# Novel Therapies in Diabetic Kidney Disease and Risk of Hyperkalemia: A Review of the Evidence From Clinical Trials

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Concerns about hyperkalemia may result in the underuse of established and novel therapies that improve kidney and/or cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Hyperkalemia-related issues are of particular relevance in patients with CKD, who are commonly receiving other hyperkalemia-inducing agents such as renin-angiotensin-aldosterone system inhibitors and nonsteroidal mineralocorticoid receptor antagonists. In contrast, sodium/glucose transporter 2 (SGLT2) inhibitors mitigate the risk of serious hyperkalemia in clinical trials. We aim to review recent evidence surrounding the risk of hyperkalemia in patients with T2DM and CKD treated with established and novel therapies for diabetic kidney disease, focusing on SGLT2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists. We conclude that SGLT2 inhibitors can be used safely in patients with T2DM at high CV risk with CKD without increasing the risk of hyperkalemia. Routine potassium monitoring is generally required when finerenone is used as a kidney- and CV-protective agent in patients with T2DM. Based on existing data, when added to the standard of care, combining SGLT2 inhibitors with finerenone is safe and has the potential to exert additional cardiorenal benefits in patients with diabetic kidney disease. The use of potassium binders should be considered to enable optimal doses of guideline-based therapies for patients with diabetic kidney disease to maximize the kidney and CV benefits.

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Maintaining a physiologically constant serum potassium level is critical, and fluctuations in serum potassium levels are linked to all-cause and cardiovascular (CV) death.[1] Patients with type 2 diabetes mellitus (T2DM), especially those with chronic kidney disease (CKD), are at increased risk of hyperkalemia,[2] often in the context of hyporeninemic hypoaldosteronism.[3] Hyporeninemic hypoaldosteronism is a syndrome associated with a decrease in the release of renin from juxtaglomerular apparatus cells and aldosterone from the adrenal gland on the basis of juxtaglomerular apparatus injury.[3] In addition, antihypertensive drugs such as renin-angiotensin-aldosterone system (RAAS) inhibitors and potassium-sparing diuretic agents can increase serum potassium levels.[2]

Sodium/glucose cotransporter 2 (SGLT2) inhibitors are a class of glucose-lowering medications that reduce the risk of kidney disease progression and CV events in persons with or without T2DM and CKD.[4,5] This class of medications also protects against the development of hyperkalemia without increasing the risk of hypokalemia.[6] More recently, nonsteroidal mineralocorticoid receptor (ns-MR) antagonists (ns-MRAs) have been evaluated in 2 trials in participants with T2DM and CKD and have consistently shown CV benefits and a reduction in kidney disease progression.[7,8] However, ns-MRAs can increase serum potassium levels, limiting the use of these novel therapies in a population at high risk of kidney and CV events.

Accordingly, we will review the current evidence regarding the impact of SGLT2 inhibitors and ns-MRAs on serum potassium levels in patients with T2DM and CKD, as well as how to safely combine guideline goal-directed medical therapies to optimize their kidney and CV benefits without increasing the risk of hyperkalemia.

## The Effect of SGLT2 Inhibitors on Serum Potassium in Patients With Diabetic Kidney Disease

Current KDIGO (Kidney Disease: Improving Global Outcomes) guidelines advise the use of SGLT2 inhibitors for kidney and CV protection in patients with T2DM and CKD who have an estimated glomerular filtration rate (eGFR) of >20 mL/min/1.73 $m^2$.[9] SGLT2 inhibitors increase distal sodium and water delivery, which may influence potassium excretion in the distal tubule.[10,11] Based on the primary renal tubular site of action of SGLT2 inhibitors and observations in clinical trials, the effects on potassium are interesting and clinically relevant. In a secondary analysis of the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial, Neuen and colleagues examined the impact of SGLT2 inhibitors on serum potassium.[6] The average baseline potassium concentration was 4.5 mmol/L, and >99% of the patients were already using RAAS inhibition.[6] They reported that, in patients with T2DM and CKD, canagliflozin lowered the risk of significant hyperkalemia (potassium concentration >6.0 mmol/L) without increasing the risk of hypokalemia.[6] Subsequently, Neuen and colleagues conducted a meta-analysis involving 6 SGLT2 inhibitor clinical trials to evaluate the impact on hyperkalemia in participants with T2DM and high CV risk or underlying CKD.[12] SGLT2 inhibitors consistently reduced the overall risk of significant hyperkalemia (serum potassium concentration >6.0 mmol/



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**Table 1.** Effects of SGLT2 Inhibitors on Serious Hyperkalemia

| | CANVAS-Program | CREDENCE | DAPA-CKD | DECLARE-TIMI 58 | EMPA-REG | VERTIS CV | EMPA-Kidney |
|---|---|---|---|---|---|---|---|
| **SGLT2 inhibitor** | | | | | | | |
| n/N | 137/5,795 | 121/2,202 | 159/1,455 | 53/8,582 | 216/4,687 | 291/5,493 | 92/3,304 |
| Events per 1,000 p-ys | 8.2 | 21.6 | 56.9 | 1.6 | 17.2 | 18.7 | 1.44 |
| **Placebo** | | | | | | | |
| n/N | 85/4,347 | 154/2,199 | 179/1,451 | 78/8,578 | 124/2,333 | 157/2,745 | 109/3,305 |
| Events per 1,000 p-ys | 9.2 | 27.9 | 65.3 | 2.3 | 20.5 | 21.2 | 1.72 |
| HR (95% CI) | 0.89 (0.67-1.17) | 0.77 (0.61-0.98) | 0.88 (0.71-1.09) | 0.67 (0.47-0.95) | 0.83 (0.67-1.04) | 0.90 (0.74-1.09) | 0.83 (0.63-1.09) |

Serious hyperkalemia defined as central laboratory–determined serum potassium ≥6.0 mmol/L.
CANVAS, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-Kidney, Empagliflozin in Patients with Chronic Kidney Disease; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; p-y, patient-year; SGLT2, sodium/glucose cotransporter 2; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

L; Table 1), without evidence of heterogeneity across levels of baseline kidney function, heart failure history, and MRA and diuretic agent use, and without increasing the risk of hypokalemia.[12] These findings were consistent with an earlier meta-analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program, which showed that canagliflozin did not affect serum potassium levels in the general population, regardless of canagliflozin dosing, RAAS inhibitor use, or baseline eGFR.[13] In addition, hyperkalemia-related adverse events were less common in the canagliflozin group than in the placebo group.[13] These findings suggest that SGLT2 inhibitors reduce kidney and CV event rates without increasing the risk of hyper- or hypokalemia, irrespective of the use of other kidney protective therapies such as RAAS inhibitors and MRAs. Furthermore, SGLT2 inhibitors reduced the risk of serious hyperkalemia, potentially enabling the use of other kidney protective therapies that are associated with hyperkalemia.

The proposed mechanism responsible for potassium lowering with SGLT2 inhibitors relates to increasing the sodium and water delivery rates to the distal nephron, thereby increasing the electronegative charge in the distal tubule, favoring potassium secretion.[12] SGLT2 inhibitors also increase plasma aldosterone levels, which could facilitate potassium secretion.[12] Finally, maintenance of kidney function with prolonged SGLT2 inhibitor use over time may also explain the lower frequency of hyperkalemia.[12]

## The Effect of Nonsteroidal Mineralocorticoid Receptor Antagonists on Serum Potassium in Patients with Diabetic Kidney Disease

Finerenone, an ns-MRA, blocks MR overactivation, which contributes to inflammation and fibrosis, leading to kidney and CV damage.[14,15] Finerenone has a unique binding mechanism and distribution compared with steroidal MRAs (s-MRAs), resulting in high potency and selectivity on MR cofactor binding.[14,15] The use of s-MRAs such as spironolactone in patients with CKD increases the risk of hyperkalemia by 2-3 fold, with an absence of evidence of long-term kidney or CV benefits.[16] Spironolactone also has biologically active metabolites with long half-lives and can be seen in the urine several weeks after ending treatment.[17] Conversely, finerenone is a selective ns-MRA that interacts with the MR in a different way than s-MRAs. Finerenone has a half-life of 2-4 hours in patients with CKD, which could explain the lower risk of hyperkalemia with finerenone compared with s-MRAs.[14,15]

Based on this pharmacological profile and substantial supportive evidence in experimental studies, the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials were designed to determine the impact of finerenone on CV and kidney benefits beyond the standard of care in patients with DKD.[7,8] FIDELIO-DKD showed a significant reduction in a primary composite kidney outcome of kidney failure,



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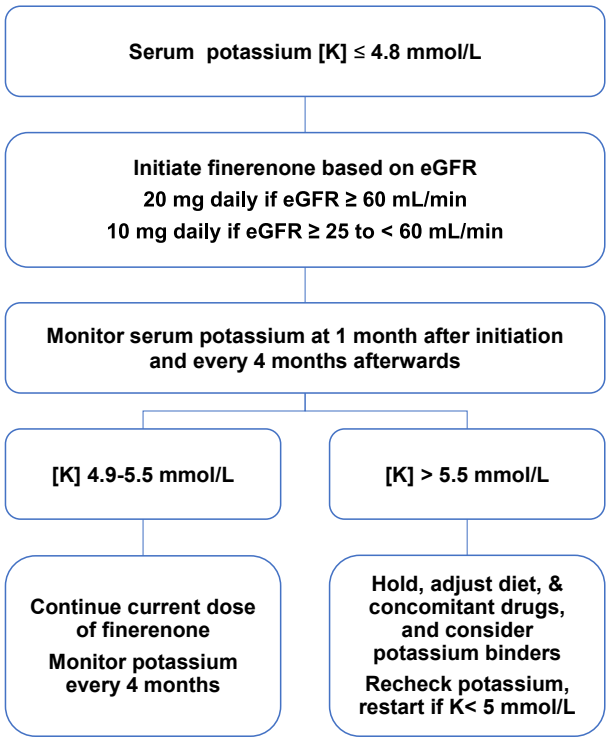


**Figure 1.** Serum potassium monitoring during treatment with finerenone adapted from the FIDELIO-DKD trial.

sustained 40% decrease in eGFR from baseline, or death of renal causes (hazard ratio [HR], 0.82; 95% CI, 0.83-0.93).[7] Finerenone also lowered the risks of death of CV causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure.[7] These findings were demonstrated again in the FIGARO-DKD trial, which used the CV composite outcome as its primary end point (HR, 0.87; 95% CI, 0.76-0.98).[8] In the pooled FIDELITY (Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease)analysis, the mean baseline eGFR of all participants was 57.6 ± 21.7 mL/min/1.73 $m^2$, with a median urine albumin-creatinine ratio (UACR) of 515 (198-1147) mg/g.[18] Acknowledging the low number of participants with more advanced CKD (162 participants or 1.2% with eGFR <25 mL/min/1.73 $m^2$ in the FIDELITY analysis) in whom hyperkalemia may have been more of a concern, finerenone and placebo generally had similar adverse effect profiles. Hyperkalemia-related discontinuation of the study drug occurred in 2.3% of those receiving finerenone versus 0.9% in the placebo group.[7] Anticipating an increased risk of hyperkalemia, the FIDELIO-DKD investigators limited enrollment to patients with normal serum potassium concentrations (after maximizing RAS inhibitors) and implemented a standardized potassium monitoring protocol (Fig 1; Table 2).[7] Before starting the drug, the protocol required serum potassium levels to consistently be ≤4.8 mmol/L. Serum potassium levels were subsequently measured in both trials 1 month after drug administration and every 4 months after that. When serum potassium concentration was >5.5 mmol/L, finerenone was temporarily withheld, and the serum potassium concentration was rechecked within 72 hours. Dietary potassium restriction and concomitant medications such as diuretic agents and potassium binders were permitted, and the drug was restarted when potassium concentrations returned to 5.0 mmol/L. Based on this regimen and the relatively low risk of hyperkalemia in the clinical trial environment, it is likely that such an approach can be used in practice to achieve similar levels of safety in regard to potassium. Moreover, in the FIDELIO-DKD trial, the independent risk factors for hyperkalemia were higher with baseline serum potassium concentrations >4.8 mmol/L, lower eGFR, and age <65 years and in patients taking β-blockers (Box 1).[19]

## The Effects of Combining SGLT2 Inhibitors and MRAs on Serum Potassium in Patients With Diabetic Kidney Disease

s-MRAs and SGLT2 inhibitors both lower UACR in patients with CKD, raising interest in their combined use to effect heart and kidney protection.[20] To examine this interaction, Provenzano et al conducted a randomized crossover clinical trial in patients with CKD and T2DM. They evaluated the impact of the SGLT2 inhibitor dapagliflozin and the s-MRA eplerenone individually and when used together on decreasing albuminuria.[21] After 4 weeks of dapagliflozin/eplerenone combination therapy, there was a 53% reduction in albuminuria, compared with 19.6% with dapagliflozin alone and 33.7% with only eplerenone.[21] The incidence of hyperkalemia was lower with combination therapy than with eplerenone alone.[21] Hyperkalemia was more frequently reported with eplerenone (n = 8; 17.4%) compared with dapagliflozin (n = 0) or dapagliflozin/eplerenone (n = 2; 4.3%; P = 0.003 between groups).[21]

**Table 2.** Finerenone Dose Adjustment Protocol From the FIDELIO-DKD Trial Based on Serum Potassium Levels

| | Initial Dose | |
|---|---|---|
| **Potassium Level** | **10 mg** | **20 mg** |
| ≤4.8 mmol/L | Increase to 20 mg/d[a] | Continue dose |
| >4.8-5.5 mmol/L | Continue dose | Continue dose |
| >5.5 mmol/L | Hold finerenone, follow potassium-lowering strategies (Fig 2), and consider restarting at 10 mg/d if potassium is <5 mmol/L after 2 wk | |

[a]If estimated glomerular filtration rate decreases >30% from baseline, stay with 10-mg daily dose.



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**Box 1.** Risk Factors for Hyperkalemia Associated With the Use of Finerenone

1. Patients with high baseline serum potassium level >4.8 mmol/L
2. Patients with low estimated glomerular filtration rate (<45 mL/min/1.73 $m^2$)
3. Younger patients (age <65 y)
4. Patients using concomitant β-blocker drugs

These observations are consistent with previous observations by Shen et al in the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) clinical outcome trial, in which the effect of dapagliflozin on the primary study outcome and safety outcomes was evaluated in patients taking or not taking an s-MRA at baseline.[22] Dapagliflozin was equally effective in patients with heart failure with reduced ejection taking an s-MRA compared with those not taking an s-MRA.[22] Importantly, the risk of moderate to severe hyperkalemia (potassium concentration >6.0 mmol/L) was significantly lower in participants taking an sMRA in combination with dapagliflozin compared with s-MRA–treated participants in the placebo group (HR, 0.50; 95% CI, 0.29-0.85).[23] In a similar analysis of the DAPA-CKD trial, the protective effect of dapagliflozin on hyperkalemia was consistent among s-MRA– and non–s-MRA–treated patients at baseline (HR, 0.87; 95% CI, 0.69-1.10; P = 0.96 for interaction).[23]

Interestingly, and in line with observations from the DAPA-HF study, in the FIDELIO-DKD trial, there were lower rates of hyperkalemia-related adverse events that had to be treated emergently in participants treated with an SGLT2 inhibitor plus finerenone (8.1% for finerenone plus an SGLT2 inhibitor vs 3.0% for placebo plus an SGLT2 inhibitor, 18.7% for finerenone without an SGLT2 inhibitor, and 9.3% for placebo without an SGLT2 inhibitor).[24] A similar analysis is planned using data from the FIGARO-DKD trial, in which a greater number of participants were taking an SGLT2 inhibitor at baseline compared with FIDELIO-DKD (8.3% vs 4.6%). Collectively, these findings support the rationale for combining SGLT2 inhibitors with MRAs to potentially achieve better efficacy on clinical end points while lowering the risk of hyperkalemia in patients with diabetic kidney disease. Based on the cardiorenal benefits observed individually with SGLT2 inhibitors and ns-MRAs on kidney and CV end points, recent interest has focused on the concomitant use of SGLT2 inhibitors with finerenone to achieve additional risk reduction and to mitigate the risk of hyperkalemia with ns-MRA treatment alone.[20] The CONFIDENCE (Controlled Delivery for Improved Outcomes with Clinical Evidence) trial (NCT03752866) is a proposed randomized, double-blind, phase II clinical trial designed to study the effects of a combination of finerenone and empagliflozin compared with each drug alone on UACR and hyperkalemia in 807 participants with T2DM, stage 2/3 CKD, and a UACR ≥300 but <5,000 mg/g.[20]

## Strategies to Reduce the Risk of Hyperkalemia While Maximizing CV and Kidney Benefits in Patients With Diabetic Kidney Disease

The treatment of hyperkalemia often involves the down-titration or discontinuation of potential culprit drugs, including RAAS inhibitors and MRAs. However, this strategy may not be entirely benign. The risks of cardiac events and mortality are consistently greater in patients who are receiving a submaximal dose of RAAS inhibitor in the setting of heart failure.[25] Similarly, a strategy of discontinuing RAAS inhibition because of a low eGFR was associated with increases in mortality, CV events, and CKD progression among patients with CKD.[26] Recently, Leon et al investigated the relationship between stopping RAAS inhibitors in response to hyperkalemia and all-cause death in patients with CKD with a mean eGFR of 41 mL/min/1.73 $m^2$ and a mean potassium level of 5.7-5.8 mEq/L.[27] Dialysis initiation, fatal and nonfatal CV events, and CV death were studied as secondary outcomes.[27] Greater all-cause mortality, CV mortality, and progression to dialysis were all associated with the discontinuation of RAAS inhibition.[27] Compared with stopping therapy, the administration of submaximal doses of RAAS inhibitors reduced the risk of CV and all-cause mortality; however, individuals receiving maximal doses of RAAS inhibitors had the greatest survival benefit.[27] It is worth noting that the results of observational studies of the discontinuation of RAAS inhibition in the context of hyperkalemia are not entirely consistent, as reported by Hundemer and colleagues.[28] Moreover, the majority of these studies had few, if any, participants undergoing concomitant SGLT2 inhibition, reflecting a "pre–SGLT2 inhibitors era" of diabetic kidney disease/CKD therapies.

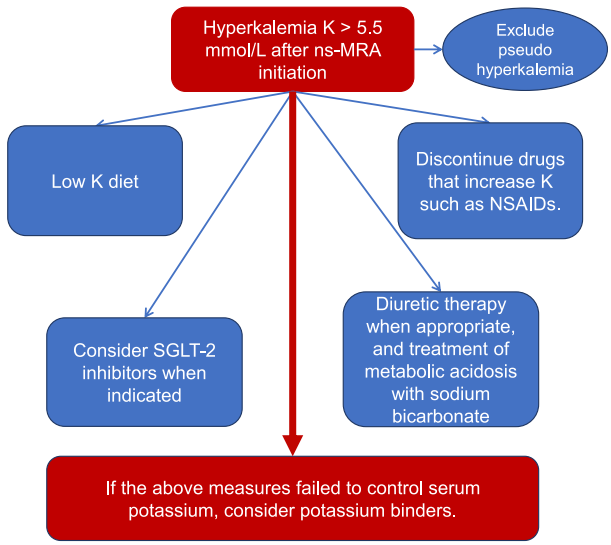


**Figure 2.** Treatment algorithm for management of ns-MRA–induced hyperkalemia. NSAID, nonsteroidal anti-inflammatory drug; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; SGLT-2, sodium/glucose cotransporter 2.



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Balancing the risk of hyperkalemia with the benefits of continuing agents at doses that confer maximal cardiorenal protection remains challenging. However, strategies do exist to help achieve and maintain this balance (Fig 2). First, it is recommended to identify patients in whom hyperkalemia is most likely to develop (Box 1). Second, concurrent medications that may further contribute to hyperkalemia, such as nonsteroidal anti-inflammatory drugs or potassium-sparing diuretic agents, should be identified and may have to be stopped if feasible and safe.[27] Evaluating these baseline risk factors and considering more frequent monitoring may help in managing the risk of hyperkalemia. After starting medications that confer cardiorenal benefit but pose an increased risk of hyperkalemia, monitoring of serum potassium concentrations with temporary drug discontinuation and dose reduction in case of hyperkalemia is recommended. Such an approach was also successfully incorporated into the FIDELIO-DKD trial protocol (Fig 1; Table 2).[7] In cases in which the underlying precipitant of hyperkalemia is identified and addressed, these medications may be used in a rechallenge with appropriate monitoring. In terms of combination therapies, the 2022 American Diabetes Association guidelines recommend the use of combination therapy with RAAS inhibitors and/or ns-MRAs with SGLT2 inhibitors in patients who meet clinical indications to maximize kidney and CV benefits; this may also reduce the risk of hyperkalemia. Finally, the management of hyperkalemia involves the maintenance of diuretic therapy when appropriate and the treatment of metabolic acidosis with sodium bicarbonate.

When these strategies are insufficient, the use of potassium-binding therapies such as sodium zirconium cyclosilicate or patiromer should be considered, with the goal of reducing the risk of hyperkalemia while avoiding the need to stop cardiorenal protective therapies.[29] Potassium-binding therapies lower serum potassium levels through ion-exchange mechanisms in the digestive system.[29] Sodium zirconium cyclosilicate is a nonpolymer substance that exchanges potassium ions for sodium and hydrogen ions, whereas patiromer is a polymer that exchanges calcium ions for potassium ions.[29] Several studies have reported that patiromer significantly lowers serum potassium levels in individuals with CKD and/or cardiac disease, allowing for the use of RAAS inhibitors.[30] Similarly, sodium zirconium cyclosilicate has been observed to sustain serum potassium levels in patients with CKD and those using RAAS inhibitors, with follow-up as long as 1 year.[30] Patiromer has been studied in patients with heart failure with reduced ejection fraction who had a history of hyperkalemia.[31] The use of patiromer was associated with a lower incidence of hyperkalemia and resulted in 85% of participants successfully continuing to receive optimized guideline goal-directed medical therapy for heart failure with reduced ejection fraction.[31] Similarly, in patients with CKD who had a history of resistant hypertension, the use of patiromer enabled the initiation and up-titration of spironolactone in this higher-risk population.[17] However, even though patiromer allowed for greater adherence to spironolactone in this trial, it is important to note that there was no difference in blood pressure control between the patiromer and placebo groups.[17] The actual efficacy of this strategy of combining potassium-binding therapies with the agents that cause hyperkalemia in terms of "hard" cardiorenal outcomes has yet to be demonstrated in clinical trials.

## Conclusions

Goal-directed pharmacological therapy for diabetes and CKD now includes RAAS inhibitors, SGLT2 inhibitors, and ns-MRAs. The additional advantages of SGLT2 inhibitors include a potentially lower risk of hyperkalemia, which can optimize the use of RAAS inhibitors and ns-MRA therapies.

## Article Information

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