NEW PAPERS

Efficacy and safety of esaxerenone with and without sodium–glucose cotransporter-2 inhibitor use in hypertensive patients with type 2 diabetes mellitus: a pooled analysis of five clinical studies

HIROHIKO MOTOKI AND
KOICHIRO KUWAHARA

Department of Cardiovascular Medicine, Shinshu University School of Medicine, Japan

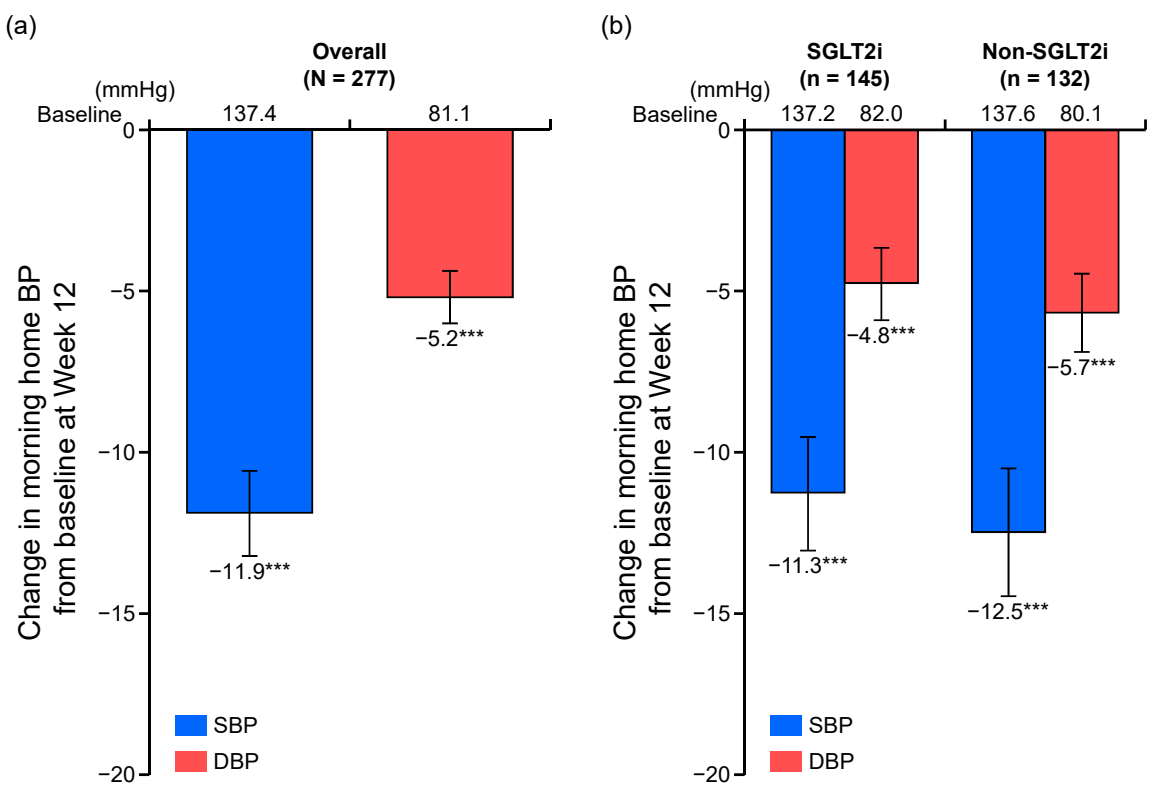
We conducted a pooled subanalysis of five multicenter, prospective, open-label, single-arm studies on esaxerenone: a nonsteroidal mineralocorticoid receptor blocker (MRB).[1-5] These studies aimed to evaluate the efficacy, organ-protective effects, and safety of esaxerenone in hypertensive patients with type 2 diabetes mellitus (T2DM), with and without concomitant sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapy. In total, we enrolled 283 and 279 patients in the safety (with SGLT2i, 148; without, 135) and full analysis sets (with SGLT2i; 145; without, 134), respectively. Significant changes in morning home systolic/diastolic blood pressure (SBP/DBP) from baseline to week 12 were shown in the overall population (mean change: −11.9/−5.2mmHg, both $P < 0.001$) and both SGLT2i and non-SGLT2i subgroups (−11.3/−4.8 and −12.5/−5.7mmHg, respectively, all $P < 0.001$) (**Figure 1**). Similar findings were observed in bedtime home and office SBP/DBP.

The proportions of patients who achieved target home SBP/DBP of under 135/85mmHg were 71.2% (overall population) and 70.5% and 71.9% in the SGLT2i and non-SGLT2i subgroups, respectively. The urine albumin-to-creatinine ratio significantly improved from baseline to week 12 in the overall population and SGLT2i subgroups (percentage change in geometric mean from baseline: −42.8%, −43.0%, and −42.6%, respectively, all $P < 0.001$) (**Figure 2**). N-terminal pro-B-type natriuretic peptide levels improved in all groups.

In terms of adverse events, serum potassium levels increased up to week 2 after starting esaxerenone treatment but stabilized thereafter through week 12 in both subgroups (**Figure 3**). The incidence of serum potassium ≥5.5mEq/L was 2.0% vs 5.2% in the SGLT2i vs non-SGLT2i subgroups. We concluded that esaxerenone demonstrated significant BP-lowering effects, and improved renal and cardiovascular parameters, regardless of SGLT2i use.

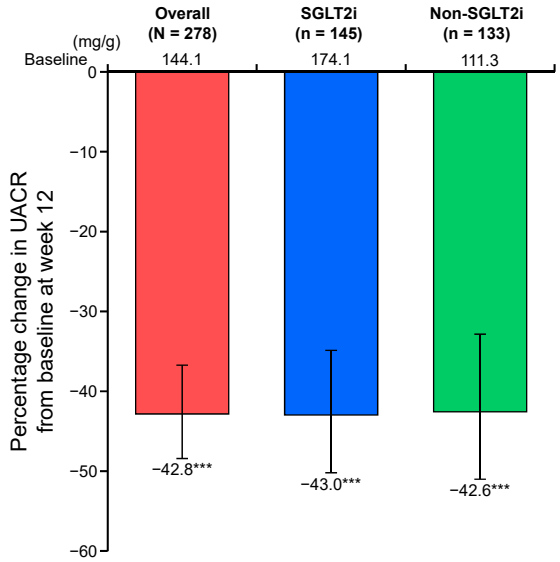
Regarding the safety of esaxerenone administration, the safety profile of esaxerenone was consistent, regardless of SGLT2i use, with the numerically lower incidence of serum potassium ≥5.5mEq/L in the SGLT2i subgroup suggesting a potential mitigating effect of SGLT2is on the risk of hyperkalemia. Thus, concomitant use of an SGLT2i may help further enhance its safety profile regarding the mitigation of hyperkalemia risk in hypertensive patients with T2DM. Of note, the consistent beneficial effects observed with esaxerenone across both subgroups in our study might suggest that the use of MRBs from an earlier stage in the clinical course could provide additional advantages. Moreover, in patients whose BP remains uncontrolled despite the addition of

Figure 1



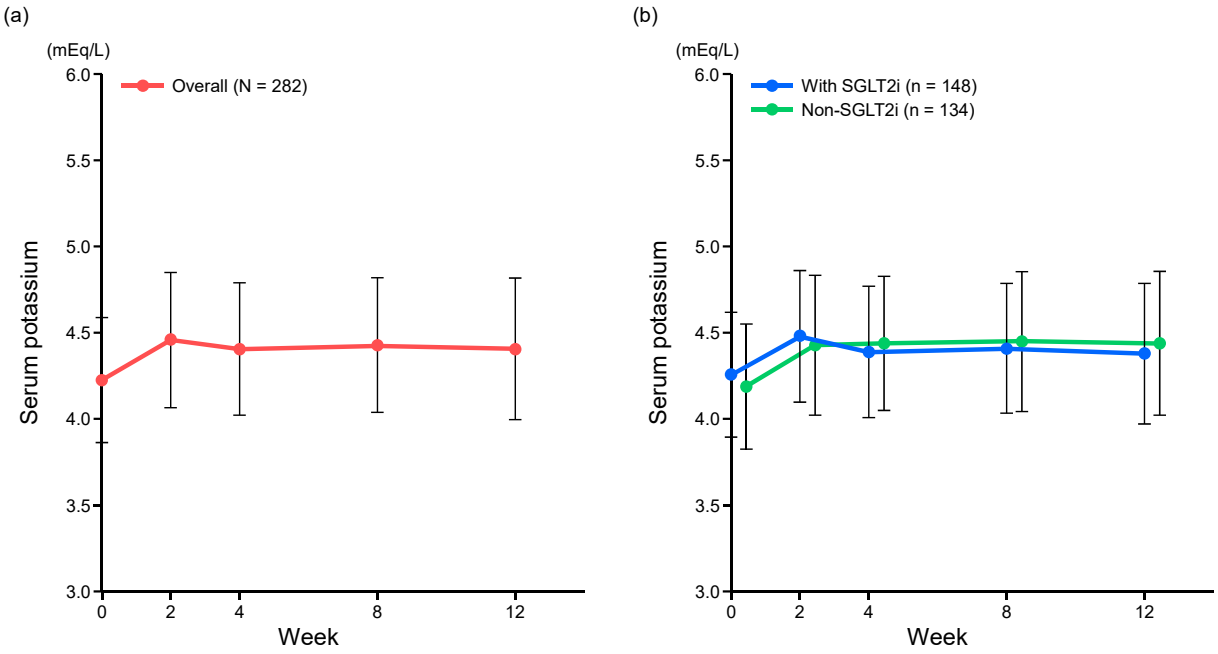
renin-angiotensin system (RAS) inhibitor, calcium channel blocker (CCB), and SGLT2i, enhanced volume management through MR blockade may help achieve more robust BP lowering. Conversely, in patients who are not receiving an SGLT2i, a relatively small degree of MR blockade may more readily reduce fluid volume and thus facilitate BP control, potentially reflecting heightened sensitivity to MR blockade in this population. SGLT2is exert their effects via the enhancement of glucose excretion through the urine while inducing natriuresis (sodium loss) and diuresis (fluid loss). In contrast, the mechanism underlying the antihypertensive effects of esaxerenone is the inhibition of sodium retention and consequent fluid overload, both of which are vital contributors to its antihypertensive effects. Therefore, the two drug classes exert their effects simultaneously without antagonizing each other, as they work via distinct biochemical pathways.

Figure 2



Importantly, esaxerenone is indicated for the treatment of hypertension; however, finerenone is not indicated for its antihypertensive effect (i.e. the treatment of hypertension). Therefore,

Figure 3



when selecting MRBs to treat hypertension, esaxerenone is suitable instead of finerenone. The JSH 2025 guideline[6] recommend MRBs as second-line therapy and permit the administration of esaxerenone as an additional antihypertensive agent when there is an inadequate antihypertensive effect with ARB or CCB monotherapy. The 2024 Japanese Clinical Practice Guidelines for the diagnosis and treatment of CKD[7] recommend SGLT2is as first-line agents for CKD complicated by T2DM, and RAS-based inhibitors for hypertension with proteinuria. Additionally, nonsteroidal MRBs are recommended for persistent albuminuria. Finerenone is recommended if serum potassium levels are normal and only the improvement of albuminuria is needed, while esaxerenone is recommended if both improvement of albuminuria and hypertension are needed.

References:

1. Uchida HA, Nakajima H, Hashimoto M, Nakamura A, Nunoue T, Murakami K, et al. Efficacy and safety of esaxerenone in hypertensive patients with diabetic kidney disease: a multicenter, openlabel, prospective study. Adv Ther. 2022;39:5158–75.

2. 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.

3. 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.

4. 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.

5. Motoki H, Inobe Y, Fukui T, Iwasaki A, Hiramitsu S, Koyama S, et al. Efficacy and safety of esaxerenone in hypertensive patients with diabetes mellitus undergoing treatment with sodium-glucose cotransporter 2 inhibitors (EAGLE-DH). Adv Ther. 2023;40:5055–75.

6. Ohya Y, Sakima A. JSH2025 guidelines new viewpoints. Hypertens Res. 2025. https://doi.org/10.1038/s41440-025-02296-8.

7. Japan Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2024. https://cdn.jsn.or.jp/medic/guideline/pdf/guide/viewer.html?file=1-178_v2.pdf. Accessed 23 July 2023.

Hirohiko Motoki – hmotoki@shinshu-u.ac.jp