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REVIEW

Sacubitril/valsartan: evaluation of safety and efficacy as an antihypertensive treatment

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Abstract

Hypertension (HTN) is a common disease state associated with extensive morbidity and mortality worldwide. It is often difficult for patients with HTN to achieve and maintain a goal blood pressure (BP), despite there being many effective treatment options available. Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that has garnered approval by the US Food and Drug Administration and the European Medicines Agency as a first-line treatment for heart failure with reduced ejection fraction. During clinical trials for heart failure as well as in independent trials for HTN, sacubitril/valsartan has demonstrated safety and efficacy when it comes to BP lowering, making it a promising antihypertensive agent. Most trials of sacubitril/valsartan were 8 to 12 weeks in length and demonstrated a clinically relevant BP lowering that was frequently more significant than its comparators. While more data are needed to confirm its role as an antihypertensive agent, the data available are promising and it is anticipated that sacubitril/valsartan will gain an indication of HTN.

Keywords: angiotensin receptor blockers, hypertension, neprilysin inhibitor.

Citation

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Introduction

The global prevalence of elevated blood pressure (BP; defined as systolic BP [SBP] and/or diastolic BP [DBP] ≥140/90 mmHg) in adults is estimated to be approximately 22% and was the leading cause of death worldwide in 2010.[1,2] Once diagnosed, treatment of hypertension (HTN) to achieve goal BP is key to reduce morbidity and mortality related to cardiovascular disease (CVD). The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults recommends thiazide diuretics, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB) as primary agents used to treat HTN.[3] While patients with HTN may be started on a single antihypertensive, many will require two antihypertensives at baseline due to the presence of stage 2 HTN and/or will ultimately require ≥ two antihypertensives to reach their BP goal.[3] When more than one agent is required, the antihypertensive agents used should have complementary mechanisms of action.[3]

Sacubitril/valsartan is a novel combination drug containing an existing ARB (valsartan) and a neprilsyn inhibitor (sacubitril) approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with heart failure with reduced ejection fraction (HFrEF).[4,5] While not yet approved for the treatment of HTN, sacubitril/valsartan has been evaluated for this indication in multiple clinical trials and has demonstrated both safety and efficacy in this condition. The beneficial effects of sacubitril/valsartan in HTN are related to inhibition of the catabolism of natriuretic peptides by neprilysin and blockade of angiotensin II, resulting in systemic vasodilation, natriuresis, and diuresis.[6]

This review aims to present and discuss the current evidence regarding the use of sacubitril/valsartan for the treatment of HTN. We conducted an English language MEDLINE search through May 2018 using the search terms 'sacubitril/valsartan', 'LCZ696', and 'hypertension'. A manual search for references identified in these trials and review articles was performed to identify additional relevant articles.

Safety and efficacy of blood pressure lowering with sacubitril/valsartan in patients with heart failure

Sacubitril/valsartan is FDA and EMA approved for use in patients with HFrEF and has been studied both in this population as well as patient with heart failure with preserved ejection fraction (HFpEF). Studies of sacubitril/valsartan that led to its approval noted the beneficial effect of the drug on BP lowering. The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) determined that in 301 patients with HFpEF, defined as left ventricular ejection fraction (LVEF) ≥45%, sacubitril/valsartan lowered BP to a greater extent than valsartan. Patients in this trial were randomized to receive sacubitril/valsartan 200 mg orally twice daily or valsartan 160 mg orally twice daily. At baseline, the median BP in the sacubitril/valsartan group was 136/80 mmHg and 136/78 mmHg in the valsartan group (*p*-value not reported), indicating well-controlled BP at baseline. At 12 weeks, 274 patients had BP data available. Those receiving sacubitril/valsartan (N=137) had a 9/5 mmHg reduction in BP compared to a 3/2 mmHg reduction in BP in patients receiving valsartan (N=137; $p=0.002$). The rates of symptomatic hypotension did not differ between groups (19% in the sacubitril/valsartan group versus 18% in the valsartan group; $p=0.88$). The study authors concluded that the ability of sacubitril/valsartan to significantly lower BP in patients with HFpEF may help to normalize hemodynamic responses and improve signs and symptoms of HF.[7,8]

Patients with HFrEF also experienced significant reductions in BP with the use of sacubitril/valsartan. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial enrolled 8442 patients with HFrEF, defined as a LVEF of <40%, and demonstrated that sacubitril/valsartan reduced SBP significantly more than enalapril. Patients enrolled in this trial were randomized to sacubitril/valsartan 200 mg orally twice daily (N=4187) or enalapril 10 mg orally twice daily (N=4212). The mean SBP at baseline was 122±15 mmHg and 121±15 mmHg in the sacubitril/valsartan and enalapril groups, respectively (*p*-value not reported). After 8 months, patients in the sacubitril/valsartan group had an SBP that was 3.2±0.4 mmHg lower than those in the enalapril group ($p<0.001$). Data from the safety analysis indicated that patients receiving sacubitril/valsartan were more likely to experience symptomatic hypotension than those in the enalapril group (14 versus 9.2%, $p<0.001$); however, this adverse effect rarely led to treatment discontinuation (0.9 versus 0.7%, $p=0.38$).[9] A subsequent analysis of patients from PARADIGM-HF demonstrated that the benefits of sacubitril/valsartan on the primary endpoints of death from cardiovascular (CV) causes or HF hospitalization were consistent across a range of SBP. The authors suggested that patients with HFrEF and a low SBP at baseline will benefit from sacubitril/valsartan, albeit at an increased risk of hypotension.[10]

Safety and efficacy of blood pressure lowering with sacubitril/valsartan in patients with hypertension

Numerous studies have demonstrated beneficial effects of sacubitril/valsartan on BP in patients without HF who have HTN (Table 1).[11–21] The BP lowering effects of sacubitril/valsartan in patients with HTN has been evaluated both alone and in combination with other antihypertensive agents. The most recently published study on this topic by Cheung and colleagues evaluated 376 patients (mean age at baseline 57.6 years old) with an SBP ≥145 mmHg and <180 mmHg (mean baseline SBP was 157.5±9.85 mmHg and mean baseline 24-hour ambulatory SBP was 139.1±14.30 mmHg) who received either sacubitril/valsartan 200 mg orally once daily or olmesartan 20 mg orally once daily. Sacubitril/valsartan provided superior reductions in both 24-hour ambulatory SBP (–4.3 versus –1.1 mmHg; $p<0.001$) and in-office SBP (–14.2 versus –10.0 mmHg) from baseline to 8 weeks, compared with olmesartan. Adverse event rates between groups were similar (23.4 versus 21.9%, respectively), with headache and dizziness being those most commonly reported.[11] A similar study by Supasyndh et al. also evaluated the BP-lowering effects of sacubitril/valsartan 200 mg orally once daily (N=296) compared with olmesartan 20 mg orally once daily (N=292) over 14 weeks, albeit in an older population (mean age at baseline 70.7 years old). At week 10 of 14, patients with BP >140/90 mmHg had their antihypertensive doses up-titrated to sacubitril/valsartan 400 mg orally daily or olmesartan 40 mg orally daily, respectively. At week 10, sacubitril/valsartan demonstrated superior SBP lowering over olmesartan (–22.71 versus –16.11 mmHg; $p<0.001$). This effect was sustained at week 14, despite more patients in the olmesartan group requiring dose up-titration (–22.53 versus –16.75 mmHg; $p<0.001$). Adverse event rates were similar between groups (47.6 versus 38.7%; *p*-value not reported) with the most common being nasopharyngitis, hyperuricemia, and upper respiratory tract infection.[12]

A study by Schmieder and colleagues compared higher doses of sacubitril/valsartan (400 mg orally once daily) and olmesartan (40 mg orally once daily) in 114 patients (mean baseline age approximately 60 years old) with HTN (SBP >140 mmHg; mean baseline SBP approximately 155 mmHg). At the end of 12 weeks, in-office SBP was reduced to a greater extent by sacubitril/valsartan compared to olmesartan (–25.7 versus –22.8 mmHg), though this difference was not statistically significant ($p=0.31$). After 52 weeks, however, the difference in SBP lowering with sacubitril/valsartan was statistically significant (–26.1 versus –20.8 mmHg; $p=0.028$). During the 40-week extension phase from week 12 to week 52, 10 patients (17.5%) in the sacubitril/valsartan group and 17 patients (29.8%) in the olmesartan group received amlodipine add-on therapy ($p=0.12$). In addition to BP lowering, left ventricular mass changes were evaluated as well. Left ventricular mass

Table 1. Blood pressure lowering with sacubitril/valsartan in patients with hypertension.

Author (year)	Drug dose (total daily mg)	N	Duration (weeks)	Δ SBP[a] (mmHg)	Δ DBP[a] (mmHg)
Cheung (2018)[11]	S/V 200	188	8	–4.5	–2.3
	Olmesartan 20	188	8	–1.1	–0.3
Supasyndh (2017)[12]	S/V 200	295	10	–22.71	–8.58
	Olmesartan 20	291	10	–16.11	–6.49
Schmieder (2017)[13]	S/V 400	57	12	–25.7	–11.9
	Olmesartan 40	57	12	–22.8	–12.1
Williams (2017)[14]	S/V 400	229	12	–13.3	–7.4
	Olmesartan 40	225	12	–9.1	–5.5
Izzo (2017)[15]	S/V 400	142	8	–21.8	–9.6
	Sacubitril 400 + valsartan 320	144	8	–20.9	–8.5
	Sacubitril 200 + valsartan 320	145	8	–23.6	–9.8
	Sacubitril 100 + valsartan 320	141	8	–21.3	–8.0
	Sacubitril 50 + valsartan 320	134	8	–19.3	–7.2
	Valsartan 320	143	8	–16.1	–7.3
	Placebo	57	8	–7.0	–3.4
Wang, TD (2017)[16]	S/V 400	36	4	–13.3	–6.2
	Valsartan 320	36	4	–5.8	–4.2
Wang, JG (2017)[17]	S/V 200 + Amlodipine 5	123	8	–13.9	–8.0
	Amlodipine 5	128	8	–0.8	–0.3
Kario (2016)[18]	S/V 200	35	2	–21.1	–12.9
	S/V 400	32	4	–23.1	–14.0
Ito (2015)[19]	S/V 100	32	2	–13.4	–5.2
	S/V 200	26	4	–19.4	–6.8
	S/V 400	18	8	–20.4	–8.1
Kario (2014)[20]	S/V 100	100	8	–16.83	–11.53
	S/V 200	98	8	–17.54	–10.98
	S/V 400	96	8	–20.35	–12.45
	Placebo	92	8	–4.97	–3.69
Ruliope (2010)[21]	S/V 100	154	8	–6.02	–3.19
	S/V 200	168	8	–11.00	–6.14
	S/V 400	170	8	–12.50	–6.85
	Valsartan 80	163	8	–4.72	–2.36
	Valsartan 160	163	8	–5.69	–3.17
	Valsartan 320	163	8	–6.44	–4.15
	Sacubitril 200	164	8	–4.20	–2.99

[a]Change from baseline sitting blood pressure.
DBP, diastolic blood pressure; SBP, systolic blood pressure; S/V, sacubitril/valsartan.

decreased to a greater extent in the sacubitril/valsartan group compared to the olmesartan group, even after adjustment for SBP. The results were not quite statistically significant at 12 and 52 weeks (–3.57 g/m^2, p=0.0619 and –2.80 g/m^2, p=0.0529); the authors note that sacubitril/valsartan may have a positive effect on LV mass reduction independent of BP lowering.[13] Similar findings to this study were reported by Williams et al. who evaluated the same drugs and doses over a 12-week

period. However, in the Williams study, a statistically significant difference in SBP lowering by sacubitril/valsartan was achieved by 12 weeks. Patients in this study had a baseline mean age of 67.7 years old and SBP of 158.6 mmHg. At 12 weeks, patients in the sacubitril/valsartan group had a decrease in SBP of 13.3 mmHg, compared to 9.1 mmHg in the olmesartan group (p<0.001). By 52 weeks, the change in SBP was no longer statistically significant between groups (–14.2 versus –14.3 mmHg; p=0.831); however, in the extension phase, patients could receive amlodipine and/or hydrochlorothiazide add-on therapy for ongoing BP ≥140/90 mmHg. Seventy-four (32%) of patients in the sacubitril/valsartan group required add-on therapy and 105 (47%) of patients in the olmesartan group did, which could have confounded the degree of SBP lowering at 52 weeks. Similar to other studies, the most commonly reported adverse effects in each group were nasopharyngitis, headache, dizziness, and cough.[14]

Izzo and colleagues compared sacubitril/valsartan 400 mg orally once daily against valsartan 320 mg orally daily monotherapy and valsartan 320 mg orally daily with increasing doses of free sacubitril (50, 100, 200, or 400 mg orally once daily) or placebo. A total of 907 hypertensive patients with an in-office SBP of 150–179 mmHg (mean 160 mmHg) were enrolled and randomized to 1 of 7 treatment groups. At the end of 8 weeks, sacubitril/valsartan 400 mg orally once daily demonstrated superior in-office (–21.8 versus –16.1 mmHg; p<0.05) and 24-hour ambulatory (–13.0 versus –9.6 mmHg; p<0.05) SBP lowering compared to valsartan 320 mg orally once daily. When all 7 groups were compared, valsartan 320 mg plus free sacubitril 200 mg orally once daily had the most comparable BP lowering to sacubitril/valsartan 400 mg orally once daily (Table 1). Interestingly, the largest proportion of patients who experienced at least one adverse effect occurred in the placebo group with diarrhea being the most common, followed by headache, dizziness, and cough.[15]

A small study by Wang and colleagues compared sacubitril/valsartan 400 mg orally once daily with valsartan 320 mg orally once daily over 4 weeks in 75 patients with salt-sensitive HTN. At 4 weeks, patients receiving sacubitril/valsartan experienced increased natriuresis, diuresis, and decreased BP, compared to patients receiving valsartan. The change in SBP was –13.3 mmHg for those in the sacubitril/valsartan group, compared with –5.8 mmHg for those in the valsartan group (p=0.002). The proportions of patients experiencing adverse events were similar between groups (32.4 versus 32.8%; p-value not reported), and the most commonly reported adverse events were dizziness, hematuria, headache, nasopharyngitis, and cough.[16]

Another recent study compared sacubitril/valsartan 200 mg orally once daily with add-on amlodipine 5 mg orally once daily therapy with amlodipine 5 mg orally once daily monotherapy in 251 patients with HTN over 12 weeks. Not surprisingly, sacubitril/valsartan plus amlodipine was far superior to amlodipine alone in BP reduction. Ambulatory blood pressure monitoring (ABPM) demonstrated an SBP reduction of 13.9 mmHg in the sacubitril/valsartan plus amlodipine group, compared with 0.8 mmHg in the amlodipine monotherapy group (p<0.001). Adverse event rates were similar between groups (20.0 versus 21.3%, respectively) and included nasopharyngitis, dizziness, and upper respiratory tract infection as those most commonly reported.[17]

Earlier studies of sacubitril/valsartan for the treatment of HTN compared various fixed-dose combinations against one another and against valsartan monotherapy.[18–21] In each case, the higher the dose of sacubitril/valsartan, the more pronounced the BP-lowering effect. Studies of sacubitril/valsartan 400 mg orally once daily yielded SBP reductions between 12.5 and 23.1 mmHg.[18–21] Additionally, the combination of sacubitril/valsartan demonstrated superior BP lowering compared to valsartan monotherapy.[21] Adverse events were generally mild and of similar frequencies between groups with nasopharyngitis being the most commonly observed.[18–20]

In contrast to the use of sacubitril/valsartan in patients with HF (either HFpEF or HFrEF), hypotension was rarely reported in patients treated with sacubitril/valsartan for HTN. Hypotension was either reported at an incidence of 1 to 2% or not reported at all.[11–21] This is likely because the patients in the sacubitril/valsartan HF studies typically had lower baseline BP values than those enrolled in the sacubitril/valsartan HTN studies and the treatment doses for HF were twice daily as opposed to once daily for HTN.

Ongoing studies of sacubitril/valsartan in patients with hypertension

This article has reviewed the sacubitril/valsartan studies that have been completed in patients with HF with and without HTN and with HTN alone. There remain many questions on the optimal role sacubitril/valsartan can play in the management of patients with chronic HTN and/or resistant HTN. There are several completed studies with results on clinicaltrials.gov, but the final results are yet to be published in peer-reviewed journals. These completed, unpublished study findings are outlined in Table 2.[22–24] These studies range from comparison trials with other ARBs, long-term tolerability studies, and studies evaluating sacubitril/valsartan as add-on therapy to amlodipine.

There are two clinical trials that have evaluated sacubitril/valsartan compared with olmesartan in the treatment of HTN that have been completed but yet to have the final results published in the medical literature.[22,23] These trials were 8 weeks in duration, similar to other published studies. These trials demonstrated a mean change in sitting SBP with sacubitril/valsartan in the range of –18 to –20 mmHg, but only one concluded sacubitril/valsartan to be noninferior to olmesartan, as the other reported no statistical analysis.[22,23]

Table 2. Summary of completed, unpublished sacubitril/valsartan hypertension trials.

Trial	N	Duration (weeks)	Intervention (total daily mg)	Primary outcome (SBP reported as mmHg)	Comments	Completion date
NCT01785472[22]	1435	8		Mean change in sitting SBP	Demonstrated non-inferiority at both doses	December 2016
			S/V 200	–20.48±0.61		
			S/V 400	–21.67±0.62		
			Olmesartan 20	–18.15±0.61		
NCT01599104[23]	1161	8		Mean change in sitting SBP	No statistical analysis reported	October 2015
			S/V 200	–18.21±0.70		
			S/V 400	–20.18±0.70		
			Olmesartan 20	–13.20±0.70		
NCT01256411[24]	341	52		Total adverse events	No statistical analysis reported	October 2015
			S/V 200	147		
			S/V 400	78		
			S/V 400 + Amlodipine 10	53		
			S/V 400 + Amlodipine 10 + HCTZ 25	0		
				Mean change in sitting SBP[a]		
			S/V 200	–24.1±12.16		
			S/V 400	–21.3±11.46		
			S/V 400 + Amlodipine 10	–28.1±13.43		
			S/V 400 + Amlodipine 10 + HCTZ 25	–29.0±9.23		

[a]Secondary outcome.
HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; S/V, sacubitril/valsartan.

It is our hope these studies will be published in their full form in the future, but with many of them completing in 2015 to 2016, we may not see these published in full form moving forward.

Long-term safety and tolerability out to one year has been evaluated in one study that has been completed and is yet to be published in full form.[24] This study evaluated the ongoing safety of sacubitril/valsartan at doses of 200 mg orally once daily and 400 mg orally once daily as monotherapy and in combination with amlodipine and hydrochlorothiazide. The primary outcome was to evaluate the total number of adverse events, serious adverse events, and deaths in each of these treatment groups. The study included 341 patients across 4 treatment groups with 67% of patients receiving monotherapy with sacubitril/valsartan and only 4 patients receiving sacubitril/valsartan in combination with both amlodipine and hydrochlorothiazide. There were 231 total adverse events reported in patients receiving monotherapy with sacubitril/valsartan, and 13 of these were deemed serious. And there were no deaths. The types of adverse events are consistent with previously published trials. Unfortunately, no statistical analysis was performed on the outcome of adverse events in this trial. Secondary outcomes demonstrated similar mean changes in sitting SBP as previous studies have (in the –20 mmHg range).

As highlighted earlier, there are a number of studies evaluating sacubitril/valsartan for HTN, which are completed but not available in full form in the medical literature. There is a need to continue to push for these studies to be published in the medical literature to further describe the role of sacubitril/valsartan in the management of hypertension. In addition, there is a greater need to further evaluate sacubitril/valsartan compared with all four of the first-line antihypertensive medication classes in a large trial in order to best determine the role of sacubitril/valsartan in HTN management across the general hypertensive population and in subpopulations.

Implications for practice

While sacubitril/valsartan is not yet FDA or EMA approved for the treatment of HTN, the data available support that it produces clinically meaningful BP lowering in patients with HTN. The FDA and EMA consider BP lowering a valid surrogate endpoint to approve medications to treat HTN. The combination of an ARNI is novel in the HTN treatment armamentarium and offers a complimentary mechanism of action to other first-line antihypertensive therapies (e.g. ACEI, CCB, thiazide diuretics). When compared to active controls, including olmesartan and valsartan, sacubitril/valsartan consistently lowers SBP and DBP to a greater extent. The side-effect profile of sacubitril/valsartan is comparable to other antihypertensive agents, meaning that it does not confer a larger risk than treatment with other agents does. Sacubitril/valsartan should also be evaluated for its role in resistant hypertension. The ability of the drug to promote systemic vasodilation, diuresis, natriuresis may make it an ideal treatment in patients with treatment refractory or resistant hypertension. However, further studies are needed to evaluate the role of sacubitril/valsartan as part of a triple or quadruple drug regimen for HTN. The issues that will likely be the most influential in the acceptance of sacubitril/valsartan as an antihypertensive agent are: 1) FDA and EMA approval for the treatment of HTN, 2) HTN guideline inclusion, and 3) cost. Having an approved indication for HTN and subsequent review of and acceptance by national and international guideline committees would cement sacubitril/valsartan's place in therapy as an antihypertensive. The current average wholesale price for 60 tablets of 200 mg sacubitril/valsartan is US$555.91. This cost is significantly more expensive than many of the current first-line antihypertensives that are available in generic form for a fraction of the cost.

Conclusion

Sacubitril/valsartan is FDA and EMA approved for the treatment of HFpEF and has demonstrated safety and efficacy as an antihypertensive agent. Completed but not yet published studies of sacubitril/valsartan need to be fully described in the literature to aid in this determination. Given the available data, sacubitril/valsartan likely has a role as an antihypertensive agent, pending an expanded indication to include hypertension. If approved, it will be important to further study this agent against currently used antihypertensive agents to determine its specific role in therapy.

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