Hypertension Research (2023) 46:2059–2061
https://doi.org/10.1038/s41440-023-01338-3

COMMENT

Esaxerenone for nocturnal hypertension and possible future direction for treatment of hypertension-cardiovascular-kidney comorbidity

Kouichi Tamura[1] · Tomohiko Kanaoka[1] · Naoki Fujiwara[1] · Keigo Hirota[1]

Keywords Esaxerenone · Mineralocorticoid receptor antagonist · Nocturnal hypertension · Cardiorenal syndrome · Vascular stiffness

Received: 7 May 2023 / Accepted: 18 May 2023 / Published online: 16 June 2023

Due to the progress of aging in recent years, the number of elderly hypertensive patients with multiple organ dysfunction is increasing compared to hypertensive patients without complications. In addition, non-communicable diseases (NCDs) such as hypertension, diabetes, dyslipidemia, and visceral obesity increase the risk of developing cardiovascular diseases such as myocardial infarction and heart failure. Recent large-scale real-world data analyzes in Japan have shown that diabetes and its comorbidity exacerbates the risk of death [1, 2]. In addition, in a large-scale cohort study of chronic kidney disease (CKD) patients in Japan, it has been reported that heart failure is more frequent than myocardial infarction and cerebrovascular disease (CVD) as complications of CKD patients [3, 4]. CKD complications with risk of acute kidney injury and cardiovascular-kidney comorbidity (i.e., cardiorenal syndrome with heart failure and CKD) are recent pathological features [3, 4].

Regarding the involvement of mineralocorticoid receptor (MR) activation in the pathophysiology, hypertension, CVD and CKD develop and progress due to MR activation due to increased circulating aldosterone levels, such as primary aldosteronism caused by adrenal adenoma, has been known [5, 6]. In addition, in such as type 2 diabetes and obesity, hyperactivation of MR can occur so as to provoke CVD and CKD, through the activated MR-mediated metabolic, hemodynamic, inflammatory and fibrotic effects [7–9].

✉ Kouichi Tamura
tamukou@yokohama-cu.ac.jp

[1] Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Spironolactone and eplerenone are traditionally used as indications for heart failure and hypertension [10–12], and recently esaxerenone, a selective nonsteroidal MR antagonist, is used for hypertension [13, 14]. Aldosterone exerts serious deleterious effects on the cardiovascular and kidney tissues via MR activation, and several large-scale clinical trials have shown that MR antagonists have organ-protective effects and improve prognosis in heart failure and post-myocardial infarction as described in clinical guidelines of heart failure [11]. Therefore, MR antagonists are recommended as therapeutic agents for heart failure, especially heart failure with decreased left ventricular systolic function (LVEF < 40%) (HFrEF), as an important therapeutic regimen of the "fantastic four" of the standard treatment for heart failure [11, 15].

In the treatment of hypertension, calcium (Ca) channel blockers, renin-angiotensin (RA) system inhibitors [angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors], diuretics (Thiazide-type and thiazide-like diuretics) and β-blockers (including αβ-blockers) are the major antihypertensive agents [10]. If the target blood pressure cannot be achieved with only one antihypertensive drug, combination therapy with antihypertensive drugs with different mechanisms of action (including combination drugs) is recommended [10]. Alternatively, it is recommended to select an appropriate antihypertensive drug according to the comorbidity and/or specific organ dysfunction requiring careful pathological consideration [10]. In addition, JSH2019 guideline stipulates that the main antihypertensive drug (first-line drug) that should be administered first for hypertension in the absence of active indications should be selected from Ca channel blockers, ARBs, ACE inhibitors, and diuretics [10].

In the blood pressure management of high-risk hypertension complicated by diabetes and/or CKD, it is important

to select an antihypertensive drug according to the pathology and to select an antihypertensive drug that can achieve the blood pressure target, but the current situation is not satisfactory [10]. According to various surveys, the target achievement rate is about 50% for those taking antihypertensive drugs, and about 40% for antihypertensive drug monotherapy [10]. Furthermore, achievement of target blood pressure in hypertension complicated by diabetes and/or CKD is reportedly less than 50% [16, 17].

On the other hand, among antihypertensive drugs, MR antagonists, which have been known to antagonize the action of aldosterone, which is involved in the maintenance of body fluid volume homeostasis, act on MR classically in the distal tubules and junction collecting ducts of the kidney [10, 12]. As a result, sodium excretion is promoted without loss of potassium, resulting in an antihypertensive effect [10, 12]. Spironolactone and eplerenone have been used clinically as MR antagonists. Although spironolactone has a strong MR inhibitory effect, it has low MR selectivity, and thus side effects mediated by sex hormones (eg, gynecomastia, menstrual disorders, etc.) have been reported [10, 12]. Although eplerenone has reduced sex hormone receptor-related side effects, it is contraindicated in patients with moderate or severe kidney dysfunction, microalbuminuria, or diabetes with proteinuria. Therefore, eplerenone is difficult to use clinically in hypertension with diabetes mellitus and/or CKD, in which the RA system is deeply involved in the pathology [10, 12].

In January 2019, esaxerenone, an MR antagonist with a non-steroidal structure, was approved for insurance coverage for hypertension [18]. The efficacy and safety of esaxerenone in patients with essential hypertension, diabetes mellitus, and hypertension with CKD have been confirmed in Japan [13, 19–21]. In this issue of *Hypertension Research*, Kario et al. extended their previous study [21] and sought to examine the effects of esaxerenone on nighttime and daytime blood pressure in patients with uncontrolled nocturnal hypertension being treated with an ARB or Ca channel blocker, with the inclusion criteria of nighttime systolic blood pressure ≥120 mmHg was set according to the definition of nocturnal hypertension in the JSH 2019 guideline (systolic blood pressure of ≥120 mmHg and/or diastolic blood pressure of ≥70 mmHg) [10, 22]. Kario K et al showed that esaxerenone reduced nighttime as well as daytime blood pressure with a reduced cardiac and renal biomarkers or arterial stiffness estimated by cardio-ankle vascular index [22]. The present study also evaluated the efficacy of new brachial and wrist home blood pressure monitoring devices in measuring bedtime blood pressure, and the results suggested that the wrist-type device can be used to monitor changes in nighttime blood pressure as well as the brachial-type device recommended in hypertension guidelines [10, 22]. This study provides new evidence supporting the efficacy of esaxerenone for nocturnal hypertension and subsequent organ protection. Therefore, "Is esaxerenone the ultimate mineralocorticoid receptor antagonist?" is a very interesting and exciting question [23, 24].

As the population ages, the number of patients suffering from combined and complex conditions such as "hypertension-cardiovascular-kidney comorbidity " is increasing, rather than having hypertension, CVD and CKD alone. Therefore, the comprehensive therapeutic management has become essential as the therapeutic strategy of complex pathophysiology such as "hypertension-cardiovascular-kidney comorbidity", in which hypertension is typically

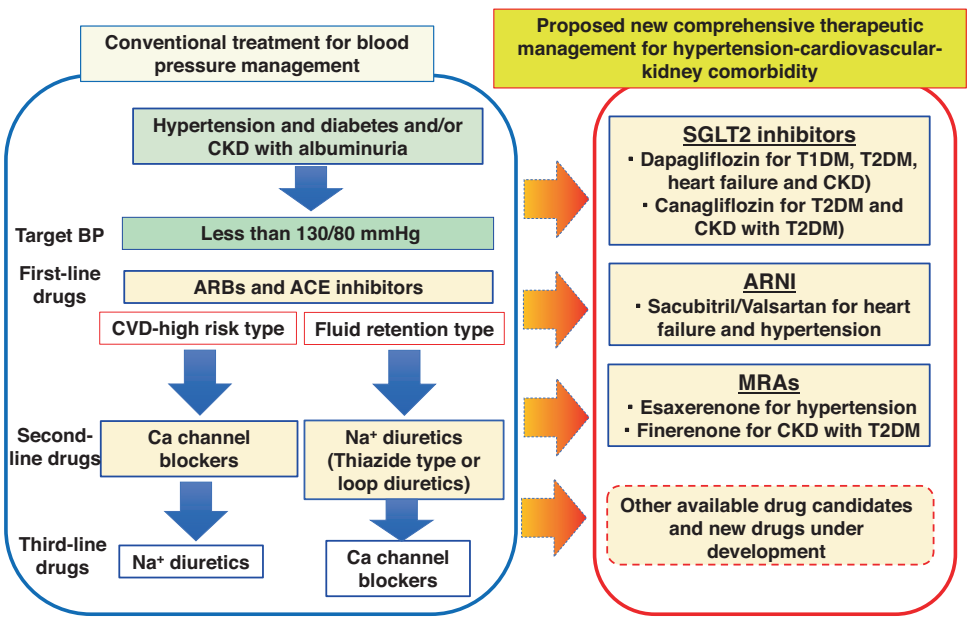

Fig. 1 Conventional treatment for blood pressure management and proposed new comprehensive therapeutic management for hypertension-cardiovascular-kidney comorbidity. CKD, chronic kidney disease; CVD, cardiovascular disease; ARBs, angiotensin II receptor blockers; ACE inhibitors, angiotensin-converting enzyme inhibitors; Ca channel blockers, calcium channel blockers; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; ARNI, angiotensin receptor-neprilysin inhibitor; MRAs, mineralocorticoid receptor antagonists

complicated by heart failure and CKD and often exhibits nocturnal hypertension [10]. Based on the recent progress in research and development of therapeutic drugs for cardiovascular-kidney disease, it is expected that new therapeutic drugs will be used to efficiently and safely control "hypertension-cardiovascular-kidney comorbidity" (Fig. 1), and further evidence is needed in the future [25]

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Kadowaki T, Komuro I, Morita N, Akiyama H, Kidani Y, Yajima T. Manifestation of heart failure and chronic kidney disease are associated with increased mortality risk in early stages of type 2 diabetes mellitus: analysis of a Japanese Real-World Hospital Claims Database. Diabetes Ther. 2022;13:275–86.
2. Kaneko H, Yano Y, Okada A, Itoh H, Suzuki Y, Yokota I, et al. Age-dependent association between modifiable risk factors and incident cardiovascular disease. J Am Heart Assoc. 2023;12:e027684.
3. Tanaka K, Watanabe T, Takeuchi A, Ohashi Y, Nitta K, Akizawa T, et al. Cardiovascular events and death in Japanese patients with chronic kidney disease. Kidney Int. 2017;91:227–34.
4. Imaizumi T, Fujii N, Hamano T, Yang W, Taguri M, Kansal M, et al. Excess risk of cardiovascular events in patients in the United States vs. Japan with chronic kidney disease is mediated mainly by left ventricular structure and function. Kidney Int. 2023;103:949–61.
5. Nomura M, Kurihara I, Itoh H, Ichijo T, Katabami T, Tsuiki M, et al. Association of cardiovascular disease risk and changes in renin levels by mineralocorticoid receptor antagonists in patients with primary aldosteronism. Hypertens Res. 2022;45:1476–85.
6. Haze T, Ozawa M, Kawano R, Haruna A, Ohki Y, Suzuki S, et al. Effect of the interaction between the visceral-to-subcutaneous fat ratio and aldosterone on cardiac function in patients with primary aldosteronism. Hypertens Res. 2023 (e-pub ahead of print 20230208; https://doi.org/10.1038/s41440-023-01170-9).
7. Shibata H, Itoh H. Mineralocorticoid receptor-associated hypertension and its organ damage: clinical relevance for resistant hypertension. Am J Hypertens. 2012;25:514–23.
8. Shibata S, Ishizawa K, Uchida S. Mineralocorticoid receptor as a therapeutic target in chronic kidney disease and hypertension. Hypertens Res. 2017;40:221–5.
9. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12:2032–45.
10. 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.
11. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure—Digest Version. Circ J. 2019;83:2084–184.
12. Naruse M, Katabami T, Shibata H, Sone M, Takahashi K, Tanabe A, et al. Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021. Endocr J. 2022;69:327–59.
13. Rakugi H, Ito S, Itoh H, Okuda Y, Yamakawa S. Long-term phase 3 study of esaxerenone as mono or combination therapy with other antihypertensive drugs in patients with essential hypertension. Hypertens Res. 2019;42:1932–41.
14. Rakugi H, Yamakawa S, Sugimoto K. Management of hyperkalemia during treatment with mineralocorticoid receptor blockers: findings from esaxerenone. Hypertens Res. 2021;44:371–85.
15. Bauersachs J. Heart failure drug treatment: the fantastic four. Eur Heart J. 2021;42:681–3.
16. Yokoyama H, Oishi M, Takamura H, Yamasaki K, Shirabe SI, Uchida D, et al. Large-scale survey of rates of achieving targets for blood glucose, blood pressure, and lipids and prevalence of complications in type 2 diabetes (JDDM 40). BMJ Open Diabetes Res Care. 2016;4:e000294.
17. Kobayashi K, Hatori N, Sakai H, Furuki T, Miyakawa M, Tamura K, et al. Comparison of questionnaire responses regarding awareness of Japanese Society of Hypertension guidelines for the management of hypertension between 2014 and 2019 in primary care. Hypertens Res. 2021;44:1147–57.
18. 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;75:51–58.
19. Itoh H, Ito S, Rakugi H, Okuda Y, Nishioka S. Efficacy and safety of dosage-escalation of low-dosage esaxerenone added to a RAS inhibitor in hypertensive patients with type 2 diabetes and albuminuria: a single-arm, open-label study. Hypertens Res. 2019;42:1572–81.
20. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, et al. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN): phase 3 randomized controlled clinical trial. Clin J Am Soc Nephrol. 2020;15:1715–27.
21. Kario K, Ito S, Itoh H, Rakugi H, Okuda Y, Yamakawa S. Effect of esaxerenone on nocturnal blood pressure and natriuretic peptide in different dipping phenotypes. Hypertens Res. 2022;45:97–105.
22. 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. https://doi.org/10.1038/s41440-023-01292-0. Online ahead of print.
23. Morimoto S, Ichihara A. Efficacy of esaxerenone-a nonsteroidal mineralocorticoid receptor blocker-on nocturnal hypertension. Hypertens Res. 2022;45:376–7.
24. Hoshide S. Is esaxerenone the ultimate mineralocorticoid receptor antagonist? Hypertens Res. 2023;46:516–7.
25. Okuda Y, Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, et al. The renoprotective effect of esaxerenone independent of blood pressure lowering: a post hoc mediation analysis of the ESAX-DN trial. Hypertens Res. 2023;46:437–44.