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COMMENT

Efficacy of esaxerenone—a nonsteroidal mineralocorticoid receptor blocker—on nocturnal hypertension

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The circadian rhythm patterns of blood pressure have been divided into different categories based on differences in nocturnal changes in blood pressure: patients who experience a 10–20% decrease in systolic blood pressure at night compared with that in the daytime are classified as "dippers," while those who have a >20% decrease in blood pressure at night are referred to as "extreme dippers." Patients with <10% lower blood pressure at night are classified as "nondippers" and those who show an increase in blood pressure at night are classified as "risers" [1]. Nocturnal hypertension, observed in nondippers or risers, is considered an important cardiovascular risk [2].

Aldosterone, a steroid hormone secreted from the adrenal glands, binds to the mineralocorticoid receptor (MR). The activation of the aldosterone/MR pathway has been implicated in the etiology of both hypertension and cardiovascular diseases. A growing body of evidence has indicated that the MR antagonists spironolactone and eplerenone are both effective in the prevention and treatment of hypertension [3, 4]. However, spironolactone has low MR-binding specificity and is frequently associated with side effects, including sex hormone receptor-related adverse events and hyperkalemia. Although eplerenone is a selective MR antagonist that inhibits sex hormone receptor-related adverse events, hyperkalemia remains the focus of clinical studies. To overcome the disadvantages of MR antagonists, novel selective agents have been developed. Esaxerenone is a potent, nonsteroidal oral MR blocker that inhibits MR activity; esaxerenone has a high specificity and long half-life [5]. Several clinical studies have shown that esaxerenone has excellent blood pressure-lowering effects, with relatively few adverse events. Furthermore, the addition of esaxerenone to renin–angiotensin system inhibitor therapy was shown to further reduce urinary albumin excretion without affecting renal function in patients with type 2 diabetes and microalbuminuria [6].

In this issue of *Hypertension Research*, Kario et al. reported the nighttime blood pressure-lowering effect of esaxerenone and its effect on N-terminal pro-B-type natriuretic peptide (NT-proBNP), a predictor of cardiovascular risk, according to different dipping patterns (extreme dippers, dippers, nondippers, and risers) of nocturnal blood pressure in a post hoc analysis of a multicenter, open-label, long-term phase III study in patients with essential hypertension [7]. Nighttime systolic blood pressure decreased in all dipping pattern groups at 28 weeks after the start of esaxerenone treatment, with the riser group showing the greatest decrease (−25.5 [95% confidence interval −30.3, −20.7] mmHg). A significant change was observed in the dipping pattern distribution from baseline to week 28 ($p < 0.0001$). The proportion of patients with the riser type decreased from 14.4% at baseline to 9.8% at week 28, while that of the nondipper type decreased from 44.7% at baseline to 32.3% at week 28. The NT-proBNP levels decreased from baseline to week 28 in all dipping pattern groups ($p < 0.001$). At baseline, the proportion of patients with NT-proBNP < 55 pg/mL was lowest in risers versus the other dipping pattern types; however, these differences disappeared after reductions in NT-proBNP in all groups at week 28. These data suggest that long-term administration of esaxerenone may be a useful treatment option for nocturnal hypertension, particularly in patients with the riser pattern.

Advanced vascular damage and increased salt sensitivity have been proposed as the main causes of nocturnal hypertension [8] (Fig. 1). Sympathetic hyperactivity, the activation of the renin–angiotensin–aldosterone system (RAAS), and renal dysfunction increase salt sensitivity. Furthermore, an increase in the circulating blood volume induced by salt sensitivity and a high-salt diet elevates both daytime and nighttime blood pressure to excrete sodium

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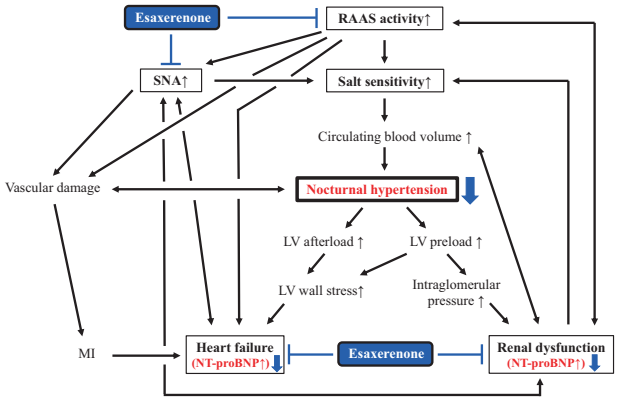

Fig. 1 Proposed mechanism of the effects of nocturnal hypertension on cardiorenal risks. Esaxerenone improved nocturnal hypertension and reduced NT-proBNP levels. The proposed sites of action of esaxerenone are shown in blue. RAAS renin–angiotensin–aldosterone system, SNA sympathetic nerve activity, LV left ventricular, MI myocardial infarction, NT-proBNP N-terminal pro-B-type natriuretic peptide

from the kidneys by pressure natriuresis. NT-proBNP levels are increased by renal dysfunction via increased blood volume and decreased excretion from the kidneys, in addition to impaired cardiac function. Nocturnal hypertension may cause heart failure by increasing the left ventricular afterload and preload, and it may cause renal dysfunction by elevating the intraglomerular pressure to increase the NT-proBNP levels. Increased sympathetic nerve activity (SNA) and RAAS activity may induce heart failure and renal dysfunction. Furthermore, the overactivation of MR in the brain increases SNA. Therefore, the mechanism by which esaxerenone decreases nocturnal BP and NT-proBNP may involve MR-inhibiting mechanisms, although this hypothesis needs to be tested in future studies.

Shibata and Itoh proposed the concept of MR-associated hypertension, where treatment with MR antagonists is effective at lowering blood pressure due to increased MR activity [9]. In addition to primary aldosteronism, other causes of MR-associated hypertension include the aldosterone breakthrough (escape) phenomenon, obesity, obstructive sleep apnea, sleep disorders, diabetes mellitus, chronic kidney disease, polycystic ovary syndrome, and excessive salt intake. It would be interesting to determine whether the existence of MR-associated hypertension or excessive salt consumption affected the results of the present study. Further subanalysis is expected to address these issues.

The present study successfully demonstrates the efficacy of esaxerenone in the treatment of nocturnal hypertension. This finding may be significant, especially in the Asian population, given its higher prevalence of hypertension-related stroke and heart failure than other races [10].

Compliance with ethical standards

Conflict of interest Both authors received lecture fees from Daiichi Sankyo Co., Ltd.

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