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Sacubitril/Valsartan as a New Possible Therapeutic Alternative for the Treatment of Hypertension

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Hypertension, a major modifiable risk factor for cardiovascular disease and global mortality, affects approximately 31.1% of adults worldwide. Resistant hypertension, observed in 13-30% of hypertensive patients, poses a challenge in treatment escalation, contributing to clinical inertia. Sacubitril/valsartan, a dual-action compound comprising valsartan (an angiotensin receptor blocker) and sacubitril (a neprilysin inhibitor), has garnered approval in China and Japan for Hypertension and FDA approval for heart failure. This article aims to review the possibility of sacubitril/ valsartan as an alternative therapy for the treatment of hypertension. Clinical evidence indicates sacubitril/valsartan's efficacy in reducing blood pressure. Notably, it also demonstrates significant blood pressure reductions in patients with heart failure, emphasizing its dual benefits. The compound's superior efficacy in improving hypertension and left ventricular hypertrophy is a focus

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of ongoing investigations. This review highlights the role of sacubitril/valsartan as a promising therapeutic option for the management of hypertension.

Keywords: Blood pressure; hypertension; sacubitril/valsartan.

1. INTRODUCTION

Hypertension stands as the foremost preventable risk factor for both cardiovascular disease (CVD) and overall mortality globally [1,2]. “In 2015, approximately 1.38 billion individuals, constituting 31.1% of the total adult population, were identified with hypertension, characterized by systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg. Of these, Resistant Hypertension (RHTN) is observed in 13-30% of the total hypertensive patients” [3]. “RHTN is characterized by elevated BP in hypertensive individuals that persist above the target level despite the administration of at least three anti-hypertensive agents such as calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB), and a diuretic, all administered at the highest or maximally tolerated doses” [4].

Failure to adequately address RHTN contributes to the absence of suitable treatment escalation in uncontrolled patients, referred to as clinical inertia, which is widespread and becomes more pronounced with an escalating number of prescribed medications. Additionally, the increasing number of prescribed medicines associated with the lack of adherence to these medications on a daily basis worsens the problem further [5]. While addressing the difficulties related to RHTN management, there is a potential for innovative approaches to be beneficial. One such recent addition to the array of options is the angiotensin receptor neprilysin inhibitor sacubitril/valsartan, which has received approval in China and Japan for the treatment of hypertension [6]. The purpose of this review is to highlight the adoption of Sacubitril/Valsartan in the management of RHTN.

2. PHARMACOLOGY OF SACUBITRIL/ VALSARTAN

“The current medication, known as sacubitril/valsartan, is presented as a fixed-dose blend of two active ingredients: valsartan, an ARB, and sacubitril, a neprilysin inhibitor” [7]. The Renin-Angiotensin-Aldosterone System (RAAS) constitutes a multi-organ endocrine system crucial for blood pressure regulation. Its primary role involves the oversight of sodium and water reabsorption within the kidneys, thereby exerting a direct influence on systemic blood pressure. Activation of the RAAS ensues in response to a decline in blood pressure, characterized by diminished blood volume, prompting an orchestrated elevation in water and electrolyte reabsorption within the renal system. This compensatory mechanism serves to counteract the reduction in blood volume, ultimately leading to an augmentation of blood pressure [8].

“Sacubitril/Valsartan has a dual impact on both the RAAS and the natriuretic peptide (NP) system. By inhibiting angiotensin II and neprilysin, sacubitril/valsartan works to counteract the detrimental cardiac effects associated with RAAS activation. Simultaneously, it raises the levels of endogenous NPs, promoting protective cardiac effects. Notably, this approach avoids the heightened risk of angioedema linked to the combination of ACE inhibitors and neprilysin inhibition” [9].

3. ROLE OF SACUBITRIL/VALSARTAN IN HYPERTENSION IN CLINICAL EVIDENCE

3.1 Clinical Evidence

3.1.1 Efficacy in hypertension

In a study conducted by Ruilope et al., 1215 patients with mild-to-moderate hypertension were given various combinations of valsartan and sacubitril, either individually or together, to assess their impact on blood pressure. After an initial period with a mean blood pressure of 155–157/99–100mm Hg, sacubitril alone (200 mg) reduced diastolic blood pressure by 3mm Hg. In contrast, sacubitril/valsartan combinations at 200mg and 400mg demonstrated statistically significant reductions (p=0·0055) compared to their corresponding valsartan dosages. Ambulatory monitoring further confirmed the efficacy of sacubitril/valsartan in lowering blood pressure. Notably, the combination was well-tolerated, demonstrating its safety and additive benefits over valsartan alone in hypertensive patients [10].

In another study conducted by Kario et al., 389 Asian patients with mild-to-moderate hypertension were involved to compare the efficacy and safety of placebo with three different dosages of sacubitril/valsartan (100mg, 200mg, and 400mg) administered once daily. “After 8 weeks, all dosages demonstrated significant reductions in both diastolic and systolic blood pressure (P<0.01 and P<0.001) compared to placebo, with no reported angioedema and good tolerance. Interestingly, this study suggested a more potent anti-hypertensive effect of sacubitril/valsartan in Asian patients compared to similar dosages observed in predominantly white populations, indicating a potentially favorable response in Asians due to their suppressed renin-angiotensin system, linked to higher salt sensitivity and intake” [11].

“Also, in another 8-week study involving 32 Japanese patients with hypertension and renal dysfunction, sacubitril/valsartan (100mg titrated up to 400mg once daily as needed) demonstrated a significant reduction in blood pressure by 20.5/8.3mm Hg without adverse effects on renal function” [12].

3.1.2 Effect on BP in heart failure patients

“PARADIGM-HF trial was an important randomized clinical trial study that involved 8399 patients with heart failure and reduced ejection fraction (HFrEF). Sacubitril/valsartan significantly reduced the risk of cardiovascular death or first hospitalization for heart failure compared to enalapril (hazard ratio 0.80, 95% confidence interval 0.73–0.87; P < 0.001). This benefit was particularly evident in patients already on ACE inhibitors. While the study primarily focused on heart failure, sacubitril/valsartan also demonstrated efficacy in reducing hypertension, as indicated in earlier studies” [13].

“The PARAMOUNT trial, which randomized 301 patients with HFpEF (94% having hypertension), compared sacubitril/valsartan (titrated up to 200mg twice daily) with valsartan alone (titrated up to 160mg twice daily). Over 12 weeks of treatment, the combination significantly reduced systolic blood pressure by 9.3mm Hg compared to 2.9mm Hg with valsartan alone (P = 0.001), and diastolic blood pressure was reduced by 4.9mm Hg with sacubitril/valsartan versus 2.1mm Hg with valsartan alone (P = 0.09). Continued treatment for 36 weeks resulted in sustained blood pressure reductions of 7.5/5.1mm Hg with sacubitril/valsartan compared to 1.5/0.3mm Hg reductions with valsartan alone (P = 0.006 for systolic blood pressure and P = 0.001 for diastolic blood pressure)” [14].

3.1.3 Tolerability and safety

In a meta-analysis comprising 20 RCTs involving 22,510 patients in patients with hypertension and heart failure, sacubitril/valsartan demonstrated comparable safety and tolerability to standard therapy. However, the occurrence of angioedema associated with sacubitril-valsartan was identified as a concerning adverse event [15]. “Other adverse reactions associated with sacubitril/valsartan include hyperkalemia, cough, dizziness, and renal failure, although they are considered clinically insignificant” [16].

The use of sacubitril/valsartan is contraindicated in specific cases to ensure patient safety, which include instances of angioedema associated with prior ACE inhibitor or angiotensin II receptor blocker therapy, as well as hypersensitivity to sacubitril, valsartan, or any component of the product. Additionally, caution must be exercised in diabetic patients, particularly those receiving concomitant aliskiren, and concurrent use with ACE inhibitors is to be avoided, with a recommended 36-hour interval between administrations [16]. Also, future studies are recommended to prioritize investigating the safety aspects of sacubitril/valsartan in greater detail.

4. PLACE IN MANAGEMENT OF HYPERTENSION

Research in patients with hypertension has demonstrated that sacubitril/valsartan leads to a notable reduction in BP. Notably, the treatment with sacubitril/valsartan has been associated with a decrease in 24-hour, daytime, and nighttime BP in hypertensive patients [6,17]. Furthermore, its approval for hypertension treatment has been recently granted in both Japan and China [6].

5. ONGOING TRIALS FOR SACUBITRIL/ VALSARTAN IN THE MANAGEMENT OF HYPERTENSION

“Multiple ongoing studies are investigating the impact of sacubitril/valsartan on hypertensive patients with distinct characteristics. Among these, four studies focus on obese individuals, those with left ventricular hypertrophy or resistant hypertension, while another study specifically targets perimenopausal women with

hypertension. The first study, a phase 2/3 randomized interventional trial with an estimated enrolment of 160 patients, compares the morning and evening doses of sacubitril/valsartan or valsartan, evaluating mean nocturnal systolic blood pressure" [18]. "The HEVA study compares sacubitril/valsartan with optimized anti-hypertensive agents, and the third study enrolls 264 perimenopausal patients to assess treatment efficacy on urinary microalbumin content and pulse wave velocity [19]. The PARASTRAIN study, involving 120 patients, aims to measure the superior efficacy of ARNi in improving hypertension and left ventricular hypertrophy compared to amlodipine" [20].

6. CONCLUSION

Sacubitril/valsartan has been approved in China and Japan for the management of hypertension and has also obtained FDA approval for managing heart failure. Recent clinical studies have indicated its superior efficacy in reducing blood pressure, supporting its potential role in hypertension management. Additional clinical trials and real-world evidence are essential to facilitate the broader adoption of sacubitril/valsartan in hypertension management.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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