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Original Article



ORIGINAL ARTICLE

# The association of vascular access flow with sacubitril/valsartan and left ventricular ejection fraction in hemodialysis patients with heart failure with reduced ejection fraction

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## ABSTRACT

**Background.** Sacubitril/valsartan improves heart function in maintenance hemodialysis (HD) patients with heart failure with a reduced ejection fraction of <40% (HFrEF). However, the effect of sacubitril/valsartan on vascular access flow (Qa) in this population is still unclear.

**Methods.** Hemodialysis patients with HFrEF were enrolled and divided into sacubitril/valsartan and non-sacubitril/valsartan treatment groups and received echocardiographic and Qa measurements at baseline and after 12 months. We compared the changes in Qa (△Qa) and echocardiographic parameters after 12 months. Correlations between △Qa and echocardiographic parameters were also examined. Multiple linear regression analysis was performed to predict △Qa.

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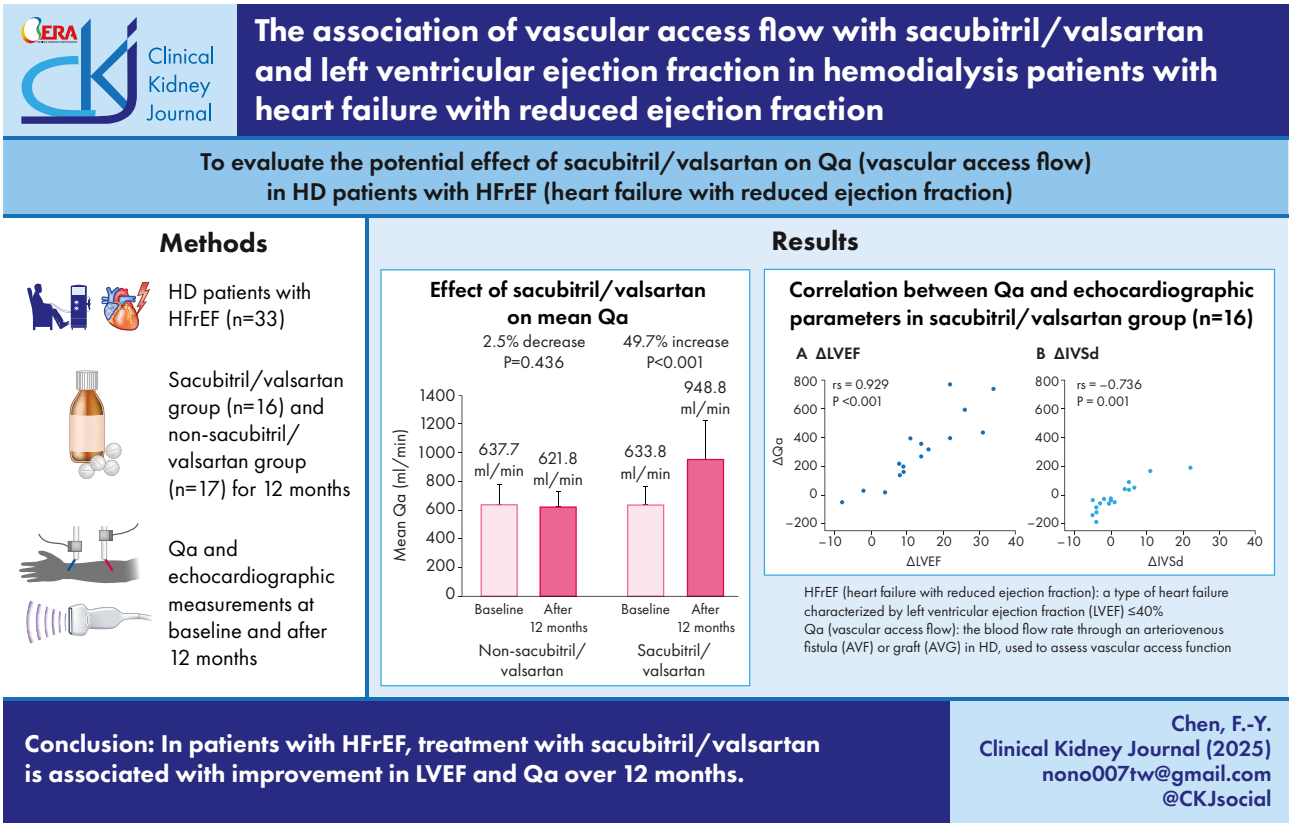
**Results.** Thirty-three HD patients with HFrEF were enrolled. Sixteen patients received sacubitril/valsartan treatment. Their mean Qa significantly increased from 633.8 to 948.8 mL/min ($P < .001$). There was no significant change in Qa for the non-sacubitril/valsartan treatment group (from 637.7 to 621.8 mL/min; $P = .436$). The change in left ventricular ejection fraction (△LVEF) differed significantly between the sacubitril/valsartan and conventional treatment groups (13.63 ± 11.35% and 1.59 ± 6.99%, respectively; $P = .001$). The △Qa was significantly correlated with △LVEF ($r_s = 0.929$; $P < .001$) and with the change in interventricular septum thickness in diastole (△IVSd, $r_s = -0.736$; $P = .001$) in the sacubitril/valsartan group. The △Qa was predicted as $-44.034 + 15.868 \times$ △LVEF$-25.072 \times$ △IVSd $+ 145.964 \times A$ ($A = 1$ for sacubitril/valsartan use and $A = 0$ for non-sacubitril/valsartan treatment) mL/min ($R^2 = 0.909$).
**Conclusion.** In HD patients with HFrEF, treatment with sacubitril/valsartan is associated with improvement in LVEF and Qa over 12 months.

## GRAPHICAL ABSTRACT




**Keywords:** access flow, heart failure with reduced ejection fraction, hemodialysis, sacubitril/valsartan, vascular access

## INTRODUCTION

Vascular access is vital for the well-being and survival of hemodialysis (HD) patients [1]. The preferred vascular access is an arteriovenous fistula (AVF), a direct connection between an artery and vein, or an arteriovenous graft (AVG), where an artificial vascular graft (polytetrafluoroethylene) is used for punctures when superficial veins are abandoned. However, AVF and AVG can experience dysfunction and diminished vascular access flow (Qa). Qa, the volume of blood flow per minute (mL/min), depends on perfusion pressure and access resistance. Various factors can influence Qa, including systemic hemodynamics, the size and endothelial function of vessels supplying and draining the access site, and significant vascular stenosis [2]. Over time, neointimal hyperplasia induced by hemodynamic factors such as wall shear stress or inflammatory changes associated with vascular remodeling can lead to stenosis [3]. This progression may cause thrombosis, ultimately resulting in access failure. Loss of vascular access patency not only reduces HD efficiency, potentially causing underdialysis and increasing morbidity and mortality rates but also diminishing patients' quality of life [1]. Hemodynamic factors, cardiac output, and arterial segment resistance are chief determinants of Qa in both AVF and AVG. There is an interrelation between cardiac output and Qa. Wakabayashi *et al.* Keiichi et al. demonstrated that postoperative arteriovenous (AV) access blood flow is lower in patients with reduced ejection fraction than those with normal ejection fraction [4]. Left ventricular ejection fraction (LVEF) may also influence AVF maturation. One of the most critical determinants of AVF maturation is the ability of the inflow artery and outflow vein to respond to the increased blood flow that occurs upon

## KEY LEARNING POINTS

**What was known:**

- Sacubitril/valsartan improved left ventricular systolic and diastolic function in patients with heart failure with reduced ejection fraction <40% (HFrEF) and end-stage renal disease.
- Arteriovenous fistula or arteriovenous graft are the preferred types of vascular access for maintenance hemodialysis (HD) and sufficient vascular access flow (Qa) is crucial for hemodialysis adequacy.
- This study aims to investigate the effect of sacubitril/valsartan on Qa of vascular access in HD patients with HfrEF.

**This study adds:**

- A 12-month treatment with sacubitril/valsartan improves Qa in HD patients with HFrEF compared with non-sacubitril/valsartan treatment.
- In addition to the sacubitril/valsartan treatment, the improvement of left ventricular ejection fraction (LVEF) and interventricular septum thickness in diastole are also associated with the increase of Qa.

**Potential impact:**

- Improvement in access flow is possibly a beneficial effect of treating reduced LVEF with sacubitril/valsartan.

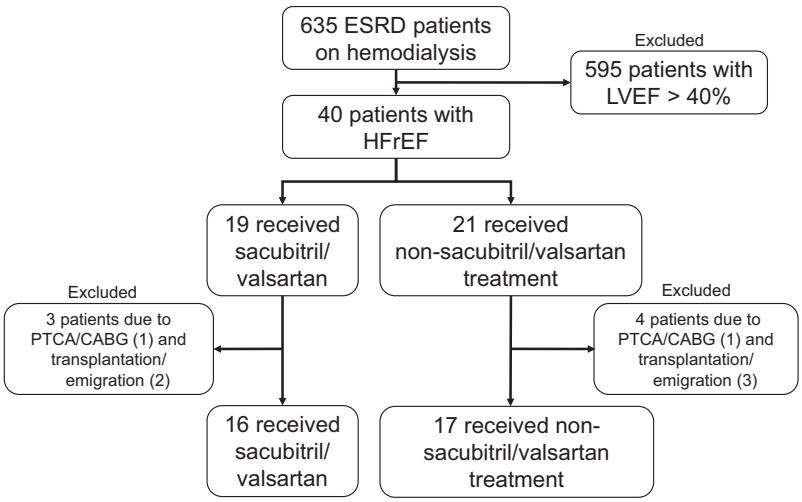



**Figure 1:** Study patient enrollment flowchart. LVEF, left ventricular ejection fraction; HfrEF, heart failure with reduced ejection fraction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

anastomosis of the artery and vein, often screened by ultrasound with a Qa record. Farrington *et al*. demonstrated that higher preoperative LVEF was associated with greater unassisted AVF maturation [5]. Gan *et al*. also showed that preoperative LVEF was an independent influential factor for AVF maturation [6].

Cardiovascular disease is the most common cause of death in patients with end-stage renal disease (ESRD) on HD, with heart failure (HF) being a major type in this population. Approximately 20% of HD patients have heart failure with reduced ejection fraction (HFrEF) [7]. Dialysis patients with HF have a lower 2-year survival rate after initiation of dialysis (65%) compared with those without HF (83%) [8]. Sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), has been recommended in clinical practice guidelines to reduce morbidity and mortality in patients with chronic symptomatic HfrEF [9]. A retrospective cohort study of 48 patients with HFrEF treated with sacubitril/valsartan showed a significant increase in LVEF from 25.33% at baseline to 30.14% at follow-up ($P < .001$) [10]. Observational studies exploring the effects of sacubitril/valsartan on cardiovascular risk in patients with chronic kidney disease (CKD) showed significant improvement in LVEF [11]. Another retrospective study found that sacubitril/valsartan could safely improve LVEF in HFrEF patients with ESRD on HD or peritoneal dialysis (PD) [12]. Recent research indicates that sacubitril/valsartan can improve LVEF and diastolic function, in patients with HFrEF and ESRD on HD or PD [13].

While sacubitril/valsartan has shown promise in managing HF, its association with Qa in HD patients remains unexplored. We propose that sacubitril/valsartan may potentially enhance Qa by improving LVEF. This study therefore aims to investigate the effect of sacubitril/valsartan on the Qa of maintenance HD patients with HFrEF.

## MATERIALS AND METHODS

### Study design

Annual cardiac echocardiography is routinely performed for heart function and structural screening at the Taipei Veterans General Hospital HD center. We retrospectively collected data on maintenance HD patients with AVF or AVG diagnosed with HFrEF using cardiac echocardiography results in 2019. The in-

**Table 1: Baseline clinical parameters.**

| Parameter | Sacubitril/valsartan ($n = 16$) | Non-sacubitril/valsartan treatment ($n = 17$) | $P$-value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, years | 63.62 ± 11.44 | 72.41 ± 12.49 | .079 |
| Female | 4 (25) | 7 (41.2) | .465 |
| Dialysis vintage, years | 4.37 ± 5.30 | 5.06 ± 3.23 | .177 |
| Weight, kg | 60.24 ± 8.96 | 62.21 ± 21.29 | .638 |
| Height, cm | 163.4 ± 7.62 | 162.5 ± 8.56 | .810 |
| SBP, mm Hg | 136.88 ± 20.16 | 144.88 ± 14.95 | .103 |
| DBP, mm Hg | 68.69 ± 11.12 | 73.41 ± 12.86 | .330 |
| Medical history | | | |
| Diabetes | 10 (62.5) | 11 (64.7) | 1.000 |
| Hypertension | 14 (87.5) | 14 (82.4) | 1.000 |
| Coronary artery disease | 10 (62.5) | 13 (76.5) | .465 |
| Causes of ESRD | | | |
| Diabetic kidney disease | 10 (62.5) | 10 (58.8) | 1.000 |
| Chronic glomerulonephritis | 4 (25) | 6 (35.3) | .708 |
| Polycystic kidney disease | 0 (0) | 1 (5.9) | 1.000 |
| Others | 2 (12.5) | 0 (0) | .227 |
| Medications | | | |
| ARNI | 16 (100) | 0 (0) | <.001* |
| ACEI or ARB | 1 (6.3) | 10 (58.8) | .002* |
| $\beta$-Blocker | 12 (75) | 16 (94.1) | .175 |
| MRA | 2 (12.5) | 4 (23.5) | .656 |
| Digoxin | 0 (0) | 1 (5.9) | 1.000 |
| Ivabradine | 4 (25) | 1 (5.9) | .175 |
| Calcium channel blocker | 2 (12.5) | 8 (47.1) | .057 |
| Nitrate | 7 (43.8) | 3 (17.6) | .141 |
| Antiplatelet | 7 (43.8) | 7 (41.2) | 1.000 |
| Anticoagulant | 1 (6.3) | 1 (5.9) | 1.000 |
| Laboratory data | | | |
| Hemoglobin, g/dL | 10.17 ± 1.43 | 10.28 ± 2.30 | .600 |
| Albumin, g/dL | 3.87 ± 0.39 | 3.68 ± 0.58 | .347 |
| HbA1c, % | 6.15 ± 1.65 | 6.69 ± 2.37 | .709 |
| Potassium, mmol/L | 4.28 ± 0.70 | 4.47 ± 0.75 | .625 |
| Calcium, mg/dL | 8.69 ± 0.78 | 8.65 ± 0.80 | .866 |
| Phosphate, mg/dL | 4.28 ± 1.43 | 5.12 ± 1.60 | .124 |

Continuous variables are presented as mean ± SD and categorical variables are presented as numbers and percentages.
SBP, systolic blood pressure; DBP, diastolic blood pressure; ESRD, end-stage renal disease; ARNI, angiotensin receptor-neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; HbA1c, hemoglobin A1c. *$P < 0.05$.

clusion criteria for the study were as follows: patients aged ≥18 years with ESRD undergoing HD via AVF or AVG for at least 6 months and a baseline LVEF of ≤40%. Patients were excluded if they had experienced acute coronary syndrome within the previous 3 months, had inadequate dialysis, or had undergone percutaneous transluminal coronary angioplasty or coronary artery bypass grafting during the follow-up period. For patients who were enrolled, we divided them into two groups based on their treatment for heart failure: the sacubitril/valsartan group and the non-sacubitril/valsartan treatment group.

## Data collection

Patient-related clinical data, medical history, and medication lists were obtained from hospital medical records. Using 2-D echocardiography (Philips EPIQ CVx), LVEF was evaluated the day after the HD session to eliminate potential biases due to HD-induced myocardial stunning or fluid overload. The following echocardiographic parameters were collected: left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular internal diameter at end-diastole (LVIDd), left ventricular internal diameter at end-systole (LVIDs), left atrial dimension (LAD), left atrial volume index, mitral E/A ratio (MV E/A), lateral E/e′ ratio, medial E/e′ ratio (E/Med E′), peak tricuspid regurgitation velocity, interventricular septum thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), and aortic root diameter. Measurements were conducted according to the European Association of Cardiovascular Imaging and the updated American Society of Echocardiography guidelines. The left ventricular (LV) mass index was calculated using LV mass divided by body surface area, where LV mass (g) = 0.8 [1.04 ([LVIDd + IVSd + LVPWd]$^3$ – LVIDd$^3$)] + 0.6. All the enrolled patients had their cardiac ultrasound data recorded at enrollment and again after 12 months. Blood biochemistry data were examined in all patients monthly. Blood pressure measurements were recorded during the HD sessions three times a week. Vascular access flow was measured by duplex ultrasonography.

## Statistical analysis

All statistical analyses were performed using SPSS version 25.0 and GraphPad Prism. Continuous variables are presented as mean ± SD and categorical variables are presented as numbers

**Table 2: Baseline echocardiographic parameters and vascular access flow.**

| Parameters | Sacubitril/valsartan ($n = 16$) | Non-sacubitril/valsartan treatment ($n = 17$) | $P$-value |
|---|---|---|---|
| LV systolic function | | | |
| LVEF, % | 30.38 ± 5.92 | 35.64 ± 4.87 | .027* |
| LVEDV, mL | 145.43 ± 45.48 | 129.94 ± 39.72 | .225 |
| LVESV, mL | 100.50 ± 35.77 | 84.24 ± 25.03 | .253 |
| LVIDd, mm | 58.69 ± 5.07 | 56.71 ± 8.64 | .612 |
| LVIDs, mm | 49.56 ± 5.67 | 45.38 ± 7.71 | .143 |
| LV diastolic function | | | |
| LAD, mm | 49.06 ± 5.88 | 47.00 ± 6.07 | .175 |
| LAVI, mL/m$^2$ | 60.65 ± 28.22 | 53.65 ± 15.35 | .650 |
| MV E/A | 1.57 ± 0.75 | 1.36 ± 0.60 | .314 |
| E/Lat E′ | 17.45 ± 9.17 | 18.36 ± 9.09 | .776 |
| E/Med E′ | 27.06 ± 19.98 | 25.61 ± 8.99 | .484 |
| Peak TR Vel, cm/s | 284.68 ± 72.02 | 314.05 ± 89.30 | .356 |
| LV hypertrophy | | | |
| IVSd, mm | 10.81 ± 2.01 | 11.60 ± 1.69 | .150 |
| LVPWd, mm | 10.38 ± 1.86 | 11.71 ± 1.32 | .031* |
| LV mass index, g/m$^2$ | 161.78 ± 46.25 | 174.00 ± 50.32 | .465 |
| Other parameters | | | |
| Aortic root, mm | 33.69 ± 5.50 | 35.01 ± 5.66 | .448 |
| Vascular access flow | | | |
| Qa, mL/min | 633.75 ± 136.03 | 637.65 ± 137.46 | .894 |

Continuous variables are presented as mean ± SD.
LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal diameter at end-systole; LAD, left atrial dimension; LAVI, left atrial volume index; MV E/A, mitral E/A ratio; E/Lat E′, lateral E/e′ ratio; E/Med E′, medial E/e′ ratio; Peak TR Vel, peak tricuspid regurgitation velocity; IVSd, interventricular septum thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole; Qa, access flow. *$P < 0.05$.

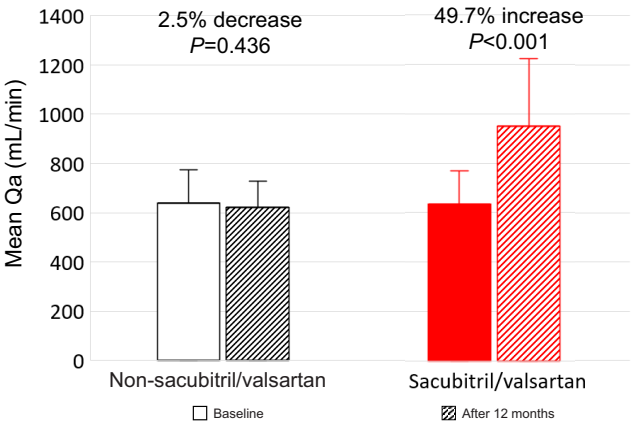



**Figure 2:** Comparison of mean access flow (Qa) between non-sacubitril/valsartan and sacubitril/valsartan treatment groups at baseline and after 12 months.

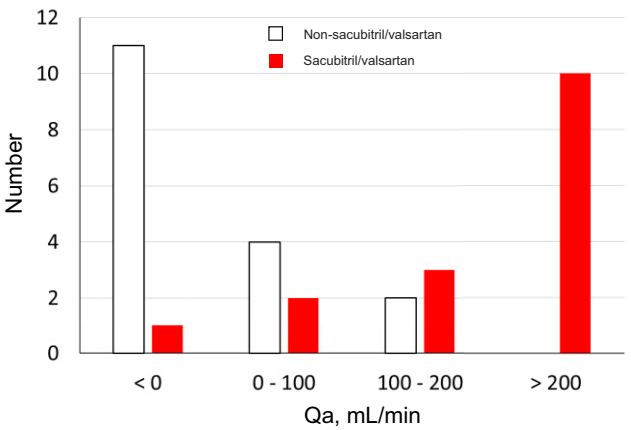



**Figure 3:** Comparison of change in access flow (△Qa) between non-sacubitril/valsartan and sacubitril/valsartan treatment groups.

and percentages. The Mann–Whitney $U$ test compared the data of the two groups at baseline and after the 12-month treatment. The Wilcoxon signed-rank test compared the self-matched data before and after treatment in each group. Fisher's exact test analyzed the categorical variables. All tests were two-tailed and $P < .05$ was considered statistically significant.

The outcome measures compared between the two groups were change in Qa (△Qa), echocardiographic parameters, and clinical events after the 12-month treatment. Spearman rank correlation analysis examined the correlation between △Qa and the changes in echocardiographic parameters in the two groups. Multiple linear regression analysis was performed to evaluate the correlation of △Qa with the changes in echocardiographic parameters and the use of sacubitril/valsartan.

## RESULTS

### Baseline clinical parameters of the participants

A total of 635 patients undergoing regular HD with AVF or AVG received cardiac echocardiographic screening, with 40 (6.3%) having a baseline LVEF of ≤40% (Fig. 1). Of these 40 patients with HFrEF, two were excluded due to coronary angioplasty or coronary artery bypass graft surgery, and five did not complete the 12-month echocardiographic follow-up due to transplant or emigration. Thirty-three patients with HFrEF enrolled in the study,

**Table 3: Changes in echocardiographic parameters, Qa, and clinical events in patients with and without sacubitril/valsartan.**

| Parameters | Sacubitril/valsartan ($n = 16$) | Non-sacubitril/valsartan treatment ($n = 17$) | $P$-value |
|---|---|---|---|
| LV systolic function | | | |
| △LVEF, % | 13.63 ± 11.35 | 1.59 ± 6.99 | .001* |
| △LVEDV, mL | −21.64 ± 46.85 | −3.22 ± 58.36 | .747 |
| △LVESV, mL | −30.50 ± 36.83 | −11.12 ± 21.89 | .092 |
| △LVIDd, mm | −4.31 ± 9.39 | −0.34 ± 3.35 | .406 |
| △LVIDs, mm | −8.63 ± 8.94 | −0.81 ± 4.18 | .002* |
| LV diastolic function | | | |
| △LAD, mm | −3.25 ± 5.45 | −1.60 ± 3.76 | .255 |
| △LAVI, mL/m$^2$ | −11.42 ± 21.09 | 0.64 ± 11.68 | .087 |
| △MV E/A | −0.67 ± 0.69 | 0.09 ± 0.32 | .001* |
| △E/Lat E′ | −3.77 ± 5.85 | −0.81 ± 6.59 | .115 |
| △E/Med E′ | −7.50 ± 11.86 | 2.05 ± 5.98 | .018* |
| △Peak TR Vel, cm/s | −47.71 ± 59.44 | −21.71 ± 42.7. | .185 |
| LV hypertrophy | | | |
| △IVSd, mm | 0.12 ± 2.13 | −0.12 ± 1.71 | .907 |
| △LVPWd, mm | 0.19 ± 1.87 | −0.61 ± 1.44 | .173 |
| △LV mass index, g/m$^2$ | −18.83 ± 52.76 | −9.70 ± 37.62 | .845 |
| Other parameters | | | |
| △Aortic root, mm | −0.69 ± 3.22 | 0.04 ± 1.99 | .662 |
| Vascular access flow | | | |
| △Qa, mL/min | 315.00 ± 244.84 | −15.88 ± 102.29 | <.001* |
| Vascular access interventions | | | |
| All | 5 (31.3) | 6 (35.3) | .731 |
| Endovascular intervention | 5 (31.3) | 4 (23.5) | .800 |
| Surgical intervention | 1 (6.3) | 5 (29.4) | .113 |
| Admissions | | | |
| All | 7 (43.8) | 10 (58.8) | .494 |
| CV admission | 4 (25) | 5 (29.4) | 1.000 |

Continuous variables are presented as mean ± SD and categorical variables are presented as numbers and percentages.
LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal diameter at end-systole; LAD, left atrial dimension; LAVI, left atrial volume index; MV E/A, mitral E/A ratio; E/Lat E′, lateral E/e′ ratio; E/Med E′, medial E/e′ ratio; Peak TR Vel, peak tricuspid regurgitation velocity; IVSd, interventricular septum thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole; Qa, access flow; CV, cardiovascular. *$P < 0.05$.

with a mean dialysis vintage of 4.7 years. Of these, 16 patients received sacubitril/valsartan, starting at 50 mg (24 mg sacubitril + 26 mg valsartan) twice daily, with dose titration every 2–4 weeks to a maximum of 200 mg (97 mg sacubitril + 103 mg valsartan) twice daily. The remaining 17 patients received conventional treatment. Table 1 presents the baseline clinical parameters for the sacubitril/valsartan and non-sacubitril/valsartan treatment groups. No statistically significant differences were observed between the groups in terms of clinical characteristics, causes of ESRD, and medical history. Fifty-nine per cent of patients in the non-sacubitril/valsartan treatment group were prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The sacubitril/valsartan group had a lower utilization rate of calcium channel blockers compared with the non-sacubitril/valsartan treatment group (12.5% vs 47.1%, $P = .057$) and a lower mean blood pressure (136±20 vs 145±15 mm Hg, $P = .103$). Among the 33 study patients, the mean LVEF was 33% and the mean left ventricular LVESV was 93 mL, indicating moderate to severe systolic heart failure. The mean mitral E/A ratio (MV E/A) was 1.5, the average E/e′ ratio was 22.5, and the peak tricuspid regurgitation velocity was 299 cm/s, reflecting increased left ventricular filling pressure. Baseline echocardiographic parameters, as shown in Table 2, revealed no significant differences except for a significantly lower LVEF in the sacubitril/valsartan group compared with the non-sacubitril/valsartan treatment group (30.38 ± 5.92% vs 35.64 ± 4.87%, respectively; $P = .027$), suggesting that clinicians tended to prescribe sacubitril/valsartan for patients with more severe systolic dysfunction.

## Change in Qa

The baseline mean Qa for the sacubitril/valsartan group was 633.8 mL/min, which significantly increased to 948.8 mL/min ($P < .001$) after 12 months of treatment. In contrast, no significant change in Qa was observed in the non-sacubitril/valsartan treatment group, where values decreased from 637.7 to 621.8 mL/min ($P = .436$) over the same period (Fig. 2). All but one patient receiving sacubitril/valsartan for 12 months experienced a positive change in Qa, with most showing an increase of >200 mL/min. Conversely, Qa decreased in most patients receiving non-sacubitril/valsartan treatment after 12 months (Fig. 3).

## Changes in echocardiographic parameters, Qa, and clinical events

All patients received regular dialysis treatment, and their dry weight remained consistent during the study period. The changes in the echocardiographic parameters, Qa, and clinical events are compared between the two groups in Table 3. There were statistically significant differences seen between the sacubitril/valsartan group compared with the non-sacubitril/valsartan treatment group in △LVEF (13.63 ± 11.35% vs 1.59 ± 6.99%, respectively; $P = .001$), △LVIDs (−8.63 ± 8.94 vs −0.81 ± 4.18, respectively; $P = .002$), △MV E/A (−0.67 ± 0.69 vs 0.09 ± 0.32, respectively; $P = .001$), △E/Med E′ (−7.50 ± 11.86 vs 2.05 ± 5.98, respectively; $P = .018$), and △Qa (315.00 ± 244.84 vs −15.88 ± 102.29, respectively; $P < .001$).

**Table 4: Correlation between △Qa and changes in echocardiographic parameters.**

| Parameters | Sacubitril/valsartan ($n = 16$) | Non-sacubitril/valsartan treatment ($n = 17$) |
|---|---|---|
| LV systolic function | | |
| △LVEF, % | $r_s = 0.929$<br>$P < .001^*$ | $r_s = 0.876$<br>$P < .001^*$ |
| △LVEDV, mL | $r_s = -0.433$<br>$P = .122$ | $r_s = -0.063$<br>$P = .837$ |
| △LVESV, mL | $r_s = -0.617$<br>$P = .019^*$ | $r_s = -0.306$<br>$P = .310$ |
| △LVIDd, mm | $r_s = -0.258$<br>$P = .335$ | $r_s = -0.094$<br>$P = .721$ |
| △LVIDs, mm | $r_s = -0.424$<br>$P = .101$ | $r_s = -0.281$<br>$P = .275$ |
| LV diastolic function | | |
| △LAD, mm | $r_s = -0.309$<br>$P = .243$ | $r_s = 0.562$<br>$P = .019^*$ |
| △LAVI, mL/m$^2$ | $r_s = -0.494$<br>$P = .103$ | $r_s = -0.512$<br>$P = .073$ |
| △MV E/A | $r_s = -0.035$<br>$P = .914$ | $r_s = -0.301$<br>$P = .369$ |
| △E/Lat E' | $r_s = -0.459$<br>$P = .156$ | $r_s = -0.424$<br>$P = .149$ |
| △E/Med E' | $r_s = -0.379$<br>$P = .250$ | $r_s = -0.072$<br>$P = .816$ |
| △Peak TR Vel, cm/s | $r_s = -0.440$<br>$P = .115$ | $r_s = -0.375$<br>$P = .207$ |
| LV hypertrophy | | |
| △IVSd, mm | $r_s = -0.736$<br>$P = .001^*$ | $r_s = -0.342$<br>$P = .178$ |
| △LVPWd, mm | $r_s = -0.544$<br>$P = .03^*$ | $r_s = -0.495$<br>$P = .043^*$ |
| △LV mass index, g/m$^2$ | $r_s = -0.734$<br>$P = .001^*$ | $r_s = -0.317$<br>$P = .215$ |
| Other parameters | | |
| △Aortic root, mm | $r_s = 0.244$<br>$P = .363$ | $r_s = 0.346$<br>$P = .174$ |

LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal diameter at end-systole; LAD, left atrial dimension; LAVI, left atrial volume index; MV E/A, mitral E/A ratio; E/Lat E′, lateral E/e′ ratio; E/Med E′, medial E/e′ ratio; Peak TR Vel, peak tricuspid regurgitation velocity; IVSd, interventricular septum thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole. *$P < 0.05$.

During the 12-month follow-up, although there were no significant differences in the vascular access intervention times and admissions between groups, there was a tendency of lower frequency of surgical interventions in the sacubitril/valsartan group, which may be related to the increase of Qa by sacubitril/valsartan.

### Correlation between △Qa and changes in cardiac echocardiographic parameters

In Table 4 and Fig. 4, in the sacubitril/valsartan group, △Qa was positively correlated with △LVEF ($r_s = 0.929$; $P < .001$) and was negatively correlated with △LVESV ($r_s = -0.617$, $P = .019$), △IVSd ($r_s = -0.736$; $P = .001$), △LVPWd ($r_s = -0.544$; $P = .03$), and △LV mass index ($r_s = -0.734$; $P = .001$). In the non-sacubitril/valsartan treatment group, △Qa was positively correlated with △LVEF ($r_s = 0.876$; $P < .001$) and △LAD ($r_s = 0.562$; $P = .019$) and was negatively correlated with △LVPWd ($r_s = -0.495$; $P = .043$). However, compared with the sacubitril/valsartan group, no significant correlation was found between △Qa and △LVESV, △IVSd, and △LV mass index. Using the total number of 33 patients for the multiple linear regression analysis, △Qa can be predicted as $-44.034 + 15.868 \times$ △LVEF $- 25.072 \times$ △IVSd $+ 145.964 \times A$ ($A = 1$ for sacubitril/valsartan use or $A = 0$ for non-sacubitril/valsartan treatment) mL/min ($R^2 = 0.909$). For every 1% increase in LVEF there will be an increase in Qa of ~15 mL/min, while for every 1 mm decrease in IVSd there will be an increase in Qa of ~25 mL/min. A 12-month treatment of sacubitril/valsartan will result in an increase in Qa of ~150 mL/min.

## DISCUSSION

To our knowledge, this is the first study to examine the possible effect of sacubitril/valsartan on Qa in maintenance HD patients with HFrEF. Our findings indicate that sacubitril/valsartan significantly improves Qa compared with non-sacubitril/valsartan treatments, likely through its effects on enhancing cardiac function. These results indicate that sacubitril/valsartan could be beneficial in managing HFrEF in the HD population, potentially by improving both cardiovascular and dialysis outcomes.

Several significant findings were observed in this study. First, sacubitril/valsartan significantly improved Qa in HD patients with HfrEF, a benefit not observed in patients receiving non-sacubitril/valsartan treatments. Second, the improvement in Qa in these patients may be partially attributed to the improvement in echocardiographic parameters, particularly LVEF and IVSd. Third, the changes in Qa in HD patients with HFrEF after the 12-month treatment could be reasonably predicted by changes in LVEF and IVSd, and the use of sacubitril/valsartan. According to the predictive model, the improvement in Qa was possible in patients receiving non-sacubitril/valsartan treatment, provided their heart function significantly improved. The observed improvement in Qa in HD patients with HFrEF may be indirectly linked to enhanced LVEF following sacubitril/valsartan treatment. By improving cardiac function, sacubitril/valsartan may alleviate hemodynamic stress and enhance vascular function, thereby benefiting Qa. These findings should not be interpreted as a direct causal effect of sacubitril/valsartan on Qa, but rather as a reflection of the downstream benefits of improved cardiac performance in patients with HFrEF.

AVF is the preferred type of vascular access for maintenance HD, but it may have deleterious effects on cardiac structure and function [14, 15]. After AVF creation, blood is shunted from the high-pressure arterial side to the low-pressure venous side. The heart initially increases its output via increased heart rate and stroke volume [16]. As the fistula increases in size and blood flow, there are increases in left ventricular filling pressure and subsequent changes in atrial and ventricular chamber dimensions and function [14, 15]. The physiological consequences may lead to left ventricle dilation, reduced LVEF, and eventual high-output HF [14–17].

Decreased Qa in HD patients is typically associated with underlying stenosis and thrombosis. The development of progressive vascular access stenosis with subsequent vascular access failure contributes to significant morbidity and costs to the healthcare system [18]. In addition, recirculation occurs when Qa decreases, which lowers HD adequacy and affects long-term outcomes. Sacubitril/valsartan improves Qa,

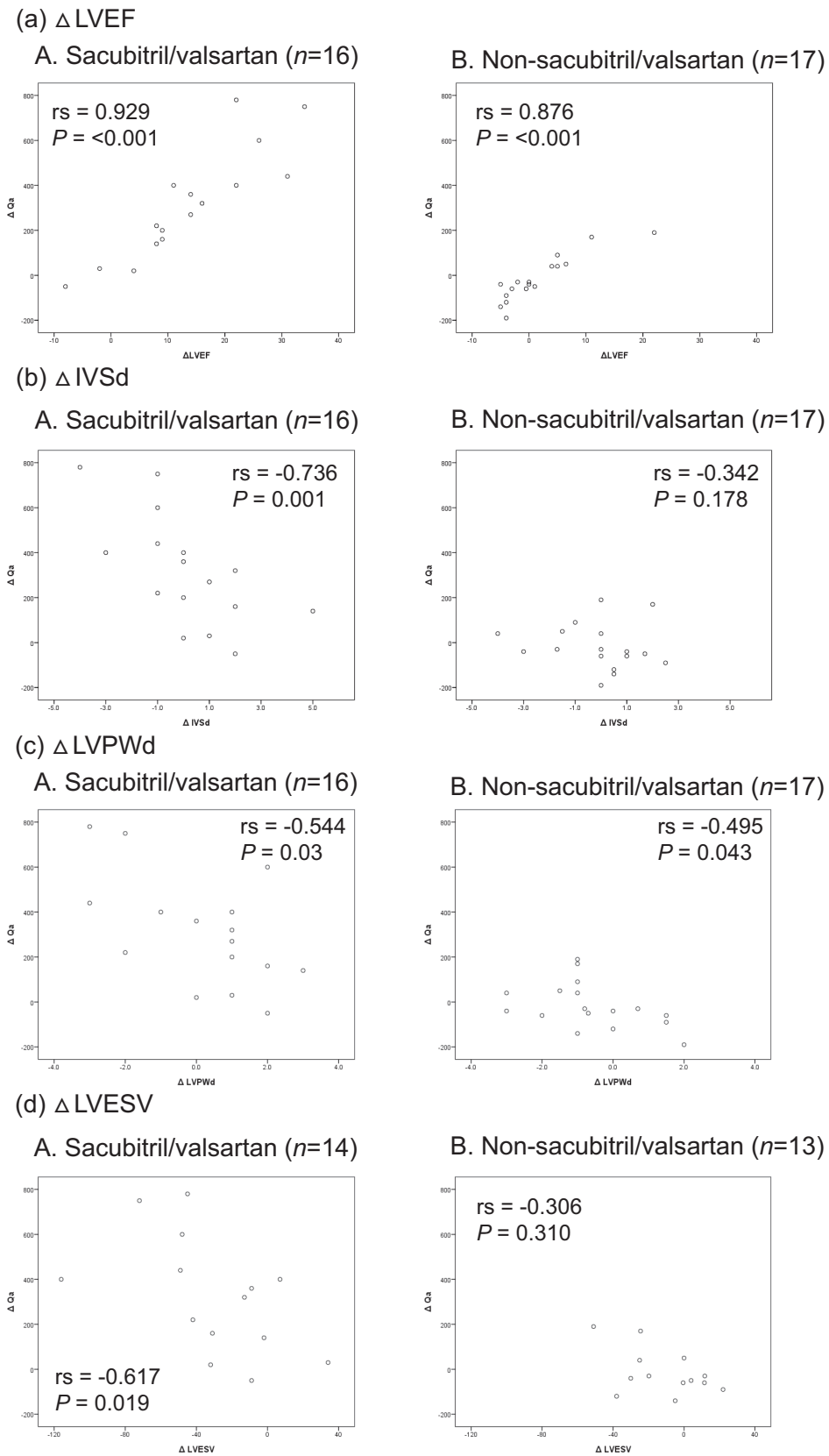



**Figure 4:** Correlation of change in access flow (△Qa) and echocardiographic parameters between sacubitril/valsartan and non-sacubitril/valsartan treatment groups. LVEF, left ventricular ejection fraction; IVSd, interventricular septum thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole; LVESV, left ventricular end-systolic volume.

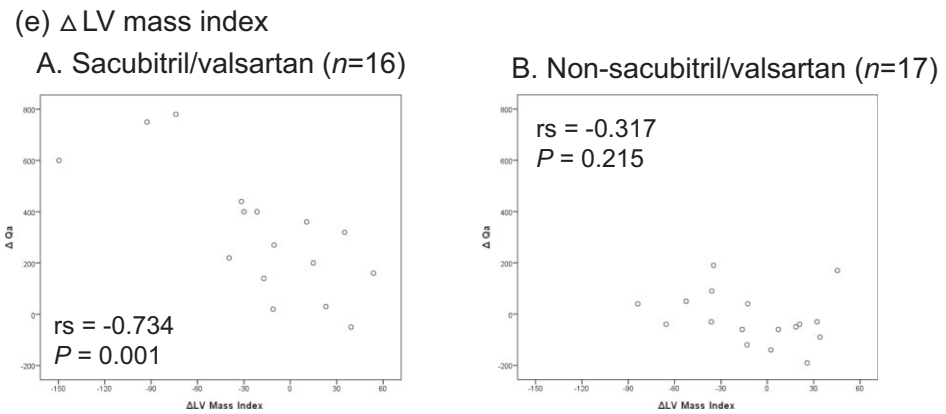



**Figure 4:** (Continued)

indicating the improvement in vascular access patency, which may decrease the thrombosis rate and further surgical intervention for these patients. However, there was no significant difference in the study.

Sacubitril/valsartan is a combination of an angiotensin receptor blocker (valsartan) and a neprilysin inhibitor prodrug (sacubitril). In binding to the angiotensin II receptor type 1, valsartan attenuates the vasoconstrictive, sodium-retaining, and profibrotic and promitotic effects of angiotensin II. Neprilysin is responsible for the breakdown of a variety of vasoactive peptides. Sacubitril inhibits neprilysin activity, thereby increasing endogenous levels of these peptides, resulting in increased vasodilation, natriuresis, and diuresis, along with a reduction in cardiac fibrosis and hypertrophy [19]. Previous studies have demonstrated that sacubitril/valsartan improves heart functions in HD and PD patients with HfrEF [13, 20, 21]. Our formula suggests that Qa is significantly correlated with three factors—treatment with sacubitril/valsartan, LVEF, and IVSd. Among these factors, treatment with sacubitril/valsartan is associated with the highest slope of Qa increase. It is reasonable to postulate that sacubitril/valsartan improves Qa through mechanisms other than only the improvement in heart function. In PARADIGM-HF, treatment with sacubitril/valsartan led to significant reductions in aldosterone, soluble suppression of tumorigenicity 2, matrix metalloproteinase-9, and its specific inhibitor, tissue inhibitor of metalloproteinases-1, reflecting a reduction in profibrotic signaling [22, 23]. Procollagen aminoterminal propeptide type I and III levels were also reduced compared with enalapril, reflecting reduced collagen synthesis. Reduced profibrotic signaling and collagen synthesis may partly explain the increased Qa, but further studies are needed to confirm this effect.

There are several limitations in the study. First the non-randomized design of this retrospective study may introduce selection bias, since the prescription of sacubitril/valsartan could have been influenced by unmeasured factors such as patient age, comorbidities, and disease duration. Second, the relatively small sample size of 33 participants may impact the generalizability of the findings, necessitating larger multi-center studies to confirm these results. In addition, the lack of randomization could introduce selection bias. The 12-month follow-up period may also be insufficient to assess the long-term effects of sacubitril/valsartan fully. Although Qa was measured using duplex ultrasonography, technique and operator skill variations may affect measurement accuracy. Lastly, the study was conducted at a single medical center, which may limit the applicability of the results to other settings and populations. Further research in diverse environments and larger cohorts is needed to validate these findings.

In conclusion, treatment with sacubitril/valsartan for 12 months is associated with improvement in LVEF and an improvement in Qa in HD patients with HFrEF. Future research is needed to explore the long-term effects of sacubitril/valsartan on vascular access and overall patient outcomes.

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The study protocol was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital (approval number 2021-12-007C), where it has been granted an exemption from requiring written informed consent.

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## AUTHORS' CONTRIBUTIONS

Conceptualization: C.-C.L. Data analysis: F.-Y.C., A.C.T., C.-M.C., S.-Y.L., T.-J.L., Z.-K.K., C.-T.T., Y.-H.F., C.-C.L. Resources: C.-Y.Y., K.-H.L., S.-M.O., M.-T.T., S.-Y.L., Y.-H.F., C.-C.L. Visualization: F.-Y.C., C.-M.C., Y.-H.F. Writing—original draft: F.-Y.C., A.C.T., Y.-H.F. Writing—review and editing: A.C.T., C.-M.C., C.-Y.Y., K.-H.L., S.-M.O., M.-T.T., S.-Y.L., T.-J.L., Z.-K.K., C.-T.T., Y.-H.F., C.-C.L. All authors have read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors, [Y.-H. Fu and C.-C.L.], upon reasonable request.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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