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COMMENT

Will esaxerenone be added to the antihypertensive treatment strategy of practicing physicians as a second-line antihypertensive drug?

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Overcoming the "*Hypertension paradox*" is a challenge that practicing physicians must resolve. To achieve this, we need to break away from clinical inertia and develop new antihypertensive treatment strategies. In order to lower blood pressure (BP) to the target level as early as possible without increasing the number of drugs too much, it is necessary to add an antihypertensive drug that matches the background of the rise in BP. Esaxerenone, which has recently become available as an antihypertensive drug, is one of the mineralocorticoid receptors (MR) antagonists with a non-steroidal structure [1]. Esaxerenone is expected to be an effective antihypertensive especially for hypertensive patients with increased salt sensitivity, like diuretics. However, it has not been clarified whether it is more effective than diuretics as a second-line antihypertensive drug.

In this issue of *Hypertension Research*, Kario et al. [2]. conducted the first randomized controlled trial to evaluate whether the antihypertensive effect of esaxerenone, a second-line antihypertensive drug, is non-inferior to trichlormethiazide in patients with uncontrolled essential hypertension, focusing on early morning home BP, which is closely associated with the onset of cardiovascular events [3]. This exploratory intervention study targets patients with essential hypertension who are receiving an angiotensin receptor blocker (ARB) or a calcium channel blocker (CCB) as their base medication and have not yet achieved sufficient BP reduction. The non-inferiority of esaxerenone was demonstrated as a second-line antihypertensive agent compared to the trichlormethiazide in the antihypertensive effect on morning homeBP. Furthermore, bedtime home BP and office BP were also reduced sufficiently. These antihypertensive effects were consistent with the results of the past study of esaxerenone performed in Japan [4, 5]. In this study, morning home BP was mainly evaluated, but its antihypertensive was almost the same as EARLY-NH study [4], (−12.2/6.5 mmHg and −12.2/4.9 mmHg, respectively), so it is expected to have an antihypertensive effect on nocturnal BP. Nocturnal BP is more related to the development of cardiovascular events than the office BP, as in morning BP [6]. In other words, the antihypertensive effect of esaxerenone on the morning BP as well as nocturnal BP may lead to a future suppression of cardiovascular events. From the aspect of organ protection, urinary albumin-to-creatinine ratio and serum N-terminal pro-brain natriuretic peptide (NT-pro BNP), which are risk factors for cardiovascular events, were also significantly decreased. Similar trends were observed in other studies [4, 7] in which esaxerenone was added to an ARB or a CCB. In another study [5], esaxerenone significantly reduced the primary endpoint of left ventricular mass index from baseline to end of treatment (EOT) in the total population ($-9.9\ g/m^2$) and in the renin-angiotensin system inhibitor (RASi) and CCB subcohorts ($-13.9\ g/m^2$ and $-8.2\ g/m^2$, respectively). Considering these results, esaxerenone is expected to have not only an antihypertensive effect but also a cardioprotective effect, and although this was not verified in this study, it may be effective in inhibiting the progression of heart failure stages.

I speculate that practicing physicians have been hesitant to prescribe MR antagonists, despite the high likelihood of efficacy given the pathology of hypertension, due to concerns about the risk of hyperkalemia associated with these drugs. However, no clinically significant hyperkalemia was observed in EXICTE-HT study, and this was also the case

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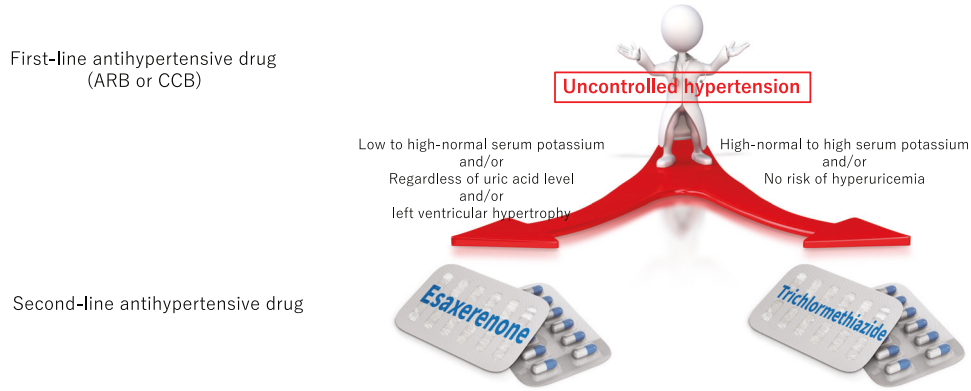

Fig. 1 How to select esaxerenone or a diuretic as a second-line antihypertensive drug in hypertensive patients inadequately controlled with an ARB or a CCB

in previous studies [4, 5, 7] involving the addition of esaxerenone. Furthermore, recent reports [8] have shown that the combined use of MR antagonists and SGLT2 inhibitors reduces the risk of hyperkalemia. Therefore, for diabetic patients whose MR receptors may be activated, it is thought that these combinations can be easily administered without excessive fear of hyperkalemia. In this way, there must be a considerable number of hypertensive patients who would be candidates for esaxerenone.

In the 2019 Japanese Society of Hypertension Guidelines [9], the trichlormethiazide are one of the second-line antihypertensive drugs for patients with poor controlled hypertension. On the other hand, MR antagonists are positioned as the fourth option of treatment resistant hypertension. The current EXCITE-HT study showed that esaxerenone, one of the MR antagonists, is an antihypertensive agent that can be selected on the second-line, which is earlier in actual clinical practice. I want to consider the significance of administering mineralocorticoid antagonists on the second-line. First, many of the treatment resistant hypertension are caused by primary aldosterone syndrome and sleep apnea syndrome, which have high blood aldosterone concentration [10]. Moreover, primary aldosterone is more frequent than previously considered and sleep apnea syndrome is also common disease. If the antihypertensive agent administered in the first-line is inadequate, it is relatively likely that hyperaldosteronemia may be involved in the background. Therefore, administering aldosterone antagonists at an early stage of treatment may prevent the progress to resistant hypertension. Next, it has been also reported that high salt intake, diabetes, and chronic kidney disease mainly activate the MR that combines aldosterone via Ras-related C3 botulinus toxin substrate 1 (Rac-1) [11]. As a result, it has been reported that even if the blood aldosterone concentration is not high, it will be a condition that is difficult to antihypertension [12]. These are independent routes with the effects of low renin activity and are unlikely to be expected to have the antihypertensive effect of RASi, causing uncontrolled hypertension. Furthermore, in actual clinical practice, it is assumed that uncontrolled hypertension related to MR activity are often due to the number of patients with diabetes and chronic kidney disease in Japan. After all, the administration of MR antagonists like esaxerenone at an early stage can be considered in order not to increase the number of antihypertensive drugs.

The strength of this study is that it was conducted at multicenter and had a large sample size. The evaluation is conducted at the stage when ARBs or CCBs, which are first-line antihypertensive drugs commonly used in clinical practice, are administered as the base antihypertensive medication, making the results easy for practicing physicians to put into practice.

Finally, as practicing physicians, what antihypertensive treatment strategies can we implement based on these research results? If BP does not decrease sufficiently when an ARB or a CCB is administered as a first-line antihypertensive drug, what should we imagine when adding a second-line drug? I believe that when BP is not sufficiently lowered with a single drug, it is highly likely that increased salt sensitivity is the cause of insufficient BP control. Therefore, what is required of a second-line antihypertensive drug is that extracts “salt” and “water.” This needs to be considered particularly in cases where salt sensitivity is increased, excessive salt intake, or the patient is suffering from diabetes, chronic kidney disease, or metabolic syndrome. So, should we add esaxerenone or trichlormethiazide? What markers should be used to select the appropriate drug? The safety analysis findings from EXICTE-HT may provide some clues: the trends in serum potassium and uric acid levels. Although esaxerenone increased serum potassium in some patients, it hardly changed from baseline to EOT. On the other hand, trichlormethiazide continuously decreased serum potassium, and the incidence of not only hypokalemia but also hyperuricemia is not uncommon. In other words, if there is hyperkalemia at baseline, it is difficult to add esaxerenone, but if serum potassium levels are low or at the lower limit of

normal or if there is hyperuricemia, it is difficult to add trichlormethiazide. Furthermore, as mentioned above, it has been suggested that esaxerenone may improve left ventricular hypertrophy [5], which is thought to be the rate-limiting step in the progression of heart failure. Based on these findings, a treatment strategy such as that shown in the figure (Fig. 1) can be devised, which is expected to make it easier to achieve BP targets and resolve the "*Hypertension paradox*".

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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References

1. Ito S, Itoh H, Rakugi H, Okuda Y, Yoshimura M, Yamakawa S. Double-blind randomized phase 3 study comparing esaxerenone (CS-3150) and Eplerenone in Patients With Essential Hypertension (ESAX-HTN Study). Hypertension. 2020;75:51–8.
2. Kario K, Ohbayashi H, Hashimot M, Itabashi N, Kato M, Uchiyama K, et al. Home blood pressure-lowering effect of a non-steroidal mineralocorticoid receptor blocker, esaxerenone, versus thichlormethiazide for uncontrolled hypertension: the EXCITE-HT randomized controlled study. Hypertens Res. https://doi.org/10.1038/s41440-024-01762-z.
3. Kario K, Wang JG, Chia YC, Wang TD, Li Y, Siddique S, et al. The HOPE Asia network 2022 up-date consensus statement on morning hypertension management. J Clin Hypertens. 2022;24:1112–20.
4. Kario K, Nishizawa M, Kato M, Ishii H, Uchiyama K, Nagai M, et al. Nighttime home blood pressure lowering effect of esaxerenone in patients with uncontrolled nocturnal hypertension: the EARLY-NH study. Hypertens Res. 2023;46:1782–94.
5. Yamamoto E, Usuku H, Sueta D, Suzuki S, Nakamura T, Matsui K, et al. Efficacy and Safety of Esaxerenone in Hypertensive Patients with Left Ventricular Hypertrophy (ESES-LVH) Study: a multicenter, open-label, prospective, interventional study. Adv Ther. 2024;41:1284–303.
6. Kario K, Hoshide S, Mizuno H, Kabutoya T, Nishizawa M, Yoshida T, et al. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP Study. Circulation. 2020;142:1810–20.
7. Katsuya T, Inobe Y, Uchiyama K, Nishikawa T, Hirano K, Kato M, et al. Exploratory study on the relationship between urinary sodium/potassium ratio, salt intake, and the antihypertensive effect of esaxerenone: the ENaK Study. Hypertens Res. 2024;47:835–48.
8. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, et al. Sodium-glucose Cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. Circulation. 2022;145:1460–70.
9. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res. 2019;42:1235–481.
10. Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. JAMA. 2014;311:2216–24.
11. Shibata S, Nagase M, Yoshida S, Kawarazaki W, Kurihara H, Tanaka H, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. Nat Med. 2008;14:1370–6.
12. Shibata H, Itoh H. Mineralocorticoid receptor-associated hypertension and its organ damage: clinical relevance for resistant hypertension. Am J Hypertens. 2012;25:514–23.