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1 **Effect of Sacubitril/Valsartan on lipid metabolism in patients with**
2 **chronic kidney disease combined with chronic heart failure: a**
3 **retrospective study**

4 **Abstract**

5 **Background and Objective**

6 Dyslipidemia is significantly more common in those with concurrent chronic kidney
7 disease (CKD) and chronic heart failure (CHF). Sacubitril/Valsartan has showcased its
8 influence on both cardiac and renal functions, extending its influence to the modulation
9 of lipid metabolism pathways. This study aims to examine how Sacubitril/Valsartan
10 affects lipid metabolism within the context of CKD and CHF.

11 **Methods**

12 This study adopted a retrospective design, focusing on a single center and involving
13 participants who were subjected to treatment with Sacubitril/Valsartan and Valsartan.
14 The investigation assessed the treatment duration, with a particular emphasis on
15 recording blood lipid indicators, including triglyceride (TG), total cholesterol (TC),
16 low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol
17 (HDL-C), apolipoprotein A (ApoA), and apolipoprotein B (ApoB). Furthermore,
18 cardiac and renal functions, blood pressure, potassium levels, and other factors
19 influencing the blood lipids were analyzed in both groups at identical time points.

20 **Results**

21 After 16 weeks of observation, the Sacubitril/Valsartan group exhibited lower TG levels
22 compared to the Valsartan group. Noteworthy was the fact that individuals undergoing

23 Sacubitril/Valsartan treatment experienced an average reduction of 0.84 mmol/L in TG
24 levels, in stark contrast to the control group, which registered a decline of 0.27 mmol/L
25 ($P < 0.001$). The Sacubitril/Valsartan group exhibited elevated levels of HDL-C and
26 ApoA in comparison to the Valsartan group ($P_{\text{HDL-C}} = 0.023$, $P_{\text{ApoA}} = 0.030$). While TC,
27 LDL-C, and ApoB decreased compared to baseline, the differences between groups
28 were not statistical significance. Regarding cardiac indicators, there was an observed
29 enhancement ³ in the left ventricular ejection fraction (LVEF) within the
30 Sacubitril/Valsartan group when compared to the baseline, and it was noticeably higher
31 than that of the Valsartan group. Spearman correlation analysis and multifactorial
32 logistic regression analysis revealed that medication, body mass index, and glycated
33 hemoglobin had a direct influencing effect on TG levels.

34 **Conclusion**

35 Sacubitril/Valsartan demonstrated improvements in lipid metabolism and cardiac
36 indicators in patients with CKD and CHF. Specifically, it presented promising benefits
37 in reducing TG levels. In addition, both BMI and HbA1c emerged as influential factors
38 contributing to alterations in TG levels, independent of the administration of
39 Sacubitril/Valsartan.

40 **Keywords**

41 Sacubitril/Valsartan, lipids, chronic kidney disease, chronic heart failure.

42 **Introduction**

43 Globally, approximately 15-20% of adults endure the presence of chronic kidney
44 disease (CKD).

45 Extended retention of fluid induces increased cardiac stress and activates the renin-
46 angiotensin-aldosterone system (RAAS)^[1]. Chronic sympathetic stimulation can result
47 in compromised cardiomyocyte function, diminished ventricular contractility, and the
48 onset of cardiac insufficiency^[2]. In individuals with CKD, cardiovascular disease (CVD)
49 has emerged as the primary factor of adverse long-term outcomes^[3]. Those with CKD
50 and CVD commonly experience dyslipidemia. Substantiated by pertinent research,
51 dyslipidemia independently contributes to the risk of CKD and CVD, exerting harm on
52 the kidneys through systemic inflammatory responses, vascular injury, and oxidative
53 stress^[4]. Moreover, individuals experiencing hyperlipidemia face a cardiovascular
54 disease risk twice as high as that of the general population. The chronic impact of lipid
55 overload on the structural composition and function of the heart may contribute to
56 initiation and advancement of chronic heart failure (CHF). Excessive lipid levels exert
57 influence on both renal and cardiac systems, reciprocally influencing each other.
58 Therefore, proactive management of lipid levels proves crucial for slowing disease
59 progression and enhancing the prognosis for individuals with concurrent CKD and CHF.

60 Prior investigations have demonstrated the potential of statins in mitigating
61 atherosclerotic risk among individuals grappling with both CKD and CVD. However,
62 their use is marred by adverse effects such as rhabdomyolysis and hepatic insufficiency,
63 with limited discernible benefits for patients undergoing dialysis therapy^[5]. Emerging
64 lipid-lowering interventions, such as proprotein convertase subtilisin/kexin 9 (PCSK9)
65 inhibitors, may present side effects at the injection site, including allergies and muscle
66 cramps^[6]. The American Heart Association guidelines recommended utilizing omega-

67 3 fatty acids in individuals with heart failure (HF) to mitigate the likelihood of
68 hospitalization and mortality, particularly in those categorized within New York Heart
69 Association (NYHA) classes II-IV^[7].

70 However, findings from the VITAL Rhythm study suggest that omega-3 fatty acids
71 might contribute to an elevated risk of atrial fibrillation while concurrently exhibiting
72 antiplatelet properties^[8,9]. Regular monitoring for bleeding risks is advised when using
73 them alongside anticoagulants or antiplatelet agents. Therefore, the pursuit of secure
74 and efficacious lipid-regulating strategies remains a pivotal focus for disease
75 management and enhancing patient prognoses.

76 Origins of the natriuretic peptide (NP) family, including atrial natriuretic peptide
77 (ANP) and brain natriuretic peptide (BNP), are found in atrial and ventricular myocytes.
78 Natriuretic peptides (NPs), as elucidated by numerous studies, assume the functions of
79 inducing vasodilation, promoting natriuresis, and inhibiting both the RAAS and the
80 sympathetic nervous system^[10-12]. The functional scope of NPs has been broadened by
81 the presence of natriuretic peptide receptor (NPR) in human adipose tissue^[13]. Galitzky
82 et al. discovered a sustained lipolytic action of ANP through intravenous infusion into
83 healthy and obese subjects, independent of the sympathetic nervous system^[14]. In
84 addition, Sbaraini da Silva et al. demonstrated a decrease in NP content among
85 individuals with obesity^[15]. Mice infused with BNP exhibited elevated expression of
86 markers associated with energy expenditure, oxygen consumption, and brown adipose
87 tissue compared to the non-BNP-infused group^[16], indicating a close correlation
88 between BNP and adipose tissue metabolism.

89 The adipocyte membrane's NPR and NP form a binding contact, instigating ¹³the
90 activation of the cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG)
91 pathway. Consequently, this cascade facilitates hormone-sensitive lipase (HSL)
92 phosphorylation, culminating in the hydrolysis of triglycerides and the generation of
93 glycerol and non-esterified fatty acids^[17].

94 Sacubitril/Valsartan, the novel inhibitor targeting angiotensin receptors and
95 neprilysin, consists of sacubitril and Valsartan in a balanced 1:1 ratio^[18]. Valsartan,
96 through the inhibition of the angiotensin II (AngII) receptor, imparts therapeutic
97 benefits, including antihypertensive effects, proteinuria reduction, and alleviation of
98 cardiac load. Moreover, sacubitril serves as an enkephalinase inhibitor, impeding the
99 breakdown of NPs and augmenting NP content. According to recent research, the NP
100 route that promotes lipolysis is responsible for the enhancement of lipid ⁷levels among
101 individuals with heart failure with preserved ejection fraction (HFpEF) when taking
102 Sacubitril/Valsartan^[19, 20].

103 One common risk factor for both CKD and CVD is dyslipidemia. Nevertheless, the
104 current publications lack comprehensive exploration of the influence of
105 Sacubitril/Valsartan on lipids within the CKD and CHF population. Therefore, the
106 principal objective of this investigation was to discern the influence of
107 Sacubitril/Valsartan on lipid levels among individuals with both CKD and CHF, with
108 secondary objectives encompassing an evaluation of its effects on cardiac and renal
109 function as well as blood pressure. The study hoped to contribute valuable insights into
110 lipid management strategies for this specific population.

111 **Subjects and Methods**

112 **1.1 Study methodology**

113 This retrospective study focused on 212 individuals with CKD and CHF from a single
114 center's sample. From January 2019 to November 2022, individuals within this patient
115 demographic ⁷ were admitted to the Affiliated Hospital of Xuzhou Medical University.

116 The study included patients receiving Valsartan or Sacubitril/Valsartan treatment, and
117 comprehensive clinical data was meticulously recorded utilizing an electronic case
118 system. The Xuzhou Medical University Hospital's Ethics Committee granted the study
119 approval (XYFY2023-KL142-02).

120 **1.2 Patient selection**

121 The specified inclusion criteria were as follows: manifestations and indications of HF,
122 such as exertional dyspnea, nocturnal paroxysmal dyspnea, telangiectasia, ankle edema,
123 ¹⁶ N-terminal pro-brain natriuretic peptide (NT-proBNP) levels exceeding 400 pg/mL,
124 NYHA class II - IV, ¹¹ estimated glomerular filtration rate (eGFR) less than 60
125 mL/min/1.73 m², abnormal urinary routine or renal imaging or pathology persisting for
126 ≥ 3 months, age ≥ 18 years.

127 Exclusion criteria encompassed: a history of peritoneal dialysis, hemodialysis and
128 kidney transplantation, notable bilateral renal artery stenosis, severe hepatic
129 impairment, biliary cirrhosis, or cholestasis, systolic blood pressure (SBP) < 100 mmHg,
130 potassium content > 5.5 mmol/L, history of stroke or acute coronary syndrome within
131 3 months before treatment, such as cardiac surgery or percutaneous coronary
132 interventions (PCI), tumor-related diseases and definite drug-related renal damage,

133 familial hypercholesterolemia, history of angioedema, use of PCSK9 inhibitors, poor
134 adherence, incomplete clinical data, loss of visits, intolerance of the side effects of the
135 drug use and interruptions.

136 Throughout the medication period, patients in both groups adhered to a low-salt and
137 low-fat diet, and the prescription of conventional medications such as beta-blockers,
138 aldosterone antagonists and diuretics were determined by clinicians. Commencing at
139 25 mg twice daily, the initial dose of Sacubitril/Valsartan could be adjusted every two
140 to four weeks. The dosage modifications were contingent upon the patient's tolerance
141 levels related to blood pressure, heart rate, and symptoms. Generally, the maximum
142 prescribed dose did not exceed 200 mg twice daily. The initial dose of Valsartan was 40
143 mg once daily, titrated according to guideline recommendations, without surpassing
144 160 mg twice daily.

145 **1.3 Observation indicators and study objective**

146 Baseline information and hematological indicators were collected both before and after
147 16 weeks of treatment. The utilization of antihypertensive drugs, statins, insulin, and
148 other medications during the treatment period was meticulously documented through
149 the electronic medical record system. Measurements of ⁶triglyceride (TG), total
150 cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density
151 lipoprotein cholesterol (HDL-C), apolipoprotein A (ApoA), apolipoprotein B (ApoB),
152 serum creatinine, eGFR, cystatin C, urea, uric acid, fasting blood glucose (FBG), blood
153 potassium, NT-proBNP, high-sensitive troponin T and hemoglobin A1c (HbA1c), were
154 obtained from patients using an automated biochemical analyzer (Roche, Switzerland).

155 Additionally, the color Doppler ultrasound imager (Philips, Netherlands) was utilized
156 to get the following measurements: ² left atrial diameter (LAD), left ventricular end-
157 diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF).

158 Characterized by structural or functional abnormalities lasting over 3 months,
159 chronic kidney disease (CKD) is identified. CHF is defined as abnormal systolic or
160 diastolic function of the ventricles. The following criteria have been set by the Affiliated ²⁴
161 Hospital of Xuzhou Medical University to define normal or suitable blood lipid levels:
162 ⁴ TC < 5.18 mmol/L, TG < 1.70 mmol/L, HDL-C $\geq$ 1.04 mmol/L, LDL-C < 3.37
163 mmol/L, ApoA > 1.00 mmol/L, ApoB < 1.14 mmol/L. The eGFR was calculated
164 employing a four-variable equation outlined in 2006^[21].

165 This study's primary goals were to assess changes in lipid indices within the two
166 groups post-treatment, and to analyze factors influencing these variations in blood
167 lipids. The secondary aim involved comparing alterations in cardiac and renal function
168 indices, blood pressure, and blood potassium subsequent to medication.

169 **1.4 Statistical methods**

170 In this study, ten eligible patients were randomly chosen in each group, focusing on the
171 change of TG levels in 16 weeks as the primary outcome in accordance with pertinent
172 literature. The TG level in the Sacubitril/Valsartan group measured 1.86 ± 1.16 mmol/L,
173 while in the Valsartan group, it registered at 1.36 ± 0.53 mmol/L. The study utilized
174 PASS 15.0 software, adopting a 1:1 ratio for sample size, employing a one-sided α of ¹⁰
175 0.05, and achieving a test efficiency of 80%. The minimum required sample size was
176 determined to be 84 cases in each group. To accommodate a potential loss to follow-up

177 of up to 20%, a minimum of 101 cases was included in each of the two groups. In total,
178 there were 212 participants included in the study. Sacubitril/Valsartan served as the
179 observation group and Valsartan was employed as the control group.

180 SPSS 26.0 software was used to analyze the data. For normally distributed
181 quantitative data, mean and standard deviation were utilized to represent the values.
182 Intergroup comparisons were conducted using the independent sample t test, while
183 intragroup comparisons employed the paired samples t test. Non-normally distributed
184 data were expressed using the median (quartile), with intragroup comparisons assessed
185 through the Wilcoxon rank sum test and intergroup comparisons through the Mann-
186 Whitney U test. Intergroup comparisons for categorical count data were conducted
187 using chi-square tests, which were presented as the percentage of cases. The factors
188 influencing TG decrease were examined using Spearman correlation analysis,
189 multicollinearity testing and multiple linear regression analysis. At $P < 0.05$, statistical
190 significance was taken into account.

191 **2 Results**

192 **2.1 Baseline characteristics of the study participants**

193 The study comprised 212 patients, with 106 assigned to the Sacubitril/Valsartan group
194 and the remaining 106 to the Valsartan group. Medical histories and baseline data were
195 comparable in both groups. The comparability of the clinical indicators was
196 demonstrated by the lack of significant variations in intergroup lipid levels, cardiac and
197 renal function, blood pressure and blood potassium (Table 1, Line 730).

198 **2.2 Changes in blood lipid levels before and after treatment in both groups**

199 After 16 weeks of therapy, the TG in the Sacubitril/Valsartan group exhibited a
200 noteworthy reduction to 1.13 (0.84, 1.55) mmol/L ($P < 0.001$). In parallel, the TG levels
201 in the Valsartan group also experienced a decline to 1.47 (1.15, 2.01) mmol/L ($P <$
202 0.001). A comparative analysis of the magnitude of TG alteration during the treatment
203 duration revealed a statistically distinction between groups. As depicted in Fig. 1, the
204 Sacubitril/Valsartan group exhibited a change of 0.84 (0.40, 1.14) mmol/L, surpassing
205 the Valsartan group's 0.27 (-0.11, 0.69) mmol/L ($P < 0.001$).

206 Throughout the treatment period, a significant reduction in TC was observed in the
207 Sacubitril/Valsartan group, reaching 3.68 ± 1.12 mmol/L ($P < 0.001$). The Valsartan
208 group exhibited a decrease in TC to 3.96 ± 1.36 mmol/L ($P < 0.001$). The intergroup
209 disparities in TC post-treatment did not attain statistical significance ($P = 0.096$) despite
210 these decreases. Comparing the post-treatment LDL-C levels with their respective pre-
211 treatment values, significant differences were observed (2.05 ± 0.90 mmol/L in the
212 observation group versus 2.17 ± 1.03 mmol/L in the control group, $P < 0.001$). Similarly,
213 ApoB levels also displayed statistical significance (0.75 ± 0.26 mmol/L in
214 Sacubitril/Valsartan group versus 0.82 ± 0.28 mmol/L in Valsartan group,
215 $P_{\text{Sacubitril/Valsartan}} < 0.001$, $P_{\text{Valsartan}} = 0.007$). However, post-treatment comparisons
216 between the two groups revealed no noteworthy differences in LDL-C and ApoB levels.

217 Following therapy, the Sacubitril/Valsartan group exhibited a mean HDL-C value of
218 1.24 ± 0.33 mmol/L, while the Valsartan group showed a value of 1.13 ± 0.34 mmol/L
219 ($P_{\text{Sacubitril/Valsartan}} < 0.001$, $P_{\text{Valsartan}} = 0.881$). ApoA levels were elevated in both groups
220 compared to pre-treatment ($P_{\text{Sacubitril/Valsartan}} < 0.001$, $P_{\text{Valsartan}} = 0.474$). After 16 weeks

221 of therapy, the Sacubitril/Valsartan group exhibited elevated levels of HDL-C and
222 ApoA, as indicated by intergroup analysis ($P_{\text{HDL-C}} = 0.023$, $P_{\text{ApoA}} = 0.030$, Table 2, Fig.
223 2).

224 **2.3 Changes in cardiac indexes before and after treatment**

225 After treatment, the Sacubitril/Valsartan group showed a substantial improvement in
226 LVEF and a noteworthy reduction in LVEDD, LAD, and NT-proBNP. In the control
227 group, there were discernible reductions in both LVEDD and NT-proBNP, while no
228 notable changes in LVEF and LAD were identified. After a 16-week treatment, the
229 Sacubitril/Valsartan group exhibited the LVEF of 56.00 ± 6.71 mmol/L, surpassing that
230 of the Valsartan group ($P < 0.001$). Additionally, the observation group exhibited a
231 reduction in LAD to 40.39 ± 5.55 mmol/L, contrasting with the Valsartan group ($P =$
232 0.001). Both LVEDD and NT-proBNP exhibited no significant alterations in intergroup
233 comparisons after treatment (Table 3).

234 Regarding the enhancement of cardiac function, the comprehensive efficacy rate
235 reached 59.4% in the observation group post-treatment (contrasting with 38.7% in the
236 control group), showcasing a discernible distinction between the two cohorts ($P = 0.003$,
237 Fig. 3).

238 **2.4 Changes in renal function before and after treatment**

239 The Sacubitril/Valsartan group exhibited no obvious fluctuations in eGFR, blood
240 creatinine, and uric acid after treatment ($P > 0.05$). Conversely, blood creatinine
241 increased to 129.50 (106.00 , 177.50) $\mu\text{mol/L}$ and eGFR decreased to 42.90 (29.93 ,
242 55.21) mL/min/1.73m^2 compared to the pre-treatment phase in the control group, which

243 had statistically significant differences ($P_{\text{blood creatinine}} < 0.001$, $P_{\text{eGFR}} = 0.001$). After
244 treatment, no notable differences were observed about eGFR, blood creatinine, and uric
245 acid in intergroup comparisons ($P > 0.05$), as indicated by the results presented in Table
246 4.

247 **2.5 Variations in blood pressure and serum potassium levels at baseline and** 248 **16weeks**

249 Over the course of 16 weeks, the Sacubitril/Valsartan group's systolic blood pressure
250 (SBP) dropped from 146.35 ± 20.19 mmHg to 130.94 ± 22.87 mmHg ($P < 0.001$), a
251 significant drop in intergroup comparisons ($P < 0.001$). Diastolic blood pressure (DBP)
252 and potassium levels before and after therapy did not differ statistically significantly in
253 intragroup or intergroup comparisons ($P > 0.05$), as presented in Table 5.

254 **2.6 Analysis of factors affecting the amount of TG reduction**

255 In order to investigate the factors affecting the extent of TG change, Spearman
256 correlation analysis was conducted on the dataset of 212 patients. The reduction in TG
257 was considered the outcome variable, and baseline data served as the independent
258 variable. The analysis unveiled positive correlations between BMI and HbA1c with TG
259 reduction [Spearman's rank correlation coefficient (r_s) 0.391 and 0.233, respectively].
260 Furthermore, patients undergoing Sacubitril/Valsartan treatment demonstrated a more
261 substantial decrease in TG ($r_s=0.343$, $P < 0.001$), as depicted in Table 6 and illustrated
262 in Fig. 4-5. To address confounding factors, a multicollinearity test was performed for
263 BMI, HbA1c, and group, with all variance inflation factors found to be < 5 , signifying
264 an absence of collinearity. Moreover, a multiple linear regression model was formulated,

with group, BMI, and HbA1c as independent variables and the amount of TG reduction as the dependent variable. The results revealed that, in addition to the impact of BMI and HbA1c, the group emerged as a significant factor influencing the degree of TG reduction. In essence, the Sacubitril/Valsartan group exhibited a noteworthy impact on TG reduction post-treatment ($P < 0.001$, Table 7).

3 Discussion

In this study, individuals diagnosed with CKD and CHF, exhibiting an eGFR below 60 mL/min/1.73 m², were selected as participants. The objective revolved around scrutinizing the impact of Sacubitril/Valsartan in contrast to Valsartan on serum lipids, as well as cardiac and renal function indices. The overarching aim was to enhance understanding of Sacubitril/Valsartan's role in lipid metabolism. When compared between groups, subjects who received Sacubitril/Valsartan exhibited a substantial reduction in TG levels after 16 weeks of treatment. Apart from Sacubitril/Valsartan, both BMI and HbA1c have emerged as clinical factors influencing TG levels. Within the Sacubitril/Valsartan group, elevated levels in HDL-C, ApoA, and LVEF were evident in contrast to the Valsartan group. Conversely, TC, LDL-C, ApoB, and LAD displayed a decrease in the Sacubitril/Valsartan group. Notably, no appreciable disparity in renal function was discernible between the two groups.

Lipid abnormalities among CKD patients encompass hypertriglyceridemia, elevated LDL-C, ApoB accumulation, diminished HDL-C, lowered ApoA, and elevated lipoprotein a concentration^[22, 23]. CKD individuals exhibit reduced enzyme activity of lecithin cholesterol acyltransferase, lipid accrual, and endothelial impairment,

287 accompanied by concurrent inflammatory and oxidative stress responses. Messow et
288 al.'s meta-analysis, which incorporated 13 studies examining statin-treated CKD,
289 revealed an escalation in cardiovascular risk with the progression of CKD stages^[23]. Ho
290 et al.'s cohort study found that fibrates may not effectively reduce cardiovascular risk^[24].
291 This study focused on elucidating the influence of Sacubitril/Valsartan on lipid
292 metabolism in individuals with CKD and CVD, intending to offer insights for future
293 research.

294 In conventional wisdom, elevated blood lipid levels are commonly associated with
295 advancing age. A comprehensive cohort study disclosed that, aside from age, gender
296 differences were correlated with lipid levels. As males age, there was a discernible
297 deceleration in the rate of alterations observed in TC, TG, and LDL-C, peaking before
298 40 years, while females experienced the most significant lipid level changes between
299 ages 40-49, potentially attributed to the gradual decline in estrogen levels during the
300 perimenopausal phase. Consequently, it is imperative for men to adopt suitable lipid
301 management measures before reaching 40, and women should focus on such measures
302 during the age range of 40-49^[25, 26]. The average ²age of participants in this study was
303 69 years, with a predominant male representation. Following a 16-week treatment, no
304 significant correlation emerged between the decrease in TG and age or gender. This
305 lack of correlation could be attributed to diminishing or reversing differences in blood
306 lipid levels associated with advancing age^[27].

307 Barman et al.'s single-center retrospective study found that Sacubitril/Valsartan
308 improved blood lipid levels, and its efficacy remained unaffected by statins^[28]. In

309 patients with HFpEF, the outcomes of prospective trial showed a reduction in TG, an
310 ¹⁹ increase in HDL-C, and a slight rise in LDL-C^[19]. The perspectives outlined above
311 closely align with the findings of this study, with the exception of variations in LDL-C
312 alterations. Given that the participants in this study presented with CKD in conjunction
313 with CVD, the interplay between the heart and kidneys, along with the impact of NP
314 mechanisms of action, could be responsible for the observed decline in LDL-C levels.

315 Over the course of 16 weeks of observation, alterations in TG levels consequent to
316 Sacubitril/Valsartan treatment may be attributed to its inhibition of enkephalinase,
317 preventing the decomposition of NPs. NPs are essential for fat oxidation, promoting
318 energy expenditure in brown adipose tissue, and enabling lipid mobilization within
319 white adipose tissue^[29,30]. NPs bind to receptors on the adipocyte membrane, activating
320 the guanylyl cyclase A/B (Gc-A/B) through the cGMP/PKG pathway, known as the Gc-
321 A/B/cGMP/PKG pathway^[17]. Wang's research revealed a favorable correlation between
322 ANP and HDL-C levels^[31], which was consistent with the elevated HDL-C levels
323 observed in this study. Diminished levels of ApoA, a component of HDL, were linked
324 to an unfavorable prognosis in individuals with CHF^[32]. The study found that
325 Sacubitril/Valsartan increased ApoA content, suggesting a potential beneficial impact
326 on HF patients' long-term prognosis.

327 Previous research have indicated low levels of NPs in the obese population^[33,34]. Bao
328 et al. delved into the intricate interplay between BNP and blood lipids, aiming to
329 enhance comprehension of the complex dynamics involving NPs and lipid levels. Their
330 findings revealed an inverse relationship between NT-proBNP and LDL-C^[35]. Similarly,

331 in a study by Spannella et al. conducted among an elderly population, a negative
332 correlation was observed between levels of LDL-C and NT-proBNP, irrespective of
333 whether NT-proBNP fell within the normal range^[36]. This study showed a reduction in
334 LDL-C levels after 16 weeks' Sacubitril/Valsartan medication compared to the pre-
335 treatment phase. This observed decrease in LDL-C might be attributed to the elevated
336 BNP content induced by Sacubitril/Valsartan, subsequently leading to LDL-C reduction.
337 However, intergroup analysis revealed no significant disparity, prompting an analysis
338 of the underlying reasons for this outcome. It was discovered that AngII induces LDL-
339 C aggregation, thereby elevating the expression of LDLR. Remarkably, BNP inhibits
340 AngII-induced LDLR expression, diminishing LDL-C binding and consequently
341 lowering LDL-C levels^[37,38]. Moreover, Valsartan inhibits AngII binding to the receptor,
342 which can also inhibit the metabolic processes of LDL-C. Therefore, these intricate
343 interactions provided a plausible explanation for the study's negligible difference in
344 LDL-C levels between groups. Following 16 weeks of treatment, ApoB decreased from
345 baseline in both the Sacubitril/Valsartan and Valsartan group. This suggested that
346 alterations in LDL-C may contribute to this observed phenomenon. Although TC levels
347 diminished in both groups post-treatment, the lack of significant differences may be
348 attributed to TC encompassing HDL-C and non-HDL-C, where even a slight alteration
349 in each of these indicators could influence TC levels.

350 In light of the decrease in TG levels shown with Sacubitril/Valsartan treatment, the
351 study conducted Spearman correlation analysis to unravel factors influencing TG
352 reduction. Beyond the treatment modality, BMI and HbA1c emerged as significant

353 contributors to TG level changes. Individuals with both CKD and CHF exhibit a
354 heightened prevalence of lipid abnormalities, a consequence of inflammatory factors,
355 RAAS activation, and the interplay between heart and kidney functions. Notably,
356 obesity, prevalent in the study's participants with a higher average BMI than normal
357 adults, poses a risk factor for these participants. Therefore, regulating lipids and BMI
358 become paramount in managing CKD and CHF patients. Oh et al.'s community study
359 have demonstrated a positive relationship between elevated BMI and increased TG
360 levels, highlighting the potential benefits of moderate weight management in reducing
361 TG^[39]. This study revealed a modest but positive correlation ($r_s = 0.391$) between
362 declining TG levels and BMI. Nevertheless, this observation underscored a noteworthy
363 reduction in TG levels among individuals with higher BMI following medication.
364 Additionally, there was a correlation between the extent of TG reduction and HbA1c
365 levels. Hsiung et al.'s Mendelian randomized study elucidated that elevated TG levels
366 affect genomic methylation status, leading to increased blood HbA1c^[40]. Zheng et al.
367 demonstrated a close association between poor glycemic management and elevated TG²
368 levels in individuals with type 2 diabetes, emphasizing the independent contribution of
369 elevated TG levels to suboptimal glycemic control, even in those with normal BMI.
370 Hence, managing triglyceride levels might prove more efficacious in glycemic
371 control^[41]. This correlation underscored the importance of stringent lipid control,
372 particularly in patients with high HbA1c levels, given the heightened risk of diabetic
373 microvascular complications associated with elevated triglycerides^[42].

374 On the other hand, numerous real-world clinical investigations have explored how

375 Sacubitril/Valsartan affects cardiac parameters in HF patients. By augmenting NP levels,
376 inducing vasodilation, promoting sodium and urine excretion, and concurrently
377 inhibiting the RAAS, the advantages of Sacubitril/Valsartan seem particularly
378 pronounced in reducing heart failure mortality and reversing left atrial remodeling,
379 especially among patients with a low LVEF^[43, 44]. Within this study, featuring an
380 intermediate ejection fraction type of heart failure, subjects that used
381 Sacubitril/Valsartan manifested an obvious elevation in LVEF and decrease in LAD, in
382 line with previous research. NT-proBNP holds significance in predicting heart failure
383 prevalence, mortality, and prognosis^[45], given that NT-proBNP is not an enkephalin
384 substrate, this study opted for NT-proBNP analysis, excluding enkephalin degradation
385 and providing a more accurate reflection of changes in ventricular wall pressure after
386 Sacubitril/Valsartan treatment. Nevertheless, controversies persist regarding NT-
387 proBNP alterations. A meta-analysis by Kang et al., encompassing 3460 patients,
388 observed a significant reduction in NT-proBNP following Sacubitril/Valsartan
389 treatment^[46]. However, a double-blind randomized clinical trial comprising 335 heart
390 failure patients, reported no difference in NT-proBNP reduction between Valsartan and
391 Sacubitril/Valsartan treatments^[47]. This study aligns with the latter, primarily due to the
392 influence of age, liver and kidney function, infections, and other factors on NT-proBNP
393 levels.

394 Sacubitril/Valsartan exerts its influence on the glomerular filtration rate by expanding
395 the small incoming arterioles while constricting the small outgoing arterioles.
396 Additionally, it enhances the activity of the NP system, fostering cardiac improvement

397 through the cGMP pathway, coupled with an elevation in renal perfusion^[48].
398 Multicenter randomized trials have demonstrated Sacubitril/Valsartan's potential to
399 diminish the risk of renal deterioration in people with HF, whether they had HFrEF or
400 HFpEF^[49]. However, outcomes from Haynes's HARP-III trial revealed that, after a 12-
401 month course, the impact on renal function with Sacubitril/Valsartan was comparable
402 to that of irbesartan^[50]. In a separate 8-week investigation, Huang et al. reported a 22.0%
403 incidence of renal function decline in HFrEF patients receiving Sacubitril/Valsartan^[51].
404 In this study, although the Sacubitril/Valsartan group exhibited lower creatinine levels
405 and higher eGFR levels post-treatment, no statistical distinction emerged between the
406 two groups. The included individuals exhibited suboptimal average renal function,
407 potentially accounting for this variation. The CKD population under scrutiny presented
408 heightened hemodynamic alterations and inflammatory responses, and the
409 observational period was relatively brief, preventing the manifestation of the enduring
410 renal benefits of Sacubitril/Valsartan.

411 Concerning alterations in blood pressure, the study revealed a notable reduction in
412 SBP among patients with CKD and CHF in intergroup comparisons. However, ²²there
413 was no significant change in DBP between the two groups. Prior research has
414 consistently affirmed the effectiveness of Sacubitril/Valsartan in effectively lowering
415 blood pressure, substantiating its utility in blood pressure management. Throughout the
416 course of treatment, the potassium levels in both groups remained within the safe range,
417 with no statistically significant differences.

418 **Strengths and limitations of the study**

419 This study presented the following advantages. First, the pioneering inclusion of
420 patients grappling with both CKD and CHF established a crucial groundwork for lipid
421 management, particularly in the context of employing Sacubitril/Valsartan within this
422 specific demographic. Second, the focus of this inquiry on elucidating the influence of
423 Sacubitril/Valsartan on lipid metabolism, in comparison to Valsartan, has introduced
424 novel perspectives that may hold potential for broadening the scope of
425 Sacubitril/Valsartan's utility in future scenarios.

426 However, this study was constrained by some limitations. First, patient data was
427 obtained through the electronic medical record system, with the adjustment of
428 medication doses for patients not consistently documented in real-time. The study
429 duration was brief, the sample size limited, and post-16-week blood lipid status of
430 patients was not monitored. Second, factors such as underlying patient conditions,
431 irregular drug usage in treatments, and dietary alterations may influence the study
432 outcomes, despite the absence of intergroup differences in baseline data. Third, the
433 glomerular filtration rate of the included subjects was below 60 mL/min/1.73m², and
434 renal impairment exerted a large effect on NT-proBNP, preventing a comprehensive
435 examination of cardiac function alterations due to the inability to completely exclude
436 the influence of renal factors. Therefore, the findings of the study necessitate
437 exploration through broader, multicenter studies with larger sample sizes and extended
438 prospective durations.

439 **4 Conclusions**

440 In comparison to Valsartan, Sacubitril/Valsartan demonstrates the capacity to diminish

29
441 levels of TG, elevates levels of HDL-C and ApoA in patients with CKD complicated
442 with CHF, particularly demonstrating efficacy in TG reduction. Additionally,
443 Sacubitril/Valsartan exhibits the potential to enhance cardiac function in patients
444 without inducing notable deterioration of renal function. BMI and HbA1c emerge as
445 influential factors for changes in TG levels, irrespective of Sacubitril/Valsartan. The
446 promise of Sacubitril/Valsartan in modulating lipid metabolism is evident.

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- 4

Yin Ruixing, Chen Yuming, Pan Shangling, He Fengping et al. "Comparison of Lipid Levels, Hyperlipidemia Prevalence and Its Risk Factors between Guangxi Hei Yi Zhuang and Han Populations", Archives of Medical Research, 2006
Crossref

24 words — < 1%
- 5

Jingyi Ren, Jufeng Liang, Jiaqi Wang, Bowen Yin et al. "Vascular benefits of vitamin C supplementation against fine particulate air pollution in healthy adults: A double-blind randomised crossover trial", Ecotoxicology and Environmental Safety, 2022
Crossref

23 words — < 1%
- 6

Xia Zhong, Huachen Jiao, Dongsheng Zhao, Mengqi Yang, Jing Teng. "Association of Serum Apolipoprotein B Levels with Paroxysmal Atrial Fibrillation: A Case-Control Study", Research Square Platform LLC, 2022
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-
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receptor β in a rat chemical cystitis model", Neurourology and Urodynamics, 2007

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"Unified platform for multimodal voxel-based analysis to evaluate tumour perfusion and diffusion characteristics before and after radiation treatment evaluated in metastatic brain cancer", The British Journal of Radiology, 2019

Crossref

26 Jing Xiong, Mingyu Qi, He Shi, Deli Zou, Quanxiang Liu, Wei Cheng. 8 words — < 1%

"Association between osteoporosis and coronary heart disease in the elderly", Research Square Platform LLC, 2023

Crossref Posted Content

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"Beyond LDL-c: The importance of serum oxidized LDL in predicting risk for type 2 diabetes in the middle-aged Asian Indians", Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2019

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