Journal of Drug Abuse
ISSN: 2471-853X

Open access Review Article

Sacubitril/Valsartan: A New Antihypertensive Drug in the Future?

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ABSTRACT

Hypertension is one of the leading epidemic factors of cardiovascular and cerebrovascular disease around the world. Many researchers have found that Sacubitril/Valsartan, the single angiotensin receptor-neprilysin inhibitor, played a critical role in lowering hypertension. However, Sacubitril/Valsartan's indications and usage for hypertension has not been accepted in the world, except for China. The mechanism of Sacubitril/Valsartan's antihypertensive effect is clear, including inhibiting renin-angiotensin system and reducing natriuretic peptides' degradation. In this article, we retrieved and reviewed all clinical studies that explored the effect of Sacubitril/Valsartan or its safety in the treatment of hypertension patients. Most studies concluded that in comparison with traditional antihypertensive drugs (mainly including angiotensin receptor blockers or amlodipine), Sacubitril/Valsartan was firmly effective and safe. Thus, we deduce that Sacubitril/Valsartan' indication for hypertension will be paid more attention and may be included in guideline for hypertension soon.

Key Words: Sacubitril/Valsartan; Hypertension; Efficacy; Safety

INTRODUCTION

Hypertension, as a main risk factor for cardio-cerebrovascular disease, is prevalent all over the world [1]. As a critical clinical treatment for hypertension, antihypertensive drugs have mainly included angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics, and calcium channel blockers. Although these antihypertensive drugs are used widely, the control rate of hypertension is still low [1]. In consideration that one of the main adverse events from Sacubitril/Valsartan was hypotension in the treatment of heart failure, large numbers of studies paid much attention to the antihypertensive effect of Sacubitril/Valsartan in hypertension patients. The pharmacological mechanisms of Sacubitril/Valsartan in lowering hypertension are inhibiting degradation of natriuretic peptides by neprilysin and antagonizing renin-angiotensin system [2]. Until now, Sacubitril/Valsartan's indication for the treatment of hypertension has not been enrolled, except for China. In this review, we listed these studies in **Table 1** and discussed the evidence on Sacubitril/Valsartan lowering hypertension.

Table 1: Ten RCTs, seven meta-analyses and one open-label study showed the evidence on Sacubitril/Valsartan lowering hypertension

RCT	Open-label study	RCT	RCT	RCT	RCT(the PARAMETER study)	RCT(the RATIO study)	RCT	RCT
24446062	25693859	29338113	28992296	29029087	28093466	28338503	28030431	30536595

Received:	01-August-2022	**Manuscript No:**	ipjda-22-14255
Editor assigned:	03-August-2022	**PreQC No:**	ipjda-22-14255(PQ)
Reviewed:	17-August-2022	**QC No:**	ipjda-22-14255
Revised:	22-August-2022	**Manuscript No:**	ipjda-22-14255
Published:	29-August-2022	**DOI:**	10.36648/2471-853X.22.8.111

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Citation Liu B, Rui Z, Zhang A, Jian W, Guangfang Z, et al. (2022) Sacubitril/Valsartan: A New Antihypertensive Drug in the Future? J Drug Abuse. 8:111.

https://doi.org/10.1161/hypertensionaha.113.02002	https://doi.org/10.1038/hr.2015.1	https://doi.org/10.1111/jch.13153	https://doi.org/10.1093/ajh/hpx111	https://doi.org/10.1093/eurheartj/ehx525	https://doi.org/10.1161/hypertensionaha.116.08556	https://doi.org/10.1097/fjc.0000000000000485	https://doi.org/10.1097/hjh.0000000000001219	https://doi.org/10.1111/jch.13437
Kario et al.	Ito et al.	Cheung et al.	Supasyndh et al.	Schmieder et al.	Williams et al.	Izzo et al.	Wang et al.	Huo et al.
2014	2015	2017	2017	2017	2017	2017	2017	2019
Japan	Japan	USA	Japan	Germany	The United Kingdom	USA	China	China
Sacubitril/valsartan vs. Placebo	Sacubitril/valsartan vs. Baseline	Sacubitril/valsartan vs. Olmesartan	Sacubitril/valsartan vs. Olmesartan	Sacubitril/valsartan vs. Olmesartan	Sacubitril/valsartan vs. Olmesartan	Sacubitril/valsartan vs. Valsartan	Sacubitril/valsartan/amlodipine vs. Amlodipine	Sacubitril/valsartan vs. Olmesartan
100/200/400 mg	400 mg	200 mg vs. 20 mg	200 mg vs. 20 mg	400 mg vs. 40 mg	400 mg vs. 20 mg	400 mg vs. 320 mg	200 mg/5 mg vs. 5 mg	200/400 mg vs. 20 mg
389	32	376	588	114	454	907	255	1438
9 weeks	9 weeks	8 weeks	52 weeks	15 weeks	52 weeks	8 weeks	8 weeks	8 weeks
The least squares mean differences in change from baseline in clinic diastolic blood pressure were −7.84, −7.29, and −8.76 mmHg for sacubitril/valsartan 100, 200, and 400mg, respectively, compared with placebo (all P<0.0001). Similarly, the least squares mean differences in change from baseline in clinic systolic blood pressure were −11.86, −12.57, and −15.38 mmHg for sacubitril/valsartan 100, 200, and 400mg, respectively, compared with placebo (all P<0.0001).	The mean sitting systolic blood pressure (msSBP)±s.d. was reduced from 151.6±10.3 mmHg at baseline to 138.2±12.1 mmHg at week 2, followed by a further decrease to 132.2±10.8 mmHg at week 4, which remained stable thereafter at week 6 (132.5±13.1 mmHg) and at week 8 (131.2±11.1 mmHg). The mean±s.d. decrease in msSBP from baseline to week 8 end point was 20.5±11.3 mmHg. The mean sitting diastolic blood pressure (msDBP) was reduced from 86.9±10.8mmHg at baseline to 81.7±10.1 mmHg at week 2, followed by a further decrease to 80.1±10.0 mmHg at week 4 and 79.4±10.4 mmHg at week 6 and remained stable until week 8 (78.8±10.7 mmHg). Mean±s.d. decrease in msDBP from baseline to week 8 end point was 8.3±6.3 mmHg.	Sacubitril/valsartan 200 mg provided superior reductions in 24-hour mean ambulatory systolic blood pressure from baseline to week 8 vs. olmesartan 20 mg. Compared with olmesartan, sacubitril/valsartan provided significantly greater least square mean reduction in 24-hour mean ambulatory diastolic blood pressure from baseline at week 8.	At week 10, sacubitril/valsartan provided superior office mean sitting systolic blood pressure reductions vs. olmesartan (22.71 vs. 16.11 mm Hg, respectively; P < 0.001).	Central systolic blood pressure (SBP) and diastolic blood pressure (DBP) both decreased from baseline to 52 weeks, with no-significant differences between the sacubitril/valsartan and olmesartan patients (mean difference: SBP: -3.03mmHg; 95% CI: -7.23, 1.17; P= 0.156; DBP: 0.11mmHg; 95% CI: -2.85, 3.08; P=0.939). The decrease in central pulse pressure was significantly greater in the sacubitril/valsartan group (-6.54mmHg, 95% CI: -8.4, -4.67) compared to the olmesartan group (-3.04mmHg, 95% CI: -4.91, -1.17) after 52 weeks (mean difference: -3.50mmHg; 95% CI: -6.15, -0.85; P = 0.010).	At week 12, sacubitril/valsartan reduced central aortic systolic pressure greater than olmesartan by −3.7 mmHg (P=0.010), further corroborated by secondary assessments at week 12 (central aortic pulse pressure, −2.4 mmHg, P<0.012; mean 24-hour ambulatory brachial systolic blood pressure and central aortic systolic pressure, −4.1 mmHg and −3.6 mmHg, respectively, both P<0.001). Differences in 24-hour ambulatory pressures were pronounced during sleep. After 52 weeks, blood pressure parameters were similar between treatments (P<0.002); however, more patients required add-on antihypertensive therapy with olmesartan (47%) versus sacubitril/valsartan (32%; P<0.002).	Compared with valsartan 320 mg, sacubitril/valsartan 400 mg provided significantly greater office blood pressure and pulse pressure reductions at endpoint: least squares mean (LSM) between-treatment difference (standard error) of -5.7 (1.7) mmHg for office systolic blood pressure, -2.3 (1.1) mmHg for office and diastolic blood pressure, and -3.4 (1.3) mmHg for office pulse pressure (P<0.05 for all).	Sacubitril/valsartan/amlodipine combination therapy provided greater reductions in 24-h ambulatory systolic blood pressure compared with amlodipine monotherapy, with an least-squares mean between-treatment difference of 13.1 (95% CI;14.4, 11.8) mmHg (P<0.001) at week 8.	Sacubitril/valsartan 200 mg provided a significantly greater reduction in mean sitting systolic blood pressure than olmesartan 20 mg at week 8 (between□ treatment difference: −2.33 mmHg [95% confidence interval (CI) −4.00 to −0.66 mm Hg], P < 0.05 for non□inferiority and superiority). Greater reductions in mean sitting systolic blood pressure were also observed with sacubitril/valsartan 400 mg vs olmesartan 20 mg (−3.52 [−5.19 to −1.84 mmHg], P< 0.001 for superiority).

In this study, all doses of sacubitril/valsartan were well tolerated, and no cases of angioedema or death were reported.	The incidence of any adverse events was 43.8% in patients with hypertension and renal dysfunction without a decline in renal function.	The overall incidence of adverse events was comparable between the sacubitril/valsartan (23.4%) and the olmesartan (21.9%) groups.	The incidence of adverse events was 47.6% in the sacubitril/valsartan group and 38.7% in the olmesartan group. Similar proportions of patients had adverse events related to the study treatment in both the treatment groups (sacubitril/valsartan group, 12(4.1%) patients; olmesartan group, 15 (5.1%) patients).	N/A	The incidence of adverse events was slightly higher in the sacubitril/valsartan-based regimen (57.6%) compared with the olmesartan-based regimen (53.8%), with nasopharyngitis being the most common adverse event.	N/A	The overall incidence of adverse events was similar between the sacubitril/valsartan/amlodipine group and the amlodipine group (20.0% and 21.3%, respectively).	The incidence of severe adverse events was rare and similar in all the treatment groups.

RCT	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis
35058583	28793821	31305392	30937854	30664018	32726791	33951700	35672897
https://doi.org/10.1038/s41440-021-00819-7	https://doi.org/10.1177/10742 48417693379	https://doi.org/10.1097/md.0000000000016093	https://doi.org/10.1007/s40292-019-00313-9	https://doi.org/10.1097/mjt.0000000000000925	https://doi.org/10.1159/000507327	https://doi.org/10.1097/fjc.0000000000001001	https://doi.org/10.21037/apm-22-503
Rakugi et al.	Zhao et al.	Li et al.	Vecchis et al.	Malik et al.	Geng et al.	Yang et al.	Wu et al.
2022	2017	2019	2019	2019	2020	2021	2022
Japan	China	China	Italy	USA	China	China	China
Sacubitril/valsartan vs. Olmesartan	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs	Sacubitril/valsartan vs. ARBs
200/400 mg vs. 20 mg	100/200/400 mg vs. not shown	100/200/400 mg vs. 20/40/320 mg	100/200/400 mg vs. 20/40/80/160/320 mg	200/400 mg vs. not shown	100/200/400 mg vs. 10/20/40/80/160/320 mg	100/200/400 mg vs. 10/20/40/80/160/320 mg	200/400 mg vs. 20/40/320 mg
1161	3816	6765	1513	6028	6064	7224	3323
8 weeks	8 weeks to 52 weeks	8 weeks to 52 weeks	4 weeks to 52 weeks	4 weeks to 48 weeks	5 weeks to 52 weeks	8 weeks to 52 weeks	4 weeks to 52 weeks

Sacubitril/ valsartan 200 mg provided a significantly greater reduction in mean sitting systolic blood pression from baseline than olmesartan at week 8 (between-treatment difference: −5.01 mmHg [95% confidence interval: −6.95 to −3.06 mmHg, P< 0.001 for noninferiority and superiority]). Greater reductions in mean sitting systolic blood pression with sacubitril/valsartan 400 mg vs. olmesartan, as well as in mean sitting diastolic blood pressure and mean sitting pluse pression with both doses of sacubitril/ valsartan vs. olmesartan (P < 0.05 for all), were also observed.	Sacubitril/ valsartan was more effective in reducing blood pressure (odds ratio [OR]= 5.34; 95% CI: 4.49 to 6.36; P < 0.01) and had a higher rate of blood pressure control compared with ARBs (OR =1.52; 95% CI: 1.37 to 1.69; P < 0.01).	Evidences showed sacubitril/valsartan, compared with ARBs, achieved a better blood pressure control rate (OR 1.24, 95% CI: 1.14 to 1.35), specifically, sacubitril/ valsartan was better at reducing systolic blood pressure [weighted mean difference (WMD) 4.11 mmHg, 95% CI: (5.13, 3.08) mmHg], diastolic blood pressure [WMD 1.79 mmHg, 95% CI: (2.22, 1.37) mmHg], mean 24-hour ambulatory systolic blood pressure [WMD 3.24 mmHg, 95% CI: (4.48, 1.99) mmHg] and mean 24-hour ambulatory diastolic blood pressure [WMD 1.25 mmHg, 95% CI: (1.81, 0.69) mmHg].	Compared with ARBs, after 12 weeks there was a significant reduction in systolic blood pressure in the sitting position and diastolic blood pressure in the sitting position (weight mean difference [WMD] = − 5.41 mmHg, 95% CI − 7.0 to − 3.8; P < 0.01), msDBP (WMD = − 1.22 mmHg, 95% CI : − 2.15 to − 0.3; P < 0.01), ambulatory systolic blood pressure (WMD = − 4.58 mmHg, 95% CI: − 5.62 to − 3.54; P < 0.01) and ambulatory diastolic blood pressure (WMD = − 2.17 mm Hg, 95% CI: − 2.78 to − 1.56; P < 0.01).	Compared with ARBs, 200 mg of sacubitril/valsartan reduced systolic blood pressure and diastolic blood pressure by 4.62 mmHg (95% confidence interval, 3.33 to 5.90, P<0.001) and 2.13 mmHg (95% confidence interval, 1.69 to 2.57, P<0.001), respectively. Similarly, 400mg of sacubitril/valsartan reduced systolic blood pressure and diastolic blood pressure by 5.50 mmHg (2.94 to 8.07, P<0.001) and 2.51 mmHg (1.80–3.21, P<0.001), respectively, in comparison with ARBs.	Compared with ARBs, sacubitril/ valsartan 100mg, 200mg, 400mg caused a significant reduction in systolic blood pressure and diastolic blood pressure,respectively. And sacubitril/ valsartan 200mg, 400mg caused a significant reduction in 24-h ambulatory systolic blood pressure and and 24-h ambulatory diastolic blood pressure.	Compared with ARBs, a significant reduction in mean sitting systolic blood pressure (WMD 24.79 mmHg; 95% CI: 25.46 to 24.11 mmHg; P<0.001) and mean sitting diastolic blood pressure (WMD 22.12mmHg; 95% CI: 22.53 to 21.71 mmHg; P<0.001) was observed with hypertensive patients receiving therapy of sacubitril/ valsartan.	The effects of reducing mean reductions in sitting systolic blood pressure and mean reductions in sitting diastolic blood pressure in the sacubitril/ valsartan group were significantly better than that in the ARBs group (mean reductions in sitting systolic blood pressure: mean difference (MD) =−4.70, 95% CI: −5.79 to −3.61, P<0.001; mean reductions in sitting diastolic blood pressure: MD =−2.29, 95% CI: −2.53 to −2.04, P<0.001).

The incidences of any adverse events were 34.9%, 35.3% and 39.1% in sacubitril/valsartan 200 mg group, sacubitril/valsartan 400 mg group and olmesartan 20mg group.	Sacubitril/valsartan had no difference in the incidence of adverse events (OR=1.05; 95% CI: 0.94 to 1.18; P=0.38) or serious adverse events (OR=0.80; 95% CI: 0.51 to 1.24; P=0.31) compared to ARBs.	There was no difference in the events of adverse events (risk ratio [RR] 1.01, 95% CI: 0.39 to 1.09), serious adverse events (RR 0.80, 95% CI: 0.52 to 1.22) and discontinuation of treatment for any adverse events (RR 0.79, 95% CI: 0.56 to 1.11) between sacubitril/valsartan group and ARB/placebo group, except sacubitril/valsartan reduced the rate of headaches (RR 0.69, 95% CI: 0.48 to 0.99) while increased cough (RR 2.12, 95% CI: 1.11 to 4.04; P = 0.02).	It showed that adverse events were more frequent in sacubitril/valsartan group than olmesartan or valsartan groups (odds ratio = 1.27, 95% CI 1.03 to 1.57, P= 0.03)	Sacubitril/valsartan therapy was not found to be associated with any higher adverse effects or serious adverse effects compared with either placebo or an ARB.	N/A	We discovered that the result shows no statistical difference in the rate of any adverse events between sacubitril/valsartan and ARBs group (RR = 1.10; 95% CI: 0.96 to 125; P = 0.17).	There was no significant difference in the incidence of adverse events, severe adverse events, and discontinuations due to adverse events between the sacubitril/valsartan group and the ARBs group (adverse events: OR =1.14, 95% CI: 1.00 to 1.31, P=0.06; severe adverse events: OR =1.06, 95% CI: 0.64 to 1.76, P=0.81; discontinuations due to adverse events: OR =0.86, 95% CI: 0.51 to 1.46, P=0.58).

THE EFFICACY OF SACUBITRIL/VALSARTAN IN LOWERING HYPERTENSION

Ten RCTs, seven meta-analyses and one open-label study showed the evidence on Sacubitril/Valsartan lowering hypertension. We detailedly presented these researches in Table 1.

The first trial on assessing Sacubitril/Valsartan's efficacy in lowering hypertension was published on Lancet in 2010. In this study, 1328 patients with mild-to-moderate hypertension were treated by Sacubitril/Valsartan or valsartan in 8 weeks. After 8 weeks' treatment, Sacubitril/Valsartan's anti-hypertension effect was more obvious in comparison with valsartan [3]. One RCT investigated the antihypertensive effects of Sacubitril/Valsartan 200 mg per day versus olmesartan 20 mg per day in hypertension patients. Sacubitril/Valsartan presented a superior effect on lowering mean sitting systolic blood pressure (msSBP) than olmesartan (-22.71 versus -16.11 mmHg; P<0.001) in 10 weeks. And this antihypertensive effect was still stable in 14 weeks (-22.53 versus -16.75 mmHg; P<0.001) [4]. Another study evaluated the effect of lowering blood pressure by Sacubitril/Valsartan or olmesartan in patients with high SBP ranging from 145 mmHg to 180 mmHg. It found that the reduction of 24 hours mean ambulatory SBP were more obvious in the Sacubitril/Valsartan group versus the olmesartan group (P<0.001) [5]. And the reduction of office SBP was larger by Sacubitril/Valsartan (-14.2 versus -10.0 mmHg) after 8 weeks in comparison with olmesartan [5]. Sacubitril inhibiting the catabolism of natriuretic peptides probably enhances Sacubitril/Valsartan's antihypertensive effect. A recent published RCT showed that the decrease of msSBP, mean sitting diastolic blood pressure and mean sitting pulse pression were more significant in Sacubitril/Valsartan 200/400 mg group versus olmesartan 20 mg group at week 8 (P<0.05 for all) [6]. The effect of drug combination therapy by Sacubitril/Valsartan and other anti-hypertension drugs was also explored. One study evaluated the efficacy of Sacubitril/Valsartan in hypertension patients who were treated by amlodipine 5 mg/day and did not obtain the standard of normal blood pressure after 4 weeks [7]. Larger reductions in 24 h SBP were obtained in Sacubitril/Valsartan+amlodipine group in week 8, compared with amlodipine group (P<0.001). The study indicated that Sacubitril/Valsartan+amlodipine might be a better choice for patients who failed to lower hypertension with amlodipine. The PARAMETER trial, enrolled elderly patients with systolic hypertension and arterial sclerosis, verified that Sacubitril/Valsartan had a more significant antihypertensive effect, especially in reduction of central aortic and brachial pressures, compared with olmesartan [8]. Another trial, enrolled 32 hypertension patients with renal disfunction from Japan, showed that Sacubitril/Valsartan not only lowered hypertension but also did not aggravate renal function [9]. Sacubitril/Valsartan might be suitable for hypertension patients with renal disfunction. But it was noteworthy that many RCTs on exploring Sacubitril/Valsartan's efficacy in hypertension patients were funded by corporations. Although the number of RCTs on evaluating Sacubitril/Valsartan's antihypertensive effect was large, the real world study was few.

Seven meta-analyses compared the efficacy between Sacubitril/

Valsartan and angiotensin receptor blockers (ARBs) in hypertension patients. A meta-analysis, enrolled 9 RCTs, provided compelling evidence that the intensity of lowering hypertension was more significant in Sacubitril/Valsartan group than ARBs group, including a higher blood pressure control rate, more obvious reduction in systolic blood pressure, diastolic blood pressure, mean 24 hours ambulatory systolic blood pressure, and mean 24 hours ambulatory systolic blood pressure [10].

All in all, Sacubitril/Valsartan was likely to have obviously antihypertensive effect in hypertension patients. Most of studies showed that Sacubitril/Valsartan lowered high blood pressure including systolic blood pressure, diastolic blood pressure, mean 24 hours ambulatory systolic blood pressure, and mean 24 hours ambulatory systolic blood pressure. And the effect might be more obvious when Sacubitril/Valsartan combined with amlodipine.

THE SAFETY OF SACUBITRIL/VALSARTAN IN LOWERING HYPERTENSION

According to statistics, the adverse events (AEs) of Sacubitril/Valsartan in lowering hypertension mainly include hyperuricemia, hypotension, dizziness, hyperkalemia, cough, headaches, nasopharyngitis, and angioedema [2]. The mechanism of happening AEs may be related with the effect of Sacubitril/Valsartan to vessels and kidney or inhibiting degradation of bradykinin. Eight RCTs, one open-label study and six meta-analyses explored Sacubitril/Valsartan's safety in hypertension patients (Table 1). A RCT detected the safety of Sacubitril/Valsartan in Asian patients who had mild-to-moderate hypertension. This trial indicated that compared with olmesartan (20 mg), Sacubitril/Valsartan (200 and 400 mg) had the slightly higher incidence of dizziness and cough. However, the incidences of hyperkalemia and hypotension were similar [11]. Another RCT, enrolled 376 hypertension patients, showed that the incidence of AEs was comparable between Sacubitril/Valsartan group (23.4%) and olmesartan groups (21.9%) [5].

A meta-analysis, including 9 RCTs, detected Sacubitril/Valsartan's safety in the treatment of hypertension patients. In detail, the meta-analysis's data indicated that the incidence of AEs (risk ratio (RR) 1.01, 95% CI: 0.39 to 1.09), serious AEs (RR 0.80, 95% CI: 0.52 to 1.22) and discontinuation of treatment for any AEs (RR 0.79, 95% CI: 0.56 to 1.11) were not significantly different between the Sacubitril/Valsartan group and the ARB/placebo group. And Sacubitril/Valsartan decreased the incidence of headaches (RR 0.69, 95% CI: 0.48 to 0.99) while increased the incidence of cough (RR 2.12, 95% CI: 1.11 to 4.04), compared with ARB/placebo [10]. Another recent meta-analysis evaluated Sacubitril/Valsartan's safety in hypertension patients who were middle-aged and elderly [12]. This meta-analysis, enrolled 7 RCTs, showed that the incidence of AEs [odds ratio (OR)=1.14, 95% CI: 1.00 to 1.31, P=0.06], serious AEs (OR=1.06, 95% CI: 0.64 to 1.76, P=0.81), and discontinuations due to AEs (OR=0.86, 95% CI: 0.51 to 1.46, P=0.58) were comparable between Sacubitril/Valsartan group and ARBs group [12].

DISCUSSION

Most of meta-analyses supported the result that Sacubitril/Valsartan was safe in the treatment for hypertension patients, compared with ARBs. However, one meta-analysis, enrolled 5 RCTs, showed the different standpoint. It proved that the incidence of AEs from Sacubitril/Valsartan was higher than the incidence from ARB in hypertension patients who were over 55 years old. The incidence of AEs was 37.6% in Sacubitril/Valsartan group versus 28.7% in ARB group. And drug-related AEs were more frequent in Sacubitril/Valsartan group in comparison with ARB groups (OR=1.27, 95% CI: 1.03 to 1.57, P=0.03) [13]. Nasopharyngitis, dizziness, hyperuricemia, and respiratory infection might be the most common AEs [13].

Although most of studies, explore Sacubitril/Valsartan's safety in hypertension patients, showed that Sacubitril/Valsartan was safe, it is necessary to implement large-scale RCTs and meta-analyses to further explore the safety of Sacubitril/Valsartan in hypertension patients.

CONCLUSION

In conclusion, RCTs and meta-analyses reported that Sacubitril/Valsartan had an obvious antihypertensive effect. And compared with ARBs, Sacubitril/Valsartan's safety was reliable in hypertension patients. Sacubitril/Valsartan is likely as a promising antihypertensive agent in the future.

ACKNOWLEDGEMENT

This work was funded by the Shandong Province Natural Science Foundation (ZR2021QH262,ZR2020QH005). The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

COMPETING INTEREST

The authors of this paper hereby validate that there were no conflicts of interest (either financial or non-financial) when conducting the study.

REFERENCES

1. Schmieder RE, Wagner F, Mayr M, Delles C, Ott C, et al. (2017) The effect of Sacubitril/Valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: The results of a randomized, double-blind, active-controlled study. Eur Heart J. 38(44):3308-3317.
2. Zhang R, Sun X, Li Y, He W, Zhu H, et al. (2022) The efficacy and safety of Sacubitril/Valsartan in heart failure patients: A review. J Cardiovasc Pharmacol Ther. 27(3):115-117.
3. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, et al. (2010) Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: A randomised, double-blind, placebo-controlled, active comparator study. Lancet. 375(9722):1255-66.
4. Supasyndh O, Wang J, Hafeez K, Zhang Y, Zhang J, et al. (2017) Efficacy and safety of Sacubitril/Valsartan (LCZ696) compared with olmesartan in elderly asian patients (≥ 65 years) with systolic hypertension. Am J Hypertens. 30(12):1163-1169.
5. Cheung DG, Aizenberg D, Gorbunov V, Hafeez K, Chen CW, et al. (2011) Efficacy and safety of Sacubitril/Valsartan in patients with essential hypertension uncontrolled by olmesartan: A randomized, double-blind, 8-week study. J Clin Hypertens. 20(1):150-158.[ResearchGate]
6. Rakugi H, Kario K, Yamaguchi M, Sasajima T, Gotou H, et al.

(2022). Efficacy of Sacubitril/Valsartan versus olmesartan in Japanese patients with essential hypertension: A randomized, double-blind, multicenter study. Hypertens Res. 45(5):824-833.

7. Wang JG, Yukisada K, Sibulo A Jr, Hafeez K, Jia Y, et al. (2017) Efficacy and safety of Sacubitril/Valsartan (LCZ696) add-on to amlodipine in Asian patients with systolic hypertension uncontrolled with amlodipine monotherapy. J Hypertens. 35(4):877-85.

8. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, et al. (2006) Effects of Sacubitril/Valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: The parameter study. Hypertension. 69(3):411-20.

9. Ito S, Satoh M, Tamaki Y, Gotou H, Charney A, et al. (2015) Safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. Hypertens Res. 38(4):269-75.

10. Li Q, Li L, Wang F, Zhang W, Guo Y, et al. (2019) Effect and safety of LCZ696 in the treatment of hypertension: A meta-analysis of 9 RCT studies. Medicine. 98(28):e16093.

11. Huo Y, Li W, Webb R, Zhao L, et al. (2019) Efficacy and safety of Sacubitril/Valsartan compared with olmesartan in Asian patients with essential hypertension: A randomized, double-blind, 8-week study. J Clin Hypertens. 21(1):67-76.

12. Wu HX, Liu KK, Li BN, Liu S, Jin JC, et al. (2022) Efficacy and safety of Sacubitril/Valsartan in the treatment of middle-aged and elderly patients with hypertension: A systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med. 1(5):1811-25.

13. De Vecchis R, Ariano C (2020) Retracted article: Vasodilatory properties of Sacubitril/Valsartan explored in hypertensives aged over 55 years: A meta-analysis. High Blood Press Cardiovasc Prev. 27(1):103.