

Article

The Angiotensin Receptor–Neprilysin Inhibitor is Related to Lower Post-transplant Use of Extracorporeal Membrane Oxygenation

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) support after heart transplant is a risk factor for mortality in patients with severe graft dysfunction. Extensive studies have shown that angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril–valsartan has a significant effect on unloading and vascular remodeling in patients with heart failure; however, the impact of ARNIs on heart transplant recipients remains unknown. **Methods:** This observational, retrospective cohort study included 152 patients who underwent heart transplantation between January 2015 and April 2021. We excluded patients <18 years old and those who underwent re-transplantation or multiple organ transplantation. Patients were divided into two groups based on whether they received an ARNI for at least one month before transplant. The clinical data of recipients and donors from our institutional medical records and the China Organ Transplant Response System were interrogated. **Results:** In total, 67 patients (mean age, 49.6 years; 81% male) were treated with sacubitril/valsartan before transplant and included in the cohort. The total rate of post-transplant ECMO use was 21.1% (n = 32). Kaplan–Meier survival analysis showed a considerable increase in 6-month mortality in heart transplant recipients supported by ECMO (log-rank $p < 0.001$). The rate of ECMO use was significantly lower in patients treated with ARNIs than for those who were not (13% vs. 27%; $p = 0.041$). The multivariate analyses that included three models with different preset covariates demonstrated a lower risk of post-transplant ECMO support in patients receiving the ARNI (all $p < 0.05$). After propensity score matching, the results also suggested that ARNIs can be a protective factor against post-transplant ECMO support ($p = 0.042$). **Conclusion:** Pretransplant use of ARNI agents was associated with a lower risk of ECMO support after HT. Randomized controlled trials are warranted to confirm the effectiveness of ARNIs in improving post-transplant hemodynamics and reducing ECMO use in HT recipients.

Keywords

heart transplantation; sacubitril/valsartan; extracorporeal membrane oxygenation

Introduction

Heart transplantation (HT) is the final and most decisive treatment for advanced heart failure [1]. Despite the favorable long-term outcomes, severe graft dysfunction that occurs after the removal of the aortic cross-clamp is the predominant cause of early death after HT [2]. The risk factors associated with graft dysfunction reported in multiple studies include pulmonary hypertension, recipient age ≥ 60 years, diabetes mellitus, donor age ≥ 30 years, length of ischemic time ≥ 240 minutes, female donor, prior cardiac surgery, inotropic support, and amiodarone use [3–7]. Among them, pulmonary hypertension plays a significant role in the development of graft dysfunction since the contractile function of the right ventricle of the cardiac graft is vulnerable to high pulmonary vascular resistance and afterload [8]. Early donor interventions [9], such as the use of cold flush preservation fluid [2], early vasopressors [10–12], and thyroid hormone replacement, can be beneficial in reducing graft dysfunction after transplantation [11,13–15]. However, there are limited data regarding the potential medical management of recipients.

The current guidelines recommend angiotensin receptor–neprilysin inhibitors (ARNIs) as one of the cornerstones in treating heart failure with reduced ejection fraction [16]. ARNIs are superior to angiotensin-converting enzyme inhibitors in reducing the length of hospital stay and cardiovascular death [17–19]. In addition, ARNIs have greater vasodilator effects due to the simultaneous inhibition of neprilysin and angiotensin receptors [17]. Given the greater vasodilator effect of ARNIs and their new role in heart failure management, we sought to examine whether ARNI therapy was associated with reduced graft failure and the rate of extracorporeal membrane oxygenation (ECMO) support after HT [5,20].



Methods

Study Population

The Food and Drug Administration (FDA) approved the use of the ARNI agent sacubitril–valsartan in 2015 [21], the same year it was approved in China. In this observational retrospective study, we summarized and screened the clinical data of all patients receiving HT from January 2015 to April 2021. Recipients who were <18 years old and those who received multiple organ transplantation or retransplantation were excluded from the analysis. Patients <18 years were excluded because (1) the number of recipients was low, and (2) the differences in choice and dosage of medication and postoperative management between adolescent and adult patients may increase bias in the analyses. Patients who underwent multiple organ transplantations were excluded due to their complicated pretransplant status with multiple organ dysfunctions, which may have induced bias in the results. Pretransplant assessment and medical optimization were performed according to the guidelines. This study was conducted in accordance with the Declaration of Helsinki and had been approved by the Zhongshan Hospital Ethics Committee (approval number: B2021-668R).

Source of Donor Hearts

The law prohibiting executed criminal donor organs was passed on Jan 1st, 2015, the same year the China Organ Transplant Response System was launched. In this study, all donor hearts were donated voluntarily, and the information of all donors was recorded and tracked in the allocation system. The first-degree relatives of all organ donors and recipients had signed informed consent forms for biomedical research. This system had no “marginal” or “alternative” types of donor grafts. The allocation of organs was automatically completed, and the donor–recipient size matching threshold was set between 80% and 120% of the recipient’s weight.

Pretransplant Medications

Information on the pretransplant medications was collected from hospital medical records and outpatient clinics. Pretransplant sacubitril–valsartan exposure was defined as sacubitril–valsartan treatment that had been tolerated for at least 30 days and continued to the day of transplantation. Titration began at 25 mg b.i.d. and gradually increased to the target dose, which was determined according to the systolic blood pressure of the patients. Other medications, such as loop diuretics, beta-blockers, aldosterone receptor antagonists, and sodium–glucose co-transporter-2 inhibitors, were also documented and included in the analyses.

Immunosuppressive Treatment

In this study, all patients were treated according to the same immunosuppressive protocol. Induction of monoclonal antibodies targeted against the IL2 receptor (basiliximab 20 mg) was administered intraoperatively and continued for four postoperative days. Patients received methylprednisolone at the time of aortic clamping. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, cyclosporine, and corticosteroids; tacrolimus levels were targeted to a trough of 10–15 ng/mL during months 0–3, while cyclosporine was adjusted to achieve a trough concentration of 300 ng/mL during the initial three months. Mycophenolate mofetil was administered at a dose of 750 mg every 12 hours, and prednisolone was administered enterally at a dose of 1 mg/kg twice daily.

Study Outcomes and Indications for Post-transplant ECMO

The primary outcome of this study was 6-month mortality, and the secondary outcome was the post-transplant support of ECMO. At our institution, the orthotopic anastomosis was the only performed operation for HT. After the aortic cross-clamp was removed, the contractility of the graft was checked by the operating surgeon and an echocardiographer. The signs of right ventricular graft failure included a dilated and rigid right ventricle, elevated central venous pressure, persistent hypotension, and unalleviated pulmonary hypertension, for which cardiopulmonary bypass was usually prolonged and supplemented alongside the inhalation of nitric oxide and higher doses of inotropic and vasoactive agents. When graft dysfunction was persistent and led to difficulties in weaning from cardiopulmonary bypass (CPB), veno–arterial ECMO was initiated, and central cannulations were transferred into the femoral. Further, we evaluated graft function, left ventricular outflow tract velocity–time integral, and the status of peripheral perfusion in the intensive care unit daily. The objective criteria for considering the initiation of ECMO included a vasoactive-inotropic score greater than 30 with a cardiac index less than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^2$, mean arterial pressure less than 50 mm Hg, central venous pressure greater than 20 mmHg, and a significant right ventricular function, as assessed by an echocardiogram [22].

ECMO Management

Effective management of VA–ECMO involves several key areas, such as circulatory support, anticoagulation, infection control, and nutritional support [23]. In brief, intravenous heparin was administered at an initial rate of 300 U/h once the chest tube drainage became serious. Partial thromboplastin time is monitored every 8 hours after beginning heparin administration to achieve a partial thromboplastin time range of 60–80 seconds. ECMO flow is typ-

ically maintained between 50 and 70 mL/kg/min (around 4–6 L/min) and generally provides adequate support. Optimizing hemodynamic stability involves using minimal vasoactive agents to maintain a central venous pressure below 13 mmHg and mean arterial pressure above 65 mmHg. Moreover, ventilator support is tapered as early as possible to reduce the risk of ventilator-associated pneumonia, and patients are extubated while still on ECMO. Weaning from ECMO is considered when there is progressive clinical improvement, such as enhanced graft function, recovery of end-organ function, and reduced dependence on vasoactive medications. A combination of echocardiographic assessments and hemodynamic data is used to evaluate indications for weaning. A bedside weaning trial is performed for suitable candidates, where ECMO flow is temporarily reduced to 1 L/min. Improvement in graft function, as observed through echocardiography, is an important factor in predicting successful weaning.

Statistical Analysis

Continuous variables are shown as the mean $\pm$ standard or median (interquartile range) based on their normality distribution and were compared using the Student's *t*-test or U-test, as appropriate. Categorical variables are expressed as numbers with percentages and compared using the chi-square test. The Kaplan–Meier method and the log-rank test were used to estimate and compare postoperative survival. We used two statistical methods to balance the baseline characteristics: (1) adjusted multivariable analysis with different preset covariates and (2) propensity score matched (PSM) analysis. The independent risk factors for post-transplant ECMO support were initially screened using the univariate logistic regression (**Supplementary Table 1**), and variables with a $p < 0.05$ were included in the multivariate logistic regression with the stepwise selection method. In the propensity score matching analysis, we calculated the propensity scores using a logistic regression model that included the following variables: recipient age, sex, height, weight, and baseline medications, including loop diuretics, beta-blockers, aldosterone receptor antagonists, and sodium–glucose co-transporter-2 inhibitors. We used the nearest neighbor matching with a caliper of 0.1; each treated patient was matched with the nearest available neighbor on the estimated propensity score with a 1:1 matching algorithm without replacement. All statistical tests were two-sided; a $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 25.0 SPSS Inc., Armonk, NY, USA).

Results

Clinical Demographics of the Study Cohort

There were 152 HT recipients enrolled in this study, including 67 (44.1%) patients who underwent ARNI therapy before transplant and 85 (55.9%) patients who did not receive ARNI therapy. The median duration of ARNI treatment was 4 (2, 36) months. With a target systolic blood pressure of 90–100 mmHg, the median ARNI dosage was titrated to a median dose of 100 (interquartile range 50–162.5) mg per day at the time of transplant. The baseline clinical characteristics of the patients are shown in Table 1. The ages, body weight, and rates of most comorbidities for the donors and recipients were comparable between the two groups, except that there were higher rates of diabetes and hypertension in the patients who received ARNI therapy. Due to the strict control policy during the COVID-19 pandemic, no recipient was infected by COVID-19 before HT, and the number of transplantations was not significantly affected. The 30-day mortality was 14.5% ($n = 22$), including 10 patients with persistent graft failure, 8 with septic shock, 3 with bleeding during ECMO support, and 1 with cerebral hemorrhage.

Pretransplant Hemodynamic Parameters

The baseline echocardiographic data demonstrated that patients receiving ARNI treatment had lower left ventricular ejection fraction than those who did not receive ARNIs in both the unmatched and matched cohorts. The right heart catheterization measurements showed that the cardiac indices of the patients with ARNI therapy were significantly lower. However, the central venous pressure was remarkably lower in the ARNI group, while no significant differences were observed in the other parameters between the two groups, such as pulmonary artery systolic pressure, pulmonary artery diastolic pressure, pulmonary vascular resistance, mean pulmonary artery pressure, and pulmonary capillary wedge pressure.

Study Endpoints

The 30-day mortality was 14.5% ($n = 22$), including 10 patients with persistent graft failure, 8 with septic shock, 3 with bleeding during ECMO support, and 1 with cerebral hemorrhage. There were no cases of hyperacute rejection. Vasoactive agents, including norepinephrine, dobutamine, and milrinone, were administered in almost all (98%) heart transplant recipients in this cohort, which prevented us from making meaningful comparisons. The strategy of choosing and titrating vasoactive agents was consistent over the study period and based on the hemodynamics of the recipients. Nitric oxide was inhaled in 59 (38.6%) patients with

Table 1. Baseline demographics of heart transplant recipients with and without ARNI therapy.

Characteristic	Before matching			After matching			
	Non-ARNI	ARNI	<i>p</i> -value	Non-ARNI	ARNI	<i>p</i> -value	Standardized difference
	N = 85	N = 67		N = 39	N = 39		
Recipient age (years)	50 (34.5, 58)	52 (43.3, 60.5)	0.44	52 (44, 57)	51 (41, 58)	0.64	−0.442
Donor age (years)	37.5 ± 8.2	38.5 ± 8.2	0.59	38.8 ± 8.2	37.9 ± 10.8	0.69	0.095
Recipient gender (male) (%)	64 (75%)	54 (81%)	0.44	25 (64.1%)	28 (71.8%)	0.47	0.165
Donor gender (male) (%)	70 (89%)	60 (92%)	0.81	31 (88.6%)	33 (89.2%)	0.93	−0.019
Recipient height (m)	1.7 ± 0.1	1.7 ± 0.1	0.90	1.7 ± 0.1	1.7 ± 0.1	0.31	0.232
Donor height (m)	1.7 ± 0.1	1.7 ± 0.1	0.50	1.7 ± 0.1	1.7 ± 0.1	0.60	0.124
Recipient weight (kg)	64.9 ± 13.5	65.0 ± 11.2	0.36	63.4 ± 15.3	64.4 ± 11.3	0.74	−0.076
Donor weight (kg)	65.9 ± 7.4	66.0 ± 9.0	0.90	64.2 ± 7.2	64.6 ± 8.7	0.86	−0.043
Recipient body mass index (kg/m ²)	22.7 ± 3.8	22.8 ± 3.2	0.90	22.1 ± 4.2	23.1 ± 3.6	0.26	−0.255
Donor body mass index (kg/m ²)	23.2 ± 1.7	23.4 ± 2.3	0.52	22.9 ± 1.8	23.3 ± 2.3	0.48	−0.166
Diabetes (%)	5 (5%)	9 (13%)	0.11	2 (5.1%)	4 (10.3%)	0.68	0.193
Hypertension (%)	2 (2.4%)	10 (14.9%)	0.006	1 (2.6%)	4 (10.3%)	0.36	−0.314
Chronic kidney disease (%)	4 (4.7%)	8 (11.9%)	0.13	2 (5.1%)	6 (15.4%)	0.26	−0.339
Type of cardiomyopathy (ischemic) (%)	9 (10.6%)	9 (13.4%)	0.59	3 (7.7%)	7 (17.9%)	0.18	−0.517
Previous cardiac surgery (%)	12 (14%)	10 (15%)	0.89	6 (15.4%)	9 (23.1%)	0.39	0.194
Pretransplant mechanical support (%)	1 (1.2%)	2 (3.0%)	0.58	0 (0%)	2 (5.1%)	0.49	−0.325
Loop diuretics (%)	54 (63.5%)	66 (98.5%)	<0.001	36 (92.3%)	38 (97.4%)	0.62	−0.231
Dose of loop diuretics (mg as furosemide)	40 (20, 40)	40 (20, 40)	0.47	40 (20, 40)	30 (20, 40)	0.52	0.271
ACEi/ARB (%)	12 (14.1%)	13 (19.4%)	0.38	11 (28.2%)	5 (12.8%)	0.16	0.383
Beta-blockers (%)	43 (56.6%)	50 (74.6%)	0.003	29 (74.4%)	28 (71.8%)	0.80	0.057
Aldosterone receptor antagonists (%)	33 (38.8%)	61 (91%)	<0.001	33 (84.6%)	33 (84.6%)	>0.99	0.000
Sodium–glucose co-transporter-2 inhibitors (%)	2 (2.4%)	14 (20.9%)	<0.001	2 (5.1%)	4 (10.3%)	0.68	−0.191
Systolic blood pressure (mmHg)	105.3 ± 19.1	97.8 ± 16.4	0.013	103.3 ± 15.6	99.0 ± 16.3	0.24	0.271
Diastolic blood pressure (mmHg)	64.8 ± 13.7	60.9 ± 13.8	0.093	64.5 ± 14.1	61.7 ± 12.9	0.36	0.214
Heart rate (bpm)	82.2 ± 15.0	82.3 ± 18.8	0.97	82.6 ± 17.3	80.5 ± 16.2	0.58	0.127
Left ventricular ejection fraction (%)	34.8 ± 15.9	28.7 ± 8.1	0.003	33.9 ± 14.7	29.9 ± 9.1	0.17	0.321
Tricuspid annular plane systolic excursion <16 mm (%)	46 (54.1%)	40 (59.7%)	0.49	21 (56.8%)	22 (57.9%)	0.92	−0.205
Cardiac index (mL/min/m ²)	2.2 (1.6, 3.0)	1.9 (1.5, 2.5)	0.011	1.9 (1.5, 2.4)	2.3 (1.5, 2.8)	0.22	0.419
Central venous pressure (mmHg)	13.5 (8, 18)	9 (5, 15)	0.022	9.5 (5, 15.3)	14 (10, 19)	0.064	0.434
Pulmonary arterial systolic pressure (mmHg)	45.1 ± 17.2	46.0 ± 17.7	0.77	44.1 ± 18.0	47.3 ± 19.8	0.45	−0.173

Table 1. Continued.

Characteristic	Before matching			After matching			Standardized difference
	Non-ARNI	ARNI	<i>p</i> -value	Non-ARNI	ARNI	<i>p</i> -value	
	N = 85	N = 67		N = 39	N = 39		
Pulmonary artery diastolic pressure (mmHg)	21.2 ± 11.5	21.6 ± 10.7	0.84	22.3 ± 11.7	22.7 ± 11.6	0.87	−0.033
Mean pulmonary artery pressure (mmHg)	30.5 ± 13.6	29.0 ± 12.2	0.51	30.4 ± 13.0	30.7 ± 14.0	0.93	−0.022
Pulmonary artery wedge pressure (mmHg)	20.2 ± 9.8	20.8 ± 8.8	0.75	20.2 ± 9.8	20.3 ± 8.5	0.96	−0.012
Pulmonary vascular resistance (Wood unit)	3.5 (2.2, 5.7)	3.1 (2, 5.6)	0.51	3.1 (2.1, 5.7)	3.4 (2.2, 7)	0.65	0.115
Plasma potassium (mmol/L)	4.1 ± 0.4	4.0 ± 0.5	0.054	4.2 ± 0.4	4.0 ± 0.5	0.095	0.382
Serum creatinine (μmol/L)	109.4 ± 60.5	122.0 ± 89.9	0.34	123.5 ± 91.9	125.9 ± 66.0	0.25	−0.279
Ischemic time (min)	170 (112, 335)	319 (237, 345)	<0.001	325.5 (239, 346.3)	230 (110, 348)	0.004	−0.710
Cardiopulmonary bypass time (min)	187.3 ± 75.2	184.0 ± 72.7	0.79	169.1 ± 65.9	185.5 ± 67.5	0.31	−0.247

Data are presented as the mean ± standard deviation, median (interquartile range, IQR) or n (%); The hemodynamic data derived from pretransplant evaluation period; ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor. The *p*-values less than 0.1 are presented in bold.

Table 2. The clinical outcomes.

Outcome	Non-ARNI	ARNI	<i>p</i> -value
	N = 85	N = 67	
ECMO, n (%)	23 (27%)	9 (13%)	0.041
Duration of ECMO (hours)	30.5 ± 58.1	31.2 ± 105.3	0.96
6-month mortality, n (%)	16 (18.8%)	10 (14.9%)	0.47

Data are presented as the mean ± standard deviation or n (%); ARNI, angiotensin receptor–neprilysin inhibitor; ECMO, extracorporeal membrane oxygenation. The *p*-values less than 0.1 are presented in bold.

Table 3. Risk factors for ECMO support post-transplant.

Variables	Univariable logistic regression	Model 1	Model 2	Model 3
	OR (95% CI); <i>p</i> -value	OR (95% CI); <i>p</i> -value	OR (95% CI); <i>p</i> -value	OR (95% CI); <i>p</i> -value
Pretransplant use of ARNI	0.418	0.317	0.317	0.269
	(0.179–0.978)	(0.103–0.98)	(0.103–0.98)	(0.081–0.891)
	0.044	0.046	0.046	0.032
Cardiopulmonary bypass time (>3 hours)	10.4	14.391	14.391	13.572
	(3.714–29.120)	(4.36–47.501)	(4.36–47.501)	(4.028–45.729)
	<0.001	<0.001	<0.001	<0.001
Mean pulmonary artery pressure (>30 mmHg)	2.5	2.487	2.487	2.806
	(1.055–5.924)	(0.888–6.968)	(0.888–6.968)	(0.96–8.196)
	0.037	0.083	0.083	0.059
The year of transplant (later than 2017)	0.771			
	(0.258–2.310)			
	0.643			
Recipient age	0.985			
	(0.956–1.014)			
	0.304			
Left ventricular ejection fraction	0.995			
	(0.965–1)			
	0.752			

elevated pulmonary artery pressure. Post-transplant tricuspid annular plane systolic excursion <16 mm was observed in 66 (43.4%) patients. The overall rate of graft dysfunction was 30.3% ($n = 46$), and 32 (21.1%) patients with severe graft dysfunction received ECMO support (Table 2). The rate of ECMO support in the ARNI group was significantly lower than in the non-ARNI group (13% vs. 27%, $p = 0.041$). The average time of ECMO support and 6-month mortality were comparable between the two groups. Nevertheless, the combined risk for mortality estimated by the Kaplan–Meier method was higher in the ECMO-supported patients (log-rank $p = 0.47$; **Supplementary Fig. 1**). In the propensity score matched cohort, the rate of post-transplant ECMO remained higher in the non-ARNI group (5% vs. 26%; $p = 0.042$). Similarly, Kaplan–Meier analysis showed comparable survival between the two matched groups (log-rank $p = 0.94$; **Supplementary Fig. 1**).

Risks for Post-Transplant ECMO

Several predictors of ECMO support were identified in the univariate logistic analysis, including pretransplant mean pulmonary artery pressure (odds ratio (OR), 2.5; 95% confidence interval (CI), 1.055–5.924; $p = 0.037$), pretransplant use of sacubitril–valsartan (OR, 0.418; 95% CI, 0.179–0.978; $p = 0.044$), and total CPB time (OR, 10.4; 95% CI, 3.714–29.120; $p < 0.001$). All univariate analyses are shown in **Supplementary Table 1**. In the multivariate analyses, we constructed three types of adjusted models: Model 1 was adjusted for the above three variables plus the year of transplant; Model 2 was adjusted for the

above three variables plus the year of transplant and recipient age; Model 3 was adjusted for the above three variables plus the left ventricular ejection fraction of the recipient before HT. The results of the multivariate analyses demonstrated that the risk of post-transplant ECMO support was lower in patients receiving ARNI (Model 1: OR, 0.317; 95% CI, 0.103–0.98; $p = 0.046$; Model 2: OR, 0.317; 95% CI, 0.103–0.98; $p = 0.046$; Model 3: OR, 0.269; 95% CI, 0.081–0.891; $p = 0.032$ (Table 3)). Nitric oxide inhalation did not significantly correlate with post-transplant ECMO support ($p = 0.065$).

Discussion

The results of this investigation indicate that administering ARNIs pretransplant may be associated with a reduced risk of ECMO support after HT. The importance of this study stems from the findings that severe graft dysfunction, despite the advances in ECMO support, remains associated with significant mortality and morbidity after HT. Therefore, every effort should be made to optimize the recipients' hemodynamic status, avoid donor–recipient mismatch, and reduce ischemic time. Our findings suggest the potential benefit of administering ARNIs to HT candidates.

Sacubitril–valsartan combines the renin–angiotensin–aldosterone system antagonism with the amplification of the natriuretic peptide system [25]. Studies have illustrated an effective application of ARNI therapy for treating reduced ejection fraction with severe pulmonary hypertension [23,26–28] and validated the superiority of adminis-

tering ARNIs compared with isolated angiotensin blockers in reversing pulmonary hypertension [29]. The existing literature also presents inconclusive evidence regarding the impact of ARNIs on hemodynamic parameters. Previous retrospective studies have shown that sacubitril–valsartan treatment significantly improved the hemodynamic profile of patients with advanced heart failure without causing hypotension or worsening renal function [29,30]. Meanwhile, other studies have reported that ARNI did not significantly alter hemodynamic parameters, including left ventricular ejection fraction, cardiac output, and pulmonary vascular resistance [31]. Similarly, the results from the unmatched cohort in the current study demonstrated that the rate of post-transplant ECMO was lower in patients receiving an ARNI despite comparable left ventricular ejection fraction, right heart function, cardiac output, pulmonary artery pressure, and vascular resistance, while pretransplant central venous pressure was significantly lower. After propensity score matching, the difference in pretransplant central venous pressure became statistically non-significant, but the correlation between ARNI therapy and post-transplant ECMO support remained. Using an ACEi/ARB was not associated with significant changes in pretransplant hemodynamic factors in a subgroup analysis of patients without ARNI therapy. These analyses suggest that the potential association between administering an ARNI and a lower rate of post-transplant ECMO was not established through isolated optimization of pretransplant hemodynamics.

The specific mechanisms underlying the benefit of using an ARNI to maintain post-transplant hemodynamics remain unclear and could be complicated by neurohormonal or immunological factors. Mouse models have shown the beneficial combinatorial effect of neprilysin inhibition and angiotensin blocking, in part through the upregulation of natriuretic peptide receptor-C signaling and cyclic guanosine monophosphate-mediated vasodilation and downregulation of inflammatory secretion [27,32]. It is hypothesized that ARNIs might reduce post-transplant ECMO use by mitigating inflammation and increasing graft compliance, especially in the right ventricle. Additionally, ARNIs enhance cardiac function by inhibiting the degradation of enkephalins, leading to improved myocardial relaxation. In a rabbit model of heart failure, ARNI therapy improved post-infarction heart function, with protein analyses indicating reverse remodeling of phosphorylated CaMKII following treatment [33]. Moreover, ARNI-induced alterations in peripheral vascular function appear to play a significant role. ARNI enhances peripheral circulation by improving endothelial cell function and exerting anti-inflammatory and antioxidant effects, leading to vasodilation and reduced cardiac workload, which may ultimately decrease the need for mechanical support. In a model of diabetic cardiomyopathy, sacubitril–valsartan treatment reduced the expression of proinflammatory cytokines and heart failure biomarkers by downregulating the expression

of cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular endothelial cell adhesion molecule-1 (VCAM-1), suggesting anti-inflammatory and anti-heart failure effects [34]. The results from basic research provide a theoretical rationale for the clinical application of ARNI in HT recipients. Future studies are warranted to examine the molecular alterations associated with ARNI during early transplantation and provide novel targets for drug discovery.

To our knowledge, the current study is the first to investigate the effect of sacubitril–valsartan treatment on ECMO support in HT recipients. The negative impacts of ARNIs include hypotension, impaired renal function, hyperkalemia, and angioedema [35]. Therefore, patients receiving continuous ARNI therapies require close follow-up assessments. Caution should be used in HT candidates who become hypotensive after receiving the lowest dosage of ARNI, which may result in low cardiac output syndrome and reliance on inotropes or mechanical support.

There are several limitations in our study. First, there is an inherent limitation of observational studies that uncover associations but preclude the determination of causal relationships. Second, the decision to initiate ECMO depended on graft function, which could result from non-graft factors such as volume status and degree of acidosis. The subjective analysis of cardiothoracic surgeons and physicians in the intensive care unit can also affect the decision, which might promote an element of selection bias due to interobserver variation. Third, this study is based on a single-center experience and a relatively small sample size, which may limit the generalizability of the findings. Moreover, there was a lack of pathological evidence of rejection because, at our institution, patients supported with ECMO were considered hemodynamically unstable and not suitable for endomyocardial biopsies. Finally, to address the potential confounding effect of operating time, we compared the clinical data of patients who underwent transplantation before and after 2017 (**Supplementary Table 2**). The results showed better adherence to guideline-directed medical therapy in patients operated on after 2017 despite a similar rate of ECMO support. Therefore, the present results will require confirmation in larger cohorts, preferably with a randomized controlled study design.

Conclusion

Pretransplant use of ARNI agents was associated with a lower risk of ECMO support after HT. Future studies are warranted to confirm the effectiveness and safety of ARNIs in reducing ECMO use in HT recipients.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LY: data collection, design, analysis manuscript preparation. ZY: data collection, design, analysis manuscript preparation. WM: concept, manuscript preparation, editing. ZY: data collection, design, analysis manuscript preparation. JL: design, editing. JC: design, editing. SY: design, editing. HZ: design, editing. FW: design, editing. HL: design, editing. CW: concept, data collection, analysis, manuscript preparation, editing. XS: concept, manuscript preparation, editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and had been approved by the Zhongshan Hospital Ethics Committee (approval number: B2021-668R).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.59958/hsf.8075>.

References

- [1] Bhagra SK, Pettit S, Parameshwar J. Cardiac transplantation: indications, eligibility and current outcomes. *Heart (British Cardiac Society)*. 2019; 105: 252–260. <https://doi.org/10.1136/heartjnl-2018-313103>.
- [2] Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmaïlian F, Luu M, *et al*. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*. 2014; 33: 327–340. <https://doi.org/10.1016/j.healun.2014.02.027>.
- [3] Segovia J, Cosío MDG, Barceló JM, Bueno MG, Pavia PG, Burgos R, *et al*. RADIAL: a novel primary graft failure risk score in heart transplantation. *The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*. 2011; 30: 644–651. <https://doi.org/10.1016/j.healun.2011.01.721>.
- [4] Cosío Carmena MDG, Gómez Bueno M, Almenar L, Delgado JF, Arizón JM, González Vilchez F, *et al*. Primary graft failure after heart transplantation: characteristics in a contemporary cohort and performance of the RADIAL risk score. *The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*. 2013; 32: 1187–1195. <https://doi.org/10.1016/j.healun.2013.08.004>.
- [5] Sabatino M, Vitale G, Manfredini V, Masetti M, Borgese L, Maria Raffa G, *et al*. Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: Epidemiology, risk factors, and outcomes. *The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*. 2017; 36: 1217–1225. <https://doi.org/10.1016/j.healun.2017.02.014>.
- [6] Segovia J, Pulpón LA, Sanmartín M, Tejero C, Serrano S, Burgos R, *et al*. Primary graft failure in heart transplantation: a multivariate analysis. *Transplantation Proceedings*. 1998; 30: 1932. [https://doi.org/10.1016/s0041-1345\(98\)00485-0](https://doi.org/10.1016/s0041-1345(98)00485-0).
- [7] Yuan L, Ma W, Cui J, Liu J, Yang Z, Yang S, *et al*. Mildly Elevated Pulmonary Artery Systolic Pressure is Associated with Extracorporeal Membrane Oxygenation Support after Heart Transplantation. *Journal of Cardiac Surgery*. 2023; 2023: 8877476.
- [8] Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. *Journal of the American College of Cardiology*. 2001; 38: 923–931. [https://doi.org/10.1016/s0735-1097\(01\)01486-3](https://doi.org/10.1016/s0735-1097(01)01486-3).
- [9] Rosendale JD, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER, *et al*. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation*. 2003; 75: 1336–1341. <https://doi.org/10.1097/01.TP.0000062839.58826.6D>.
- [10] Meers CM, Wauters S, Verbeken E, Scheers H, Vanaudenaerde B, Verleden GM, *et al*. Preemptive therapy with steroids but not macrolides improves gas exchange in caustic-injured donor lungs. *The Journal of Surgical Research*. 2011; 170: e141–e148. <https://doi.org/10.1016/j.jss.2011.05.062>.
- [11] Venkateswaran RV, Patchell VB, Wilson IC, Mascaro JG,

- Thompson RD, Quinn DW, *et al.* Early donor management increases the retrieval rate of lungs for transplantation. *The Annals of Thoracic Surgery*. 2008; 85: 278–286; discussion 286. <https://doi.org/10.1016/j.athoracsur.2007.07.092>.
- [12] Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB. Care of the potential organ donor. *The New England Journal of Medicine*. 2004; 351: 2730–2739. <https://doi.org/10.1056/NEJMra013103>.
 - [13] Souter MJ, Eidbo E, Findlay JY, Lebovitz DJ, Moguilevitch M, Neidlinger NA, *et al.* Organ Donor Management: Part 1. Toward a Consensus to Guide Anesthesia Services During Donation After Brain Death. *Seminars in Cardiothoracic and Vascular Anesthesia*. 2018; 22: 211–222. <https://doi.org/10.1177/1089253217749053>.
 - [14] Kumar TKS, Mathis C, Sathanandam S, Zurakowski D, Subramanian S, Allen J, *et al.* Effect of thyroid hormone on cardiac function following orthotopic heart transplantation in piglets. *Pediatric Transplantation*. 2017; 21: 10.1111/ptr.13002. <https://doi.org/10.1111/ptr.13002>.
 - [15] Novitzky D, Mi Z, Collins JF, Cooper DKC. Increased Procurement of Thoracic Donor Organs After Thyroid Hormone Therapy. *Seminars in Thoracic and Cardiovascular Surgery*. 2015; 27: 123–132. <https://doi.org/10.1053/j.semtcvs.2015.06.012>.
 - [16] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2021; 42: 3599–3726. <https://doi.org/10.1093/eurheartj/ehab368>.
 - [17] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England Journal of Medicine*. 2014; 371: 993–1004. <https://doi.org/10.1056/NEJMoa1409077>.
 - [18] Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, *et al.* The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet (London, England)*. 2012; 380: 1387–1395. [https://doi.org/10.1016/S0140-6736\(12\)61227-6](https://doi.org/10.1016/S0140-6736(12)61227-6).
 - [19] Mentz RJ, Ward JH, Hernandez AF, Lepage S, Morrow DA, Sarwat S, *et al.* Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure. *Journal of the American College of Cardiology*. 2023; 82: 1–12. <https://doi.org/10.1016/j.jacc.2023.04.019>.
 - [20] DeRoo SC, Takayama H, Nemeth S, Garan AR, Kurlansky P, Restaino S, *et al.* Extracorporeal membrane oxygenation for primary graft dysfunction after heart transplant. *The Journal of Thoracic and Cardiovascular Surgery*. 2019; 158: 1576–1584.e3. <https://doi.org/10.1016/j.jtcvs.2019.02.065>.
 - [21] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, *et al.* The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*. 2016; 35: 1–23. <https://doi.org/10.1016/j.healun.2015.10.023>.
 - [22] Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, *et al.* Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatric Critical Care Medicine: a Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2010; 11: 234–238. <https://doi.org/10.1097/PCC.0b013e3181b806fc>.
 - [23] Zern EK, Cheng S, Wolfson AM, Hamilton MA, Zile MR, Solomon SD, *et al.* Angiotensin Receptor-Neprilysin Inhibitor Therapy Reverses Pulmonary Hypertension in End-Stage Heart Failure Patients Awaiting Transplantation. *Circulation. Heart Failure*. 2020; 13: e006696. <https://doi.org/10.1161/CIRCHEARTFAILURE.119.006696>.
 - [24] Guglin M, Zucker MJ, Bazan VM, Bozkurt B, El Banayosy A, Estep JD, *et al.* Venoarterial ECMO for Adults: JACC Scientific Expert Panel. *Journal of the American College of Cardiology*. 2019; 73: 698–716. <https://doi.org/10.1016/j.jacc.2018.11.038>.
 - [25] Menendez JT. The Mechanism of Action of LCZ696. *Cardiac Failure Review*. 2016; 2: 40–46. <https://doi.org/10.15420/cfr.2016:1:1>.
 - [26] Andersen S, Axelsen JB, Ringgaard S, Nyengaard JR, Hyldebrandt JA, Bogaard HJ, *et al.* Effects of combined angiotensin II receptor antagonism and neprilysin inhibition in experimental pulmonary hypertension and right ventricular failure. *International Journal of Cardiology*. 2019; 293: 203–210. <https://doi.org/10.1016/j.ijcard.2019.06.065>.
 - [27] Hobbs AJ, Moyes AJ, Baliga RS, Ghedia D, Ochiel R, Sylvestre Y, *et al.* Neprilysin inhibition for pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled, proof-of-concept trial. *British Journal of Pharmacology*. 2019; 176: 1251–1267. <https://doi.org/10.1111/bph.14621>.
 - [28] Desai AS, Heywood JT, Rathman L, Abraham WT, Adamson P, Brett ME, *et al.* Early Reduction in Ambulatory Pulmonary Artery Pressures After Initiation of Sacubitril/Valsartan. *Circulation. Heart Failure*. 2021; 14: e008212. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.008212>.
 - [29] Cacciatore F, Amarelli C, Maiello C, Mattucci I, Salerno G, Di Maio M, *et al.* Sacubitril/valsartan in patients listed for heart transplantation: effect on physical frailty. *ESC Heart Failure*. 2020; 7: 757–762. <https://doi.org/10.1002/ehf2.12610>.
 - [30] Gentile P, Cantone R, Perna E, Ammirati E, Varrenti M, D'Angelo L, *et al.* Haemodynamic effects of sacubitril/valsartan in advanced heart failure. *ESC Heart Failure*. 2022; 9: 894–904. <https://doi.org/10.1002/ehf2.13755>.
 - [31] Nesterov SV, Rätty J, Nammias W, Maaniitty T, Galloo X, Stassen J, *et al.* Short-term effects of sacubitril/valsartan therapy on myocardial oxygen consumption and energetic efficiency of cardiac work in heart failure with reduced ejection fraction: A randomized controlled study. *European Journal of Heart Failure*. 2024; 26: 117–126. <https://doi.org/10.1002/ehf2.3072>.
 - [32] Baliga RS, Zhao L, Madhani M, Lopez-Torondel B, Visintin C, Selwood D, *et al.* Synergy between natriuretic peptides and phosphodiesterase 5 inhibitors ameliorates pulmonary arterial hypertension. *American Journal of Respiratory and Critical Care Medicine*. 2008; 178: 861–869. <https://doi.org/10.1164/rccm.200801-121OC>.
 - [33] Chang PC, Wo HT, Lee HL, Lin SF, Chu Y, Wen MS, *et al.* Sacubitril/Valsartan Therapy Ameliorates Ventricular Tachyarrhythmia Inducibility in a Rabbit Myocardial Infarction Model. *Journal of Cardiac Failure*. 2020; 26: 527–537. <https://doi.org/10.1016/j.cardfail.2020.03.007>.
 - [34] Ge Q, Zhao L, Ren XM, Ye P, Hu ZY. LCZ696, an angiotensin receptor-neprilysin inhibitor, ameliorates diabetic cardiomyopathy by inhibiting inflammation, oxidative stress and apoptosis. *Experimental Biology and Medicine (Maywood, N.J.)*. 2019; 244: 1028–1039. <https://doi.org/10.1177/1535370219861283>.
 - [35] Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Pérez P, Conde-Martel A, Crespo-Leiro MG, *et al.* Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review. *Frontiers in Cardiovascular Medicine*. 2021; 8: 754499. <https://doi.org/10.3389/fcvm.2021.754499>.