89 , 159]	<0.001

*Presented as median [25th-75th percentile] since values are skewed.

**Urinary cGMP presented at randomization visit (after the sacubitril/valsartan run-in) since it was not assessed at screening.

NT-proBNP, N-terminal pro-B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate.

TABLE S3. Screening Clinical Characteristics by Availability of Urinary Cyclic GMP at Randomization and the 16 Week Visit

	Urinary cGMP Unavailable N=3638	Urinary cGMP Available N=1136	P-value
Age, years	72.5 ± 8.5	73.5 ± 8.0	<0.001
Women, n (%)	1886 (51.8%)	585 (51.5%)	0.84
White race, n (%)	2838 (78.0%)	1050 (92.4%)	<0.001
NYHA, n (%)			0.33
II	2607 (71.7%)	830 (73.1%)	
III	1005 (27.6%)	302 (26.6%)	
IV	26 (0.7 %)	4 (0.4 %)	
Geographic region, n (%)			0.73
Asia-Pacific or other	653 (17.9%)	106 (9.3 %)	
Central Europe	1155 (31.7%)	554 (48.8%)	
Latin America	354 (9.7 %)	15 (1.3 %)	
North America	419 (11.5%)	135 (11.9%)	
Western Europe	1057 (29.1%)	326 (28.7%)	
KCCQ-OSS	68 ± 20	68 ± 20	0.88
Alcohol (drinks/day)*	1 (0-2)	1 (0-4)	<0.001
Physical Characteristics			
Systolic blood pressure (mmHg)	136 ± 15	137 ± 15	0.039
Diastolic blood pressure (mmHg)	76 ± 11	77 ± 11	0.41
Body mass index (kg/m^2)	30.0 ± 5.0	30.8 ± 4.9	<0.001

Heart rate (beats/min)	70 ± 14	68 ± 13	<0.001
Comorbidities, n (%)			
Hypertension	3473 (95.5%)	1090 (96.0%)	0.49
Hospitalization for HF	1886 (51.8%)	407 (35.8%)	<0.001
Atrial fibrillation or flutter	1181 (32.6%)	358 (31.6%)	0.55
Diabetes mellitus	1585 (43.6%)	470 (41.4%)	0.19
Myocardial infarction	835 (23.0%)	242 (21.3%)	0.25
Stroke	390 (10.7%)	118 (10.4%)	0.77
Current smoker	271 (7.5 %)	78 (6.9 %)	0.49
Medication Use, n (%)			
ACE-I and/or ARB	3111 (85.5%)	1012 (89.1%)	0.002
Any beta-blocker	2876 (79.1%)	940 (82.7%)	0.007
Non-selective beta-blocker	519 (14.3%)	136 (12.0%)	0.05
Calcium channel blocker	1237 (34.0%)	405 (35.7%)	0.31
Loop diuretic	2824 (77.6%)	859 (75.6%)	0.16
Thiazide diuretic	478 (13.1%)	131 (11.5%)	0.16
Mineralocorticoid antagonist	1008 (27.7%)	280 (24.6%)	0.043
Insulin	505 (13.9%)	144 (12.7%)	0.30
Oral diabetic medication	1090 (68.8%)	317 (67.4%)	0.58
Statin	2274 (62.5%)	749 (65.9%)	0.036
Fibrates	108 (3.0 %)	39 (3.4 %)	0.43
Ezetimibe	86 (2.4 %)	36 (3.2 %)	0.13

Omega-3 fatty acids	101 (2.8 %)	22 (1.9 %)	0.12
Bile acid sequestrants	2 (0.1 %)	4 (0.4 %)	0.014
Niacin	4 (0.1 %)	2 (0.2 %)	0.58
Laboratory Testing			
Estimated glomerular filtration rate (mL/min/1.73 m^2)	65 ± 20	62 ± 18	<0.001
Hemoglobin A1c (%)	6.5 ± 1.3	6.5 ± 1.3	0.7
Hemoglobin (mg/dL)	13.3 ± 1.5	13.4 ± 1.4	0.16
NT-proBNP (pg/mL)*	902 [457 , 1646]	930 [492 , 1526]	0.65
Triglycerides (mg/dL)*	118 [89 , 168]	124 [89 , 168]	0.32
HDL cholesterol (mg/dL)*	49 [40 , 59]	49 [41 , 62]	0.002
LDL cholesterol (mg/dL)*	97 [73 , 124]	93 [73 , 124]	0.33
Ejection Fraction	58 ± 8	57 ± 8	0.06

*Presented as median [25^{th}-75^{th} percentile] since values are skewed.

NYHA, New York Heart Association; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

FIGURE S1.