Research Letter

Real-World Prevalence of Adverse Events After Initiating Sacubitril/Valsartan Compared With Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Systolic Heart Failure

Sacubitril/valsartan is a novel medication that acts as a neprilysin and angiotensin receptor blocker.[1] Its overwhelming benefit as seen in its main clinical trial, PARADIGM-HF, led to its incorporation into the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines.[2–4] In the PARADIGM-HF trial, sacubitril/valsartan demonstrated a reduction in the composite end point of cardiovascular death or hospitalization for worsening heart failure compared with enalapril.[3] Despite its success, the trial design triggered concerns with the use of a run-in phase, which potentially underestimated side-effects.[5,6] The purpose of the present study was to determine the real-world prevalence of adverse events in patients with heart failure initiated on sacubitril/valsartan compared with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

This was a retrospective cohort analysis of patients ≥18 years of age with a diagnosis of HFrEF (<40%) initiated on therapy with sacubitril/valsartan, an ACEI, or an ARB at the University of Michigan Health System. Patients initiated on sacubitril/valsartan were screened for inclusion from July 7, 2015, to December 31, 2017. Patients were excluded if there were no data points or follow-up within a 30-day period after initiation of sacubitril/valsartan, ACEI, or ARB.

The primary adverse event composite end point included symptomatic hypotension, hypotension, worsening renal function, hyperkalemia, angioedema, dose reduction, and discontinuation within 30 days after initiation. Outcome definitions mirrored those in PARADIGM-HF.[3] Chi-square and Fisher exact testing were used to assess categoric variables based on events frequency. The Student *t* test was used to assess continuous variables. Inverse probability weighting was used to balance the baseline differences between groups. Variables in the model are highlighted in Table 1. All analyses were performed with the use of SAS, version 9.4 (SAS Institute, Cary, North Carolina).

A total of 1,441 patients were screened. Of these patients, 415 and 626 patients did not fulfill the criteria for study inclusion in the sacubitril/valsartan cohort and control cohort, respectively. Unweighted baseline characteristics for included patients are summarized in Table 1. Patients in the sacubitril/valsartan cohort were younger and had a higher incidence of diabetes mellitus (43.6% vs 33.2%; $P = .03$). Patients in the sacubitril/valsartan cohort had a higher baseline hemoglobin compared with the control cohort (13.5 ± 1.9 vs 12.9 ± 2; $P < .01$). Those in the control group had a lower baseline estimated glomerular filtration rate (64.4 ± 32 vs 71.0 ± 25.5 mL/min; $P < .01$). More patients in the sacubitril/valsartan cohort were on guideline-directed heart failure medications. A majority of patients in the sacubitril/valsartan cohort were receiving ACEI or ARB before initiation (96%), with most (61%) being switched to an appropriate sacubitril/valsartan dose according to package labeling.

After inverse propensity weighting, patients in the sacubitril/valsartan cohort had a higher prevalence of the primary end point compared with the control cohort (23.5% vs 17.1%; $P = .04$). This was mainly driven by a higher incidence of hyperkalemia (6.4% vs 2.5%; $P = .02$) and dose reduction (3.5% vs 1.1%; $P = .04$). There were no significant differences in symptomatic hypotension, hypotension, worsening renal function, angioedema, or discontinuation between the cohorts.

The findings of this study elucidate the incidence of real-world side-effects of sacubitril/valsartan, which to our knowledge have not been previously reported. Because the composite primary end point was driven by hyperkalemia and dose reduction, it is hypothesized that subjective factors not recorded in the data or in the electronic medical record may have driven these dose reductions. These results showed an opposite trend for hyperkalemia compared with PARADIGM-HF, with a higher incidence in the sacubitril/valsartan cohort. Reasons for this discordance are unknown, but could potentially be attributed to more stringent exclusion criteria in the PARADIGM-HF trial, including a serum potassium level of >5.2 mmol/L at screening. The present study did not exclude patients who were initiated on treatment with potassium levels >5.2 mmol/L.

There are several limitations of the present study. The sample of patients for this study was limited by the availability of electronic medical record data to confirm initiation of medications and patient outcomes. There are inherent limitations based on the design as a retrospective single-center study and an inability to capture patient data that may have led to dose reductions or discontinuations. Patients in each group were in a different stage of heart failure diagnosis, which led to baseline differences in heart failure medical therapy. However, inverse probability weighting was used to account for these differences.

Table 1. Baseline Patient Characteristics

Characteristic	ACEI/ARB (n = 205)	Sacubitril/ valsartan (n = 195)	*P* Value
Age, y*	64 ± 15	57 ± 14	<.01
BMI, kg/m^2	30.8 ± 8.4	32.1 ± 9.5	.17
Male*	81 (39.5)	154 (79)	<.01
White*	174 (84.9)	156 (80)	.03
Non-Hispanic*	204 (99.5)	193 (99)	.62
Hypertension	140 (68.3)	136 (69.7)	.75
Diabetes mellitus*	68 (33.2)	85 (43.6)	.03
Atrial fibrillation	70 (34.1)	70 (35.9)	.79
Myocardial infarction	85 (41.5)	83 (42.6)	.82
Stroke	23 (11.2)	16 (8.2)	.31
LVEF, %*	26.6 ± 8.6	24.9 ± 8.2	.05
Systolic blood pressure, mm Hg*	119 ± 19.6	115 ± 1.4	.02
Diastolic blood pressure, mm Hg	67.0 ± 15.3	67.6 ± 12.6	.68
Ischemic	88 (42.9)	75 (38.5)	.36
ICD/CRT-D*	75 (36.6)	138 (70.8)	<.01
NYHA functional class*			
I	38 (18.5)	15 (7.7)	.01
II	85 (41.5)	99 (50.8)	
III	65 (31.7)	71 (36.4)	
IV	3 (1.5)	4 (2.1)	
Sodium, mmol/L	139 ± 3	139 ± 3	.21
Potassium, mmol/L	4.3 ± 0.4	4.4 ± 0.4	.23
Serum creatinine, mg/dL*	1.4 ± 1.2	1.2 ± 1.1	.06
eGFR, mL/min*	64.4 ± 32	71.0 ± 25.5	.02
Hemoglobin, g/dL*	12.9 ± 2.04	13.5 ± 1.92	<.01
Diuretic*	131 (63.9)	154 (79)	<.01
Digoxin*	33 (16.1)	52 (26.7)	.01
β-Blocker*	166 (81)	182 (93.3)	<.01
Aldosterone antagonist*	64 (31.2)	137 (70.3)	<.01
Statin	114 (55.6)	110 (56.4)	.87
Allopurinol*	14 (6.8)	30 (15.4)	.01
Starting dose, enalapril equivalents	7.0 ± 6.7	15.2 ± 11.9	<.01

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; ICD/CRT-D, implantable cardioverter-defibrillator/cardiac resynchronization defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

*Variables included in the inverse propensity model.

Heart failure patients initiated on therapy with sacubitril/valsartan had a significant increase in the composite end point compared with those initiated receiving ACEIs or ARBs. Differences in adverse events in this real-world study were mainly driven by dose reduction and hyperkalemia.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.cardfail.2019.03.011.

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