

Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial

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Aims

To assess differences in diuretic dose requirements in patients treated with sacubitril/valsartan compared with enalapril in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.

Methods and results

Overall, 8399 patients with New York Heart Association class II–IV heart failure and reduced LVEF were randomized to sacubitril/valsartan 200 mg bid or enalapril 10 mg twice daily. Loop diuretic doses were assessed at baseline, 6, 12, and 24 months, and furosemide dose equivalents were calculated via multiplication factors (2x for torsemide and 40x for bumetanide). Percentages of participants with reductions or increases in loop diuretic dose were determined. At baseline, 80.8% of participants were taking any diuretics ($n = 6290$ for loop diuretics, $n = 496$ for other diuretics); of those, recorded dosage data for loop diuretics were available on 5487 participants. Mean baseline furosemide equivalent doses were 48.2 mg for sacubitril/valsartan and 49.6 mg for enalapril ($P = 0.25$). Patients treated with sacubitril/valsartan were more likely to reduce diuretic dose and less likely to increase diuretic dose relative to those randomized to enalapril at 6, 12, 24 months post-randomization, with an overall decreased diuretic use of 2.0% ($P = 0.02$), 4.1% ($P < 0.001$), and 6.1% ($P < 0.001$) at 6, 12, and 24 months, respectively, with similar findings in an on-treatment analysis.

Conclusion

Treatment with sacubitril/valsartan was associated with more loop diuretic dose reductions and fewer dose increases compared with enalapril, suggesting that treatment with sacubitril/valsartan may reduce the requirement for loop diuretics relative to enalapril in patients with heart failure with reduced ejection fraction.

Keywords

Diuretics • Randomized clinical trial • Heart failure with reduced ejection fraction • Sacubitril/valsartan • Enalapril

Background

In the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, sacubitril/valsartan (formerly LCZ696)

reduced the primary composite outcome of cardiovascular death or heart failure hospitalization compared to enalapril in patients with symptomatic heart failure.¹ Sacubitril inhibits the enzyme neprilysin, which plays a role in the breakdown of natriuretic peptides, increases natriuretic peptide levels, which may result in a

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natriuretic effect.² Loop diuretics, frequently used in patients with heart failure, can lead to neurohormonal activation,^{3,4} electrolyte abnormalities, and worsening renal function,⁵ and higher doses of diuretics have been associated with worse outcomes.^{6–8}

The goal of this analysis was to investigate post-randomization differences in diuretic use among participants randomized to sacubitril/valsartan compared with enalapril in the PARADIGM-HF trial. We hypothesized that sacubitril/valsartan would be associated with reduced diuretic dose requirements compared with enalapril.

Methods

Patients

The study design of PARADIGM-HF has been previously reported. Briefly, patients with New York Heart Association (NYHA) class II–IV heart failure with reduced ejection fraction ($\leq 40\%$) and mild elevation in natriuretic peptides entered sequential active run-in phases in which they were up-titrated to enalapril 10 mg bid followed by sacubitril/valsartan 200 mg bid. After run-in, they were randomized to sacubitril/valsartan 200 mg bid, or enalapril 10 mg bid. Patients were followed for a median of 27 months. The trial complies with the Declaration of Helsinki; locally appointed ethics committees approved the research protocol and informed consent was obtained from all subjects.

Assessment of diuretic use

Use of diuretics (non-loop and loop type) including name of drug and dose were collected at baseline, 6, 12, and 24 months post-randomization on case report forms. For loop diuretics, furosemide dose equivalents were calculated, with bumetanide 1 mg or torsemide 20 mg considered equivalent to 40 mg of furosemide.⁹

Statistical analysis

Baseline characteristics were summarized by diuretic use (no diuretic, non-loop diuretic, loop diuretic). For loop diuretic, categories were created based on dose: < 20 mg daily, 20–40 mg daily, > 40 mg daily). Data from participants with missing dose information for loop diuretics ($n = 803$) were excluded. Baseline characteristics between diuretic use groups were compared with chi-square test for categorical variables and ANOVA for continuous variables. The percentage of patients with reductions or increases in loop diuretic dose was calculated at 6, 12, and 24 months post-randomization and compared between enalapril and sacubitril/valsartan treatment arms via regression.

Results

Out of 8399 validly randomized patients in PARADIGM-HF, 80.8% of participants were taking any diuretics [$n = 6290$ for loop diuretics, $n = 496$ for other diuretics (e.g. thiazide)] at baseline. Of those, recorded, dosage data for loop diuretics were available on 5487 participants out of 6290 (furosemide equivalent < 20 mg, $n = 438$, 7.3%; furosemide equivalent 20–40 mg, $n = 3625$, 60.6%; furosemide > 40 mg, $n = 1424$, 23.8%). A total of 7259 participants had diuretic doses available at baseline and at least at one additional time point. Use of any diuretics was associated with higher NYHA

class, lower ejection fraction, higher body mass index, greater likelihood of prior heart failure hospitalization, hypertension, diabetes, atrial fibrillation, digoxin use, mineralocorticoid receptor antagonist (MRA) use, higher creatinine, higher N-terminal pro brain natriuretic peptide (NT-proBNP), and lower incidence of ischaemic aetiology (Table 1). Higher diuretic dose was associated with worse NYHA class, higher likelihood of prior heart failure hospitalization, hypertension, diabetes, atrial fibrillation, use of digoxin, higher creatinine, and higher NT-proBNP. In a multivariable model, changes in diuretic dose from baseline to 6 months were positively associated with baseline body mass index and NT-proBNP, and inversely associated with baseline use and dose of MRA, digoxin, baseline weight, and randomization to sacubitril/valsartan (all $P < 0.01$). Doses of spironolactone and eplerenone at 6 and 12 months were also associated with 6 and 12-month diuretic changes, but the effect of sacubitril/valsartan on diuretic dose reductions remained significant after adjustment for MRA dose changes and post-baseline changes in systolic blood pressure and weight. Systolic blood pressure, weight, and MRA use and dose did not modify the effect of sacubitril/valsartan on diuretic dose changes at 6 and 12 months (all $P > 0.1$).

Mean baseline furosemide equivalent doses were 48.2 mg for sacubitril/valsartan and 49.6 mg for enalapril ($P = 0.25$). Participants assigned to sacubitril/valsartan had more frequent diuretic dose reductions and less frequent dose increases compared to those taking enalapril at 6, 12, and 24 months (Figure 1). As a result, patients randomized to sacubitril/valsartan had lower use of diuretics at 6 months (net reduction 2.0%, $P = 0.02$), 12 months (net reduction 4.1%, $P < 0.001$) and 24 months (net reduction 6.1%, $P < 0.001$) relative to enalapril with similar differences seen in an on-treatment analysis.

Discussion

We found that in PARADIGM-HF diuretic use at baseline was associated with a more severe burden of illness. Patients randomized to sacubitril/valsartan had lower subsequent use of diuretics, with fewer loop diuretic dose increases and more frequent dose reductions compared with those taking enalapril.

Loop diuretic use has been associated in prior studies with worse outcomes in heart failure, although the extent to which diuretic use represents a marker for sicker patients and thus increased risk, or plays a causal role remains unclear. Several studies, including those with adjustment for the propensity to be treated with loop diuretics, have documented an association between loop diuretics and a greater risk for hospitalization or death due to worsening heart failure, all-cause mortality, cardiovascular death, and sudden cardiac death compared to non-use.^{5–8,10} There appears to be a dose-related association, such that higher doses of diuretics are associated with greater risk compared with lower doses.⁵

Several mechanisms have been proposed by which loop diuretics may increase risk in heart failure. Loop diuretics, through their actions on the sodium/potassium/2-chloride co-transporter, lead to secretion of renin, with resulting neurohormonal activation.^{3,11,12} Increased levels of plasma renin

Table 1 Baseline characteristics by diuretic use groups

Characteristic	No diuretics (n = 1620)	Non-loop diuretics (n = 496)	Furosemide equivalent dose			P-value
			< 20 mg (n = 438)	20–40 mg (n = 3625)	> 40 mg (n = 1424)	
Randomized to sacubitril/valsartan, n (%)	811 (50.1)	223 (45.0)	206 (47.0)	1847 (51.0)	688 (48.3)	0.06
Age, years, mean (SD)	64 (11)	65 (11)	64 (11)	64 (11)	63 (12)	0.03
Female sex, n (%)	346 (21.4)	131 (26.4)	101 (23.1)	788 (21.7)	277 (19.5)	0.02
Caucasian, n (%)	985 (60.8)	311 (62.7)	326 (74.4)	2340 (64.6)	974 (68.4)	<0.001
NYHA class III/IV, n (%)	266 (16.5)	163 (32.9)	147 (33.6)	796 (22.0)	435 (30.6)	<0.001
Ejection fraction, mean (SD)	30.3 (5.9)	31.2 (5.7)	30.3 (5.9)	29.3 (6.2)	28.0 (6.7)	<0.001
Body mass index, kg/m ² , mean (SD)	27.0 (4.8)	27.9 (5.6)	27.6 (5.2)	28.1 (5.4)	29.9 (6.3)	<0.001
Prior HF hospitalization, n (%)	869 (53.6)	235 (47.4)	278 (63.5)	2337 (64.5)	1019 (71.6)	<0.001
Hypertension, n (%)	1091 (67.3)	367 (74.0)	320 (73.1)	2571 (70.9)	988 (69.4)	0.01
Diabetes mellitus, n (%)	453 (28.0)	150 (30.2)	116 (26.5)	1268 (35.0)	638 (44.8)	<0.001
Atrial fibrillation, n (%)	472 (29.1)	181 (36.5)	177 (40.4)	1305 (36.0)	617 (43.3)	<0.001
Systolic BP, mmHg, mean (SD)	122 (15)	124 (15)	123 (14)	121 (15)	120 (16)	<0.001
ICD, n (%)	207 (12.8)	36 (7.3)	44 (10.0)	527 (14.5)	332 (23.3)	<0.001
CRT, n (%)	84 (5.2)	16 (3.2)	17 (3.9)	221 (6.1)	179 (12.6)	<0.001
ACEi use, n (%)	1213 (74.9)	364 (73.4)	354 (80.8)	2817 (77.7)	1135 (79.7)	0.001
ARB use, n (%)	409 (25.2)	133 (26.8)	83 (18.9)	818 (22.6)	298 (20.9)	0.002
Beta-blocker use, n (%)	1496 (92.3)	463 (93.3)	405 (92.5)	3357 (92.6)	1336 (93.8)	0.52
Digoxin use, n (%)	318 (19.6)	171 (34.5)	133 (30.4)	1109 (30.6)	536 (37.6)	<0.001
MRA use, n (%)	772 (47.7)	227 (45.8)	293 (66.9)	2091 (57.7)	856 (60.1)	<0.001
Serum creatinine, mg/dL, mean (SD)	1.07 (0.25)	1.07 (0.26)	1.11 (0.30)	1.12 (0.30)	1.21 (0.33)	<0.001
NT-proBNP, pg/mL, median (IQR)	1304 (768–2566)	1392 (806–2501)	1599 (905–3134)	1684 (921–3396)	2026 (1067–4207)	<0.001
Ischaemic aetiology, n (%)	1082 (66.8)	324 (65.3)	282 (64.4)	2062 (56.9)	783 (55.0)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

activity, suggestive of neurohormonal activation, have been independently associated with increased risk of mortality in patients with heart failure.¹³ Diuretic use in the presence of neurohormonal activation has also been shown to portend worse outcomes.¹⁴

The reduced relative need for diuretics in patients randomized to sacubitril/valsartan may potentially be secondary to the natriuretic effects of sacubitril or the presumed improvement in haemodynamics that may occur with sacubitril/valsartan. Sacubitril/valsartan is not associated with weight loss, however, suggesting that any diuretic effect is weak. While there are not any demonstrated haemodynamic data in heart failure patients treated with sacubitril/valsartan, sacubitril/valsartan is known to decrease NT-proBNP substantially within 4 weeks of therapy, consistent with a relatively rapid improvement in haemodynamics with administration.¹⁵ Since investigators were blinded to therapy, diuretic dose reductions were prompted by changes in patient symptoms, which improved in patients randomized to sacubitril/valsartan.¹⁶ Conversely, it is also possible that sacubitril/valsartan lowered blood pressure more than enalapril, necessitating reduction of diuretic doses.

Diuretic use has been implicated in greater risk for hypotension in patients receiving renin–angiotensin system inhibitors; if diuretic

doses were not down-titrated in patients taking sacubitril/valsartan in response to reduced clinical need, this may have resulted in over-diuresis that could contribute to hypotension. This possibility underscores the importance of assessment and potential adjustment of diuretic doses prior to and following initiation of an angiotensin receptor neprilysin inhibitor.

Several limitations of this analysis should be noted. The differential use of diuretics among participants randomized to sacubitril/valsartan compared to enalapril was not a pre-specified analysis. Doses of diuretics were not available for all participants, which could lower the precision of dose change comparisons between groups. We compared diuretic use at discrete time points and may have missed interim changes in diuretic use that may not have been captured at study visits. Diuretic dose changes were not available at earlier time points after randomization, which could have been of interest given the quick onset of NT-proBNP reduction by sacubitril/valsartan. Additionally, there was limited information on medication dose changes during the run-in period of the PARADIGM-HF trial; these data could have further informed trends on diuretic dose adjustments after initiation of sacubitril/valsartan. Reasons for diuretic dose changes were not captured in the study. Lastly, there could be incomplete capture of non-loop diuretic changes or addition of MRAs.

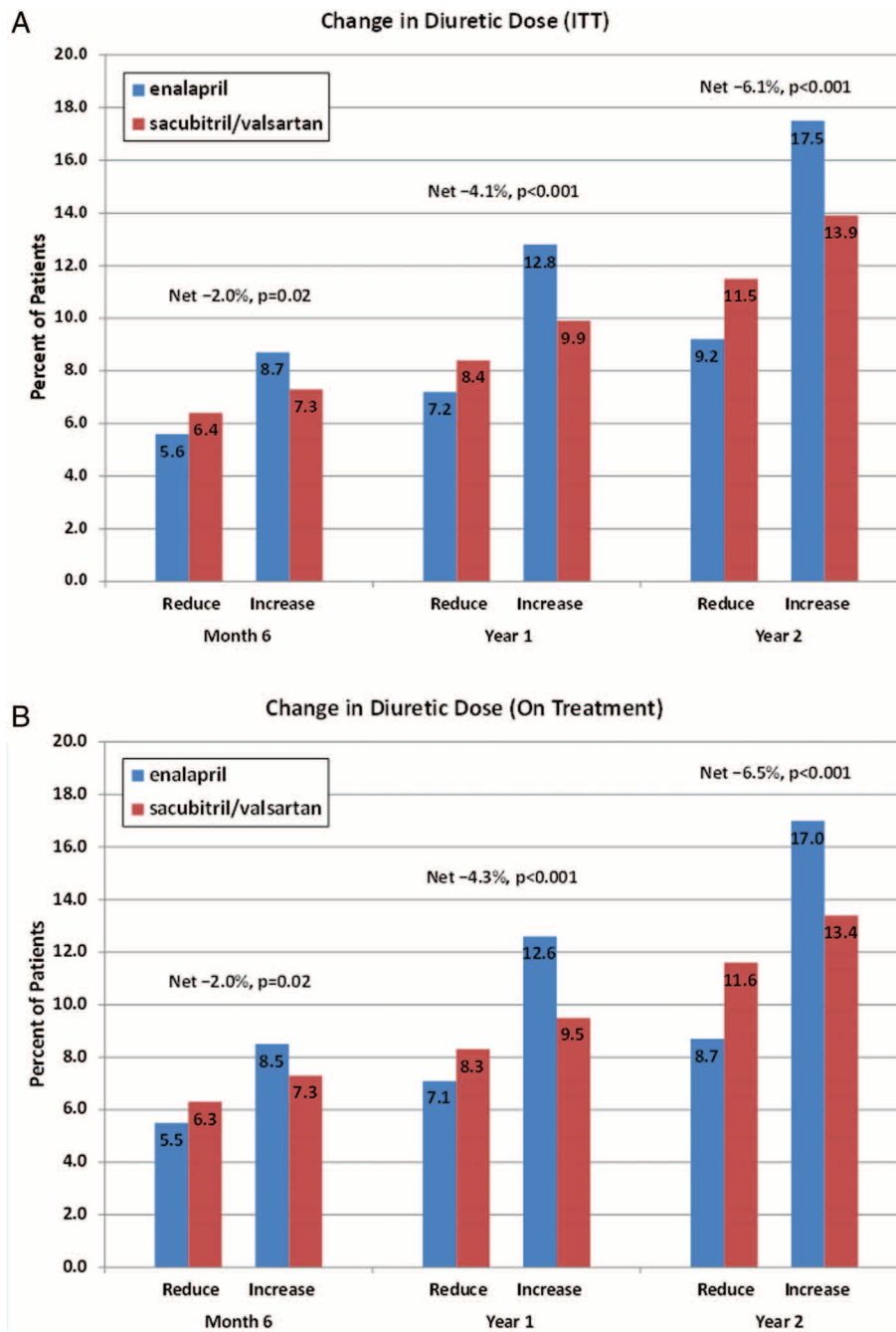


Figure 1 Changes in diuretic use during PARADIGM-HF at 6 months, 1 year, and 2 years by treatment arm based on (A) intention-to-treat (ITT) and (B) per protocol treatment.

In summary, treatment with sacubitril/valsartan was associated with more loop diuretic dose reductions and fewer dose increases compared with enalapril in the PARADIGM-HF study, suggesting that treatment with sacubitril/valsartan may reduce the relative requirement for loop diuretics in patients with heart failure with reduced ejection fraction. These findings may be relevant to clinicians treating patients concomitantly with sacubitril/valsartan and diuretics.

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