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COMMENT

Is esaxerenone the ultimate mineralocorticoid receptor antagonist?

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Spironolactone is a mineralocorticoid receptor antagonist (MRA) that was first used as an antihypertensive drug in Japan ~60 years ago. However, with the subsequent development of angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin II receptor blockers, spironolactone is now rarely used as an antihypertensive drug. In the Randomized Aldactone Evaluation Study (RALES), the results of which were published in 1999, spironolactone administration was found to improve the prognosis of patients with severe heart failure with reduced ejection fraction [1]. Since then, while spironolactone has been established as a standard treatment for heart failure, it has not been used as often as other antihypertensive drugs. One reason for this is the high number of side effects related to sex hormones. Eplerenone, approved in Japan in 2007, was developed as an improved version of spironolactone with enhanced selectivity for mineralocorticoid receptors. Eplerenone has fewer side effects related to sex hormones than spironolactone, and its efficacy as an antihypertensive drug has been shown. In addition, in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EMPHASIS-HF), which enrolled patients with acute myocardial infarction with symptomatic heart failure and an ejection fraction of no more than 35%, eplerenone was found to improve the prognosis of patients with heart failure [2]. Therefore, it was expected that MRAs would be used as general antihypertensive drugs. However, in Japan, the use of eplerenone in hypertensive patients is contraindicated in patients with a creatinine clearance <50 ml/min and in hypertensive patients with diabetes mellitus accompanied by microalbuminuria or proteinuria.

Esaxerenone was developed as a drug with high selectivity for mineralocorticoid receptors and a longer half-life than previous MRAs. The results of clinical trials have shown that esaxerenone can be used as a drug for the treatment of hypertension with fewer contraindications than previous MRAs [3–9]. Most recently, Okuda et al. examined data from a randomized, double-blind, placebo-controlled, phase 3 study of esaxerenone and reported that their mediation analysis showed that esaxerenone had a direct urinary albumin-to-creatinine-ratio lowering effect independent of blood pressure lowering and that the magnitude of this effect was much larger than that of its blood pressure-dependent effect [10]. This result adds to the robust evidence that esaxerenone can be used in hypertensive patients with albuminuria. However, we must be very cautious about hyperkalemia in the use of esaxerenone, as there is no evidence to date that esaxerenone is associated with any lower risk of incident hyperkalemia than spironolactone or eplerenone. In the real-world practice setting, the spironolactone prescription rate increased for patients with heart failure treated with ACE inhibitors after the publication of the results of the RALES study; however, there was no significant difference in the rate of readmission for heart failure or all-cause death, while hyperkalemia-related hospitalizations and hospital deaths increased compared to before the publication of the results of the RALES study [11]. Finally, I summarize the indications and main contraindications of the three MRAs under consideration in Japan (Table 1). Nighttime blood pressure has been highlighted because increased nighttime blood pressure has stronger prognostic power than daytime blood pressure [12]. Given that one of the causes of increased nighttime blood pressure is volume overload [13], esaxerenone may be an ideal choice for the treatment of nighttime blood pressure. In the future, esaxerenone may be used more often as an antihypertensive drug, but more judicious use and appropriate laboratory monitoring for renal function and potassium are necessary to prevent complications.

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Table 1 Mineralocorticoid receptor antagonists covered by health insurance for hypertension treatment in Japan

	Spironolactone	Eplerenone	Esaxerenone
Start of sales, year	1963	2007	2019
Indications	• Hypertension • Congestive heart failure • Primary aldosteronism	• Hypertension • Chronic heart failure	• Hypertension
Main contraindications	• Hyperkalemia • Anuria or acute kidney disease	• Hyperkalemia (>5.0 mEq/L) • Diabetes mellitus with microalbuminuria or proteinuria • Kidney dysfunction (CCre < 50 ml/min)	• Hyperkalemia (>5.0 mEq/L) • Kidney dysfunction (eGFR < 30 ml/min/1.73 m^2)

CCr creatinine clearance, *eGFR* estimated glomerular filtration rate

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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