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ORIGINAL ARTICLE

Less loop diuretic use in patients on sacubitril/valsartan undergoing remote pulmonary artery pressure monitoring

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Abstract

Aims Control of pulmonary pressures monitored remotely reduced heart failure hospitalizations mainly by lowering filling pressures through the use of loop diuretics. Sacubitril/valsartan improves heart failure outcomes and increases the kidney sensitivity for diuretics. We explored whether sacubitril/valsartan is associated with less utilization of loop diuretics in patients guided with haemodynamic monitoring in the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF).

Methods and results The MEMS-HF population (n = 239) was separated by the use of sacubitril/valsartan (n = 68) or no use of it (n = 164). Utilization of diuretics and their doses was prespecified in the protocol and was monitored in both groups. Multivariable regression, ANCOVA, and a generalized linear model were used to fit baseline covariates with furosemide equivalents and changes for 12 months. MEMS-HF participants (n = 239) were grouped in sacubitril/valsartan users [n = 68, 64 ± 11 years, left ventricular ejection fraction (LVEF) 25 ± 9%, cardiac index (CI) 1.89 ± 0.4 L/min/m^2] vs. non-users (n = 164, 70 ± 10 years, LVEF 36 ± 16%, CI 2.11 ± 0.58 L/min/m^2, P = 0.0002, $P < 0.0001$, and P = 0.0015, respectively). In contrast, mean pulmonary artery pressure (PAP) values were comparable between groups (29 ± 11 vs. 31 ± 11 mmHg, P = 0.127). Utilization of loop diuretics was lower in patients taking sacubitril/valsartan compared with those without (P = 0.01). Significant predictor of loop diuretic use was a history of renal failure (P = 0.005) but not age (P = 0.091). After subjects were stratified by sacubitril/valsartan or other diuretic use, PAP was nominally, but not significantly lower in sacubitril/valsartan-treated patients (baseline: P = 0.52; 6 months: P = 0.07; 12 months: P = 0.53), while there was no difference in outcome or PAP changes. This difference was observed despite lower CI (P = 0.0015). Comparable changes were not observed for other non-loop diuretics (P = 0.21).

Conclusions In patients whose treatment was guided by remote PAP monitoring, concomitant use of sacubitril/valsartan was associated with reduced utilization of loop diuretics, which could potentially be relevant for outcomes.

Keywords Drug therapy; Loop diuretics; Heart failure; Pulmonary artery pressure; Monitor

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Introduction

Heart failure is associated with a high rate of hospitalizations and healthcare costs.[1] After recompensation, a high incidence of recurring symptoms leading to readmissions is predictive of cardiovascular death during follow-up.[2,3] As hospitalization for worsening of heart failure is usually associated with volume overload leading to congestion, treatment with diuretics is mandatory to reduce hospitalizations.[4] Pulmonary artery pressure (PAP) rises days and weeks before clinical signs and symptoms develop,[5] and early treatment with diuretics might be a tool to prevent hospitalizations.[6] It has been shown that titration of heart failure medications guided by haemodynamic parameters collected remotely (CardioMEMS HF System) is feasible,[7] reduces hospitalization, and improves quality of life.[8,9] Recently, outcomes from studies using the angiotensin receptor blocker/neprilysin inhibitor sacubitril/valsartan and studies with the sodium-glucose transporter 2 inhibitors (SGLT2i) dapagliflozin[10] and empagliflozin[11] have shown a reduction in cardiovascular death and hospitalization. According to observational studies from the PARADIGM trial[11] and data from longitudinal cohort study in outpatient clinics,[12] sacubitril/valsartan reduces the utilization of loop diuretics, which was not detected with the SGLT-2 inhibitor dapagliflozin.[13] This is important as loop diuretics can cause neuro-hormonal activation[14] and electrolyte disturbances[15] associated with arrhythmias, heart failure progression, and death.[16–18] However, the utilization of diuretics has only been studied in a registry and a clinical trial (PARADIGM-HF) with drug titration left to the discretion of investigators.[12,19] Herein, we asked the question whether patients treated with sacubitril/valsartan have a lower diuretic use, less initiation of loop diuretics, and different response to diuretic changes, when PAP is individually adjusted early with diuretics to prevent later congestion and hospitalizations. Data from the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF) were utilized, and the patient population studied was stratified according to the use of sacubitril/valsartan compared with patients who were not treated with sacubitril/valsartan in addition to heart failure management guided by haemodynamic data on top of standard of care. The pre-existing therapy and incident intensification with diuretics was captured as part of the predefined study protocol.[9,20]

Methods

Trial design

Information on the study design and population of the Cardio-MEMS European Monitoring Study for Heart Failure (MEMS-HF, NCT 02693691) has been published previously.[20] In brief, MEMS-HF is a prospective non-randomized open-label multicentre cohort study to evaluate the effect of the CardioMEMS HF systems in real-world settings. The trial was conducted in 26 German centres, 4 centres in the Netherlands, and 1 centre in Ireland. Patients were enrolled from outpatient centres or while being hospitalized for worsening of heart failure. Patients had a history of New York Heart Association (NYHA) Class III symptoms on optimal, guideline-directed medical and device therapies. Ejection fraction was not an inclusion criterion, and ejection fraction at the start of treatment with sacubitril/valsartan was not captured. Patients of both sexes were eligible if 18 years of age or older, and if having been hospitalized for worsening of heart failure in the previous 12 months. The CardioMEMS™ PA Sensor estimates PAP using micro-electromechanical systems technology that does not require batteries or leads as reported previously.[7,8,21,22] Training activities for patients and staff, study flow, data collection, and follow-up details have been published previously.[20]

Medical treatment

Pulmonary artery pressure tracings were reviewed regularly in the individual study centres. Patients needed to be managed clinically to keep PAP within each patient's individually defined range. Frequency of reviewing PAP trends was dependent on the clinical status of the patient. Supervision protocols and treatment algorithms have been published previously.[6,7,20–22] The majority of medication changes in MEMS-HF was due to dose increases of diuretics [1068 medication changes compared with 312 changes in angiotensin-converting enzyme (ACE) inhibitors, 209 changes in beta-blockers, and 170 changes in mineralocorticoid antagonists]. For diuretic dose equivalents in furosemide (loop diuretics) or metolazone (thiazides), see *Table 1*. In this analysis, the total population of 232 patients was separated into those on sacubitril/valsartan (n = 68) or no sacubitril/valsartan (n = 164).

Table 1 Conversion for diuretics

Loop diuretics	TD (mg)	Furosemide equivalency conversion
Furosemide	*40*	× *1.0*
Bumetanide	1	× 40.0
Torsemide	20	× 2.0
Thiazides	**TD (mg)**	**Metolazone equivalency conversion**
Metolazone	*2.5*	× *1.0*
Bendroflumethiazide	2.5	× 1.0
Hydrochlorothiazide	2.5	× 0.1
Indapamide	2.5	× 1.0

Statistical analysis

Baseline characteristics were summarized according to sacubitril/valsartan use or non-use (*Table 2*) in those patients with recorded dosage and data for all diuretics. Cumulative changes of baseline and diastolic and systolic and mean PAP were evaluated using an area under the curve (AUC analysis), which quantifies frequency and duration of PAP values below baseline (first week of home readings) using numeric integration.[20] Patients with a complete capturing of diuretics were used for the final analysis (n = 155, on sacubitril/valsartan n = 48, without sacubitril/valsartan n = 107). The likelihood of changing diuretic dose was predicted by average daily change of PAP (30 days prior) = sum of (current reading − baseline reading) ÷ number total readings. The odds of getting an up-titration of diuretics for sacubitril/valsartan and no sacubitril/valsartan users was calculated for each mmHg increase in average daily PAP change from baseline and for 10 mmHg increase in average daily PAP. A multivariable regression analysis adjusting for baseline pressure was performed. Up-titration included increased dose, new start, and restart of medications, and down-titration included decreased dose and stop of medication. ANCOVA was applied to compare the two different groups to determine the group difference for furosemide equivalence and metolazone equivalence for non-loop diuretics as well as the difference between baseline and follow-up for all diuretic users at 6 months taking baseline values into consideration. For both of these analyses, a generalized linear model (GLM) was fitted with baseline covariates to evaluate actual dose equivalents and change in dose at 6 months. The least square means between analysis groups was tested in order to assess any differences in diuretic use between groups. Baseline variables were selected for entry into the model based on a P-value criterion of $P < 0.05$ indicating variables as different between groups. These variables included age, cardiac index, ejection fraction, and history of renal failure. The model utilized a backward elimination approach, removing covariates one at a time until all of the covariates meet the staying criterion of $P < 0.1$. This GLM allows for evaluating measures over time and between analysis groups rather than just comparing groups individually at each study visit. In order to assess the diuretic dose utilized at 6 months, values from baseline, 3 months, and 6 months were included in the models testing actually dose and change values from 3 and 6 months were included for the models testing change from baseline dose. A two-sided P-value of <0.05 was considered statistically significant. SAS Version 9.4 (SAS Institute Incorporation, Kerry, NC, USA) was used for these analyses.

Results

Between May 2016 and March 2018, 239 patients were enrolled with 232 patients entering this analysis. Seven patients with incomplete medication data or no data on loop diuretic or thiazide therapies were excluded from this analysis. Patients were separated into those on sacubitril/valsartan (N = 68) or those without sacubitril/valsartan (N = 164). In 11 of 68 patients, sacubitril/valsartan was started during the trial, but no patient stopped the drug during follow-up. *Table 2* summarizes the baseline criteria. Patients on sacubitril/valsartan had similar pulmonary wedge pressures, slightly lower cardiac output and cardiac index, had a lower ejection fraction, and were more likely to be treated with mineralocorticoid antagonists. Average mean PA pressures were similar with and without sacubitril/valsartan (28.6 ± 11.4 and 31.1 ± 10.5 mmHg, respectively, P = 0.127). Patient-reported outcomes at baseline were also similar (*Table 2*).

Diuretic utilization by use of sacubitril/valsartan

Figure 1 summarizes the time course from implantation to 9 months of follow-up of current diuretic dose by sacubitril/valsartan users for loop diuretics (A) and thiazide diuretics (B). In general, at baseline and over time, the utilization of loop diuretics was lower when patients were on sacubitril/valsartan compared with those without sacubitril/valsartan. There was a statistical difference at 6 of 7 time points [*Figure 1(A)*]. The generalized linear mixed model comparing actual diuretic loop dose up to 12 months revealed a statistical significance between the groups (P = 0.01). The covariate representing a significant predictor in the model was history of renal failure (P = 0.005) but not age (P = 0.091). *Figure 1(B)* shows the same for non-loop diuretics, where the treatment was not statistically different (P = 0.21). Loop diuretic doses, but not thiazide doses, were lower in sacubitril/valsartan users at baseline and 6 months (Supporting Information, *Figure S1*). Next, we studied loop diuretic dose changes comparing sacubitril/valsartan users with non-sacubitril/valsartan users (*Figure 2*). The change was numerically different but yielded no significant difference in the multivariable statistical models using full adjustment (P = 0.15).

Table 2 Demographics and baseline characteristics (as treated population stratified by sacubitril/valsartan, diuretic use)

	Sacubitril/valsartan users (N = 68)	Non-users (N = 164)	P-value[a]
Demographics			
Age (years)	63.9 ± 10.9 (68)	69.9 ± 9.9 (164)	0.0002
Sex (male)	82.4% (56/68)	76.8% (126/164)	0.3859
Vital signs/lab analyses			
Body mass index (kg/m^2)	28.59 ± 4.64 (68)	28.86 ± 5.56 (164)	0.7012
Systolic BP (mmHg)	116.5 ± 16.6 (68)	116.5 ± 17.0 (161)	0.9941
Diastolic BP (mmHg)	71.0 ± 11.3 (68)	67.8 ± 10.9 (161)	0.0532
Heart rate (b.p.m.)	72.8 ± 12.5 (68)	70.6 ± 11.8 (164)	0.2102
NT-proBNP (pg/mL)	4157.5 ± 7366.1 (53)	5473.5 ± 8933.9 (123)	0.3109
Implant catheter haemodynamics			
PA systolic pressure (mmHg)	44.5 ± 18.2 (68)	48.2 ± 16.4 (163)	0.1539
PA diastolic pressure (mmHg)	18.7 ± 8.2 (68)	19.7 ± 8.1 (163)	0.3782
PA mean pressure (mmHg)	28.6 ± 11.4 (68)	31.1 ± 10.5 (163)	0.127
PA wedge pressure (mmHg)	18.7 ± 9.2 (67)	20.1 ± 9.5 (161)	0.2751
Cardiac output (L/min)	3.91 ± 0.97 (68)	4.29 ± 1.29 (163)	0.0153
Cardiac index (L/min/m^2)	1.89 ± 0.44 (68)	2.11 ± 0.58 (163)	0.0015
Pulmonary vascular resistance (mmHg·min/L)	2.72 ± 1.89 (67)	2.90 ± 2.32 (161)	0.537
Medical history			
Primary aetiology of cardiomyopathy			
Ischaemic cardiomyopathy	57.4% (39/68)	51.8% (85/164)	0.4722
Non-ischaemic cardiomyopathy	36.8% (25/68)	36.0% (59/164)	1
Not determined	0.0% (0/68)	8.5% (14/164)	0.0121
Unknown	5.9% (4/68)	3.7% (6/164)	0.4844
Atrial tachycardia, flutter/fibrillation	55.9% (38/68)	64.0% (105/164)	0.2992
Ventricular arrhythmia	30.9% (21/68)	19.5% (32/164)	0.0849
Diabetes mellitus	42.6% (29/68)	47.6% (78/164)	0.5634
History of renal failure	42.6% (29/68)	64.6% (106/164)	0.0033
Renal failure requiring dialysis	0.0% (0/68)	1.2% (2/164)	1
Cerebrovascular accident	7.4% (5/68)	15.2% (25/164)	0.1327
Chronic obstructive pulmonary disease	16.2% (11/68)	22.6% (37/164)	0.3732
Hyperlipidaemia	58.8% (40/68)	60.4% (99/164)	0.8833
Myocardial infarction	42.9% (27/63)	33.3% (51/153)	0.2134
Pulmonary oedema	20.6% (14/68)	15.2% (25/164)	0.3385
Pulmonary embolus	4.5% (3/67)	1.8% (3/163)	0.3608
CRT, CRT-P, or CRT-D	23.5% (16/68)	28.0% (46/164)	0.5183
ICD	58.8% (40/68)	30.5% (50/164)	0.0001
HF medical history			
Ejection fraction (%)	25.4 ± 9.4 (67)	36.2 ± 15.9 (162)	<0.0001
NYHA Class I	0.0% (0/68)	0.0% (0/164)	1
NYHA Class II	0.0% (0/68)	0.0% (0/164)	1
NYHA Class III	100.0% (68/68)	99.4% (163/164)	1
NYHA Class IV	0.0% (0/68)	0.6% (1/164)	1
Days since last HFH prior to implant	68.4 ± 82.6 (67)	71.1 ± 88.7 (160)	0.8254
HFH within 6 months before implant	89.6% (60/67)	88.1% (141/160)	0.8237
HFH within 3 months before implant	74.6% (50/67)	75.6% (121/160)	0.8674
History of HF medications			
ACEi/ARB/ARNi	94.1% (64/68)	81.7% (134/164)	0.0143
Beta-blocker	94.1% (64/68)	86.6% (142/164)	0.1133
Mineralocorticoid antagonist	91.2% (62/68)	64.0% (105/164)	<0.0001
Diuretic	97.1% (66/68)	96.3% (158/164)	1
Baseline patient-reported outcomes			
EQ-5D-5L VAS	55.2 ± 22.4 (68)	54.0 ± 20.1 (157)	0.7004
KCCQ Overall Summary Score	49.88 ± 24.31 (68)	45.58 ± 23.97 (157)	0.2237
KCCQ Clinical Summary Score	54.52 ± 24.72 (68)	49.61 ± 24.77 (157)	0.1737
PHQ-9 Summary Score	8.4 ± 5.9 (67)	8.8 ± 6.0 (156)	0.5932

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PHQ-9, Patient Health Questionnaire-9.

[a]P-value from two-group t-test with unequal variances for continuous variables and Fisher's exact test for categorical variables.

Effect of diuretic up-titration

With increasing average daily change of PAP from baseline, the odds of being up-titrated with a diuretic was similar between patients on sacubitril/valsartan [odds ratio (OR) = 1.084, confidence interval (CI) = 0.990–1.187, P = 0.083] and no sacubitril/valsartan (OR = 1.046, CI = 0.994–1.101, P = 0.081). By adjusting for baseline PAP,

Figure 1 Use of loop diuretic (A) and use of thiazide diuretic (B) over time in patients on sacubitril/valsartan (red) or no sacubitril/valsartan (black). *P*-values denote comparison between individual time points and *P*-values for a generalized linear model to compare diuretic utilization over time.

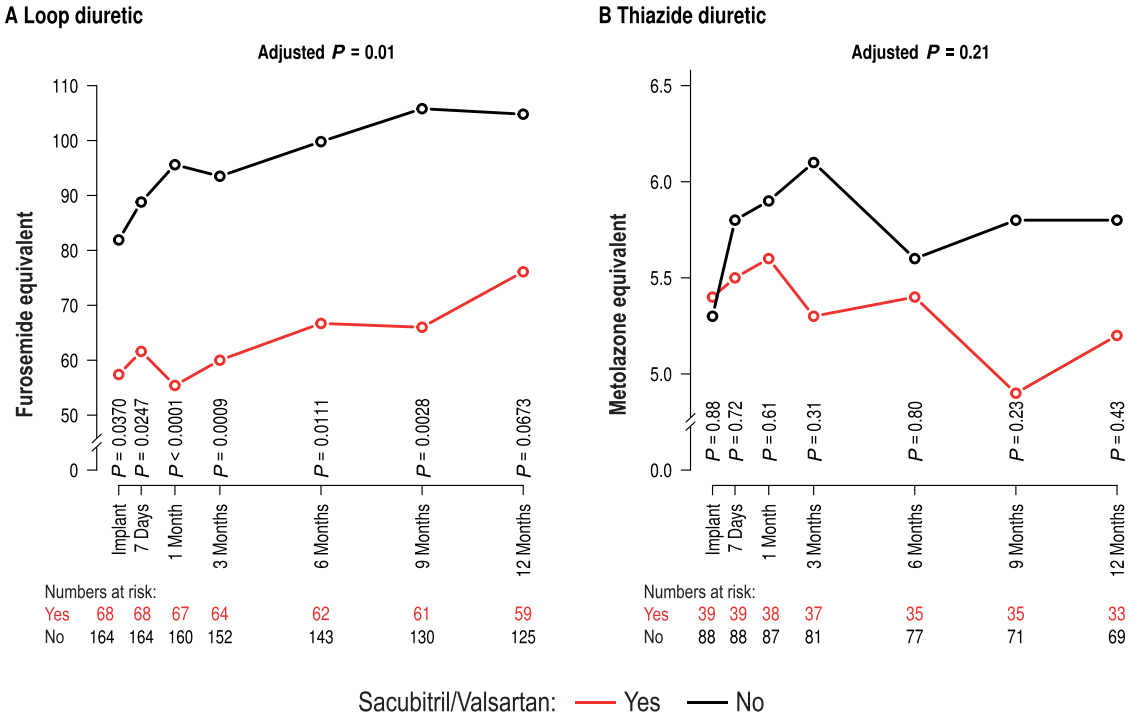
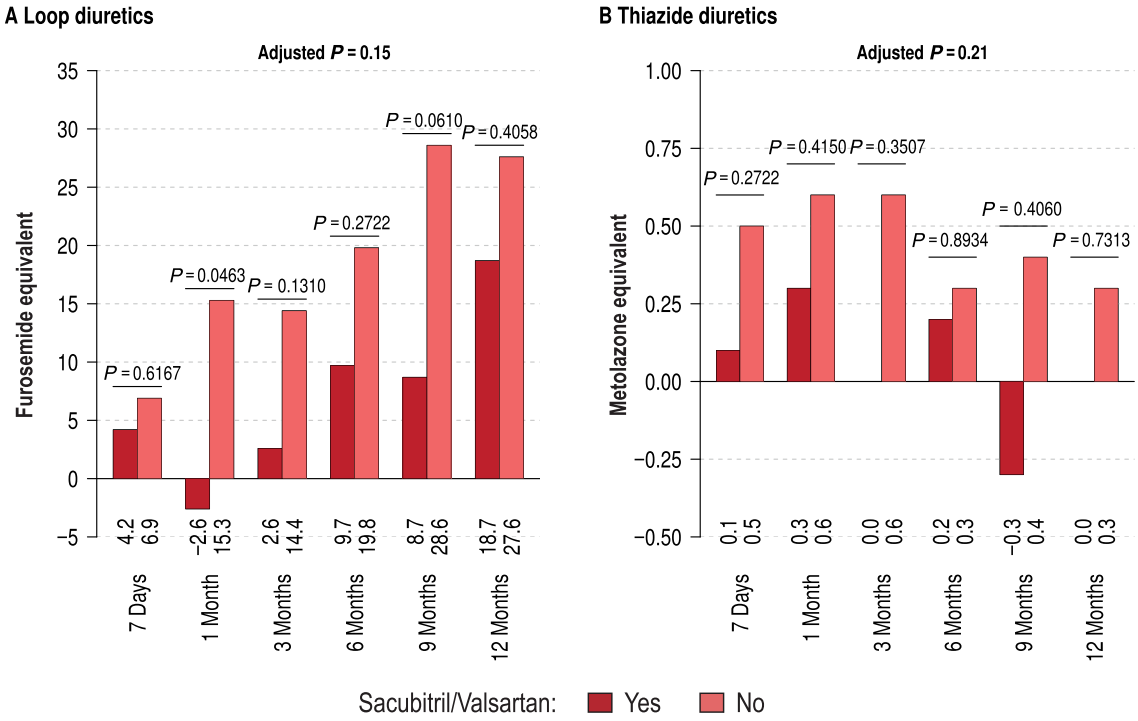


Figure 2 Change from baseline diuretic doses over time for loop diuretics (A) and thiazide diuretics (B) in patients with (dark red) and without (light red) sacubitril/valsartan.



there was an increase of loop diuretic utilization in non-users of sacubitril/valsartan (OR = 1.062, CI = 1.003–1.125, $P = 0.04$). Similar results were obtained for the multivariable regression analysis adjusted for baseline pressures. After changes in loop diuretics, the 7 day average mean PAP achieved was nominally, however, not significantly lower in patients on sacubitril/valsartan compared with no sacubitril/valsartan (*Table 3*). Nominally, but not significantly more patients on sacubitril/valsartan responded with a PAP drop compared with non-users (*Table 4*), but there were no differences in outcomes (*Table 5*).

Patient-reported outcomes

There was no significant difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score (OSS) or Clinical Summary Score (CSS) between sacubitril/valsartan users and non-users at baseline or 6 months. However, both the KCCQ OSS and CSS showed significant improvements from baseline to 6 months ($P < 0.0001$ for both OSS and CSS) and 12 months ($P < 0.0001$ OSS, $P = 0.0004$ CSS) for sacubitril/valsartan users and non-users ($P < 0.0001$ for both OSS and CSS at 6 and 12 months). Furthermore, we evaluated in patients with or without sacubitril/valsartan who had at least a 5-point increase in KCCQ over time. The proportion of patients with a 5-point improvement in KCCQ was not statistically different between the groups (55.7% vs. 50.4% in users and non-users, $P = 0.53$).

Discussion

We found that sacubitril/valsartan users compared with non-users utilized less loop diuretics at baseline and over time, when patients with symptomatic heart failure NYHA Class III underwent diuretic-based PAP-guided therapy using the CardioMEMS™ HF system to monitor PAP. This was the case despite similar baseline characteristics concerning drug treatment and comparable quality of life at baseline and at

Table 3 Add. mean pulmonary arterial pressure (7 day average) (as treated population stratified by sacubitril/valsartan)

Mean pulmonary arterial pressure (mmHg)	Sacubitril/valsartan		*P*-value[a]	Full cohort ($N = 232$)
	Yes ($N = 68$)	No ($N = 164$)		
Baseline			0.52	
Mean ± SD (*n*)	35.7 ± 11.9 (67)	36.8 ± 11.2 (158)		36.5 ± 11.4 (225)
Median (min, max)	36.4 (15.0, 71.6)	35.5 (14.3, 74.0)		36.0 (14.3, 74.0)
6 months			0.07	
Mean ± SD (*n*)	28.7 ± 11.6 (56)	32.1 ± 11.1 (134)		31.1 ± 11.3 (190)
Median (min, max)	26.2 (6.7, 54.6)	31.2 (12.1, 62.2)		29.3 (6.7, 62.2)
12 months			0.53	
Mean ± SD (*n*)	28.7 ± 11.0 (54)	29.8 ± 11.0 (116)		29.5 ± 11.0 (170)
Median (min, max)	27.4 (7.0, 62.3)	28.2 (6.4, 61.5)		28.0 (6.4, 62.3)

SD, standard deviation.
[a]Two-sample *t*-test.

Table 4 Add. mean pulmonary arterial pressure after diuretic change (as treated population stratified by sacubitril/valsartan)

Average daily change of PAP mean (within 30 days of medication change)	Down-titrated Sacubitril/valsartan		Up-titrated Sacubitril/valsartan		*P*-value[a]
	Yes ($N = 11$)	No ($N = 35$)	Yes ($N = 34$)	No ($N = 69$)	
Decrease	9 (81.82%)	26 (74.29%)	22 (64.71%)	41 (59.42%)	0.82
Increase	2 (18.18%)	9 (25.71%)	12 (35.29%)	28 (40.58%)	

PAP, pulmonary artery pressure.
[a]Breslow–Day's test for homogeneity of the odds ratios.

Table 5 Add. heart failure-related hospitalization (as treated population stratified by sacubitril/valsartan)

Event	Sacubitril/valsartan				Relative risk (95% CI)	Relative rate (95% CI)
	Yes ($N = 68$)		No ($N = 164$)			
	# Patient (%)	# Events (EPPY)	# Patient (%)	# Events (EPPY)		
Heart failure hospitalizations	27 (39.7%)	37 (0.55)	64 (39.0%)	100 (0.66)	1.0 (0.8, 1.2)	0.8 (0.6, 1.2)

CI, confidence interval; EPPY, events per patient year.

follow-up and with slightly lower ejection fractions and lower cardiac indices in patients on sacubitril/valsartan.

The use of loop diuretics, in particular at high doses, has been associated with cardiovascular outcomes[15] including arrhythmic death and progressive heart failure.[16,17] Mechanisms involved might be an increased secretion of renin due to diuretic actions on sodium-potassium-2 cotransporter[23] leading to neurocrine activation such as renin release potentially linked to poor outcomes.[15–18,24] The angiotensin receptor blocker/neprilysin inhibitor sacubitril/valsartan has been shown to reduce cardiovascular death and heart failure hospitalization in the PARADIGM trial.[25] In addition, sacubitril/valsartan reduced loop diuretic utilization in this trial[12] and also in real-world populations of outpatients treated by family doctors and cardiologists.[19] The latter two studies neither captured PAP nor did they control for quality of life measures. This study extends those findings by showing that in a population of sacubitril/valsartan users compared with non-users, loop diuretic doses at baseline and over time at follow-up are approximately 30–40% lower, when PAP-guided treatment is performed. PAP tended to be lower after diuretic treatment showing that the lower loop diuretic utilization was not due to diuretic under-treatment in the sacubitril/valsartan group. Guided by PAP values individualized for every patient,[20] the majority of treatment changes were adjustments of diuretic doses in the MEMS-HF study[9] as in previous studies showing an improved outcome compared with a control group on standard care.[7,8] As use of diuretics and reasons for changing diuretic dose were not captured in previous studies on the diuretic saving effects of sacubitril/valsartan,[12,19] MEMS-HF is first to provide an objective orientation of diuretic treatment based on the estimation and close monitoring of mean PAP.[7–9]

Neprilysin degrades vasoactive peptides, which might have an important consequence for renal haemodynamics in diabetes and heart failure[26] attenuating vasodilatory effects of circulating natriuretic peptides by impairing generation of cyclic guanosine-monophosphate, in turn reducing perfusion of the renal parenchyma.[26,27] As sacubitril/valsartan compared with enalapril further increases natriuretic peptides such as BNP and presumably also ANP and CNP,[28] a rapid response of kidney perfusion might be one of the mechanisms of the loop diuretic sparing effects of sacubitril/valsartan. Neprilysin inhibition in general exerts beneficial effects on the kidney also when combined with an ACE-inhibiting moiety integrated in the drug omapatrilate.[29] Taken together, the combination of an improved dilation of the vas afferents as well as the natriuretic effect of augmented natriuretic peptides might be the reason for the diuretic sparing effect of sacubitril/valsartan.[27–29] Direct effects of sacubitril/valsartan on filling pressures as shown within a small patient group with a CardioMEMS™ HF system in place could have contributed to saving diuretics.[30]

Strengths and limitations

If the unproven hypothesis is true that diuretics play a causal role in neuroendocrine activation and poor outcome,[15–18] then the diuretic sparing effect of sacubitril/valsartan could contribute to its beneficial effects on outcomes. Herein, we could not demonstrate fewer endpoints on sacubitril/valsartan. However, the study and this exploratory analysis were not aimed or powered to demonstrate outcome benefits of sacubitril/valsartan. Data in patients with an adjustment of PAP pressures by the CardioMEMS™ HF system might allow detailed analyses of drugs affecting volume homeostasis. These data have to be interpreted with their strengths and limitations. This is a secondary analysis of an open-label study evaluating the CardioMEMS™ HF system. There was no randomized comparison between users or non-users of sacubitril/valsartan creating a potential for residual confounding. We did not capture the ejection fraction immediately prior to sacubitril/valsartan treatment and have limited data on the initiation and duration of this therapy if the therapy was initiated before the patient was enrolled in this study. Patients on sacubitril/valsartan were on average 6 years younger and had less prevalence of renal failure. However, medical treatment and health status as assessed by the KCCQ at baseline and follow-up, which strongly depends on volume status, were similar between the two groups. Furthermore, a lower ejection fraction and lower cardiac output in sacubitril/valsartan users indicate that the difference in utilization of loop diuretics could have been underestimated rather than overestimated. A contribution to improvement of ejection fraction and/or cardiac output by sacubitril/valsartan is possible, but has not been determined in this study.

Conclusions

In summary, the CardioMEMS™ HF system has been shown to allow monitoring of PAP leading to a reduction of hospitalization rate by enabling fluid homeostasis mainly by dose adjustments of diuretics. Patients with these devices can also be studied according to other drugs, which are affecting volume homeostasis. Patients on optimal treatment with sacubitril/valsartan use less loop diuretics despite similar quality of life changes and accompanying drug treatments.

Conflict of interest

M.B. reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Medtronic, Novartis, Servier, and Vifor. B.A. reports honoraria for Bayer and Novartis, and speaker fees

from Abbott, Alnylam, Astra-Zeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, and Vifor; served on the MEMS-HF steering committee. F.W.A. has no conflicts of interest to report. J.B. reports honoraria for consultancy and speakers fees and scientific support by Abbott, Medtronic, and Biotronik and served on the MEMS-HF steering committee. M.E.B. is an employee and shareholder of Abbott. J.J.B. was on the steering committee of the Abbott-sponsored MONITOR-HF study. G.E. reports personal fees from Astra-Zeneca, Abbott, Boehringer Ingelheim, Novartis, and Vifor, all outside the submitted work. He further acknowledges non-financial support from the University Hospital Würzburg, non-financial support from Comprehensive Heart Failure Center Würzburg, and grant support from German Ministry for Education and Research (BMBF). L.H. has no conflicts of interest to report. A.W. is an employee and shareholder of Abbott. F.K. reports research funding by the German Federal Ministry of Economics and Technology, the European Commission, and the German Federal Ministry of Education and Research and served on the MEMS-HF steering committee. S.R. reports honoraria for consultancy, speaker fees, and scientific support by Abbott and has received remuneration for lectures and/or consultancy from Actelion, Bayer, BMS, MSD, Novartis, Pfizer, Vifor, and United Therapeutics, and his institution has received research grants from Actelion, Bayer, Novartis, and United Therapeutics and served on the MEMS-HF steering committee. S.D.A. reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma and grant support from Abbott and Vifor Pharma. D.M.L. reports lecture fees and research grants from Abbott, Novartis, Vifor Pharma, Boehringer, Astra-Zeneca, and Bayer. A.A. has no conflicts of interest to report. J.W. has received speaker honoraria from Bristol-Myers Squibb. Q.Z. reports grants from Boehringer Ingelheim, personal fees from Astra-Zeneca, grants and personal fees from Abbott, and personal fees from Novartis outside the submitted work. P.B.A. is an employee and stockholder of Abbott. C.E.A. reports grant support, personal fees, and/or non-financial support from Abbott, Astra-Zeneca, Boehringer Ingelheim, Medtronic, Novartis, ResMed, Thermo Fisher, and Vifor, all outside of the submitted work. She further acknowledges non-financial support from the University Hospital Würzburg, non-financial support from Comprehensive Heart Failure Center Würzburg, and grant support from German Ministry for Education and Research (BMBF).

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Diuretic doses in furosemide equivalents for loop diuretics (A) and thiazide diuretics (B) in patients with (dark red) and without (light red) sacubitril/valsartan use.

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