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Renin-Angiotensin-Aldosterone System Inhibition and Mineralocorticoid Receptor Antagonists: The Overriding Importance of Enablers and Dampers

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Practice guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) provide clinicians with an evidence-based approach to the management of patients with acute or chronic heart failure (HF).[1] Mineralocorticoid receptor antagonist (MRA)–based treatment regimens have been shown to be useful in treating HF with reduced ejection fraction, and are advocated in current guidelines. Most recently, a large global prospective trial FIDELIO-DKD Phase III Study has provided an evidence-based approach for retarding the progression of diabetic nephropathy by showing that the investigational drug finerenone significantly reduced renal and cardiovascular outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes.[2]

Systematic reviews and meta-analyses compared higher versus lower doses of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in HF with reduced ejection fraction, suggesting that guideline-mandated higher doses of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduce the risk of HF worsening compared with lower doses.[3,4]

Influence of Hyperkalemia on Renin-Angiotensin-Aldosterone System Inhibitor Activity

Whereas renin-angiotensin-aldosterone system inhibitors (RAASIs) are vital drugs in the management of CKD and HF, unfortunately these mandated guidelines frequently provoke RAASI and MRA-induced hyperkalemia which constitutes a formidable constraint to sustained treatment. In a retrospective study to ascertain the impact of hyperkalemia on RAASI therapy, we examined deidentified medical records from a large database of electronic health records (Humedica; analyzed $N = 205{,}108$ patients from 1.7 million records) to investigate the impact of hyperkalemia on RAASI dose, and to elucidate the association between dose levels and clinical outcomes. Relatively few patients were prescribed the maximum doses of RAASIs (4). RAASI dose was either down-titrated or discontinued in a substantive number of patients after hyperkalemia events. Cardiorenal adverse event/morbidity and mortality occurred in 34.3% of patients who discontinued RAASIs compared with 24.9% of patients who were taking submaximum doses.[4]

Fortunately, in 2021 hyperkalemia should no longer constitute a barrier because it can now be countered by the availability of new "enablers" (the new nonabsorbable K^+binders, both patiromer and sodium zirconium cyclosilicate [SZC]).[5] Both patiromer and SZC appear to be effective and unequivocably more tolerable than sodium polystyrene sulfonate, although there have been no head-to-head trials to date. Optimizing RAASI therapy to achieve cardiorenal benefits should constitute the clinician's therapeutic goal when practicing evidence-based medicine. Treatment with a K^+ binder, by acting as an enabler, facilitates sustained MRA therapy (avoiding down-titration or discontinuation) with consequent improved outcomes. For example, recent studies have clearly shown that treatments with patiromer were able to sustain normokalemia for 52 weeks in patients who are hyperkalemic with diabetic CKD[6] and resistant

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hypertension,[7] thereby avoiding down-titration or discontinuation and enabling continuous RAASI treatment. Similar efficacy has been shown for SZC in a 12-month phase III study.[8] Most recently, Fishbane *et al*.[9] reported that SZC is an effective and well-tolerated treatment for predialysis hyperkalemia in patients with ESRD who are undergoing adequate hemodialysis.

Balance of Benefits and Harms

Whereas both K^+ binders are efficacious in obviating hyperkalemia, both are associated with side effects.[5,6,8,9] An overriding concern in prescribing K^+ binders is to avoid concomitant changes that offset the beneficial effects of RAAS blockers that K^+ binders enable. Attention has focused on the counterion of both binders: calcium for patiromer and sodium for SZC.[5]

Sodium Intake as a Determinant of RAASI Efficacy

An additional concern in prescribing SZC is sodium acquisition. Because the counterion of SZC is sodium, concern has focused on the extra 400 mg of sodium with a 5-g SZC dose or 800 mg of sodium with a 10-g dose of SZC, especially in patients with advanced CKD or HF. The potential for sodium acquisition is a major concern. To provide context, it must be emphasized that high dietary sodium intake diminishes the efficacy of RAASIs. In a *post hoc* analysis of the REIN and REIN-2 trials, the benefit of angiotensin-converting enzyme inhibition in reducing proteinuria was blunted by high sodium intake.[S1] Comparable results were reported in a *post hoc* analysis of the 2 landmark angiotensin II receptor blocker clinical trials: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan and the Irbesartan Diabetic Nephropathy Trial studies in patients with diabetic nephropathy.[S2] Compared with non–RAASI-based antihypertensive therapy, the treatment benefit of angiotensin II receptor blockers on renal and cardiovascular event rates was greater among patients with lower versus higher sodium intake. In concert, these studies emphasize that elevated sodium intake, whether acquired through diet or drugs, augments cardiorenal risk. Lowering salt intake not only reduces blood pressure but also lowers albuminuria. The importance of salt intake in the general management of patients with CKD cannot be overemphasized.[S3] The product insert for Lokelma underscores these concerns. It provides a warning for edema particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., HF or renal disease).[S4]

The Equipoise

Controversy has recently flared regarding the incidence and clinical relevance of sodium acquisition associated with treatment with SZC.[S5,S6] In a recent review, Colbert and Lerma[S5] focused on sodium as a side effect of major concern with K^+ binders. They wrote that "Patiromer is unique from the other medications on the US market in that is not bound with any sodium, avoiding the acquisition of a cation that can worsen hypertension and volume overload".[S5] In response to the Colbert and Lerma review,[S5] in a recent letter to the editor, Cooper[S6] objected to Colbert and Lerma's discussion of edema attributable to SZC, writing that the statement concerning SZC-associated edema is potentially misleading. In the context of these conflicting formulations, what advice should the clinician adapt?

Next Steps

At the outset I will state that I believe that both K^+ binders constitute efficacious interventions for enabling sustained RAASI therapy, enabling clinicians to close the glaring gap between mandated guidelines and the real-world reality of frequent down-titration of treatment, or indeed discontinuation. Yet I believe that the issue of sodium acquisition constitutes an important and compelling concern for all sodium-based K^+ binders (both sodium polystyrene sulfonate or SZC) when treating susceptible patients with a proclivity for sodium retention and edema. The continuing controversy focusing on the reported incidence of SZC-induced frequency of edema by proponents and critics of SZC is confounded both by differences in the study cohorts differing estimated glomerular filtration rate at entry, differences in sodium intake in part related to ethnicity, nonequivalence of K^+ binder dosing; in essence we are "comparing apples and oranges" and the controversy will not be readily resolved with successive quid pro quos. But I believe there is a constructive approach that beckons that I suggest should be considered. The frequency and severity of edema can be accurately quantitated using the proven and highly reproducible methodology of water displacement volumetry, that has previously been shown to constitute a sensitive method or measurement of leg volume.[S7] In brief, Lund-Johansen *et al*.[S7] compared the leg edema–forming potential of 2 different dihydropyridine calcium channel blockers (lercanidipine or amlodipine). Importantly, a positive correlation was found between leg

volume and signs or symptoms of edema (symptoms of leg swelling 63.9% vs. 22%, $P < 0.001$) and leg heaviness (47.2% vs. 12.2%, $P < 0.001$). In accordance with the methodology used by Lund-Johansen *et al.*,[S7] I recommend that this volumetric approach be deployed in a rigorous focused clinical trial of patients treated with either SZC or patiromer to evaluate leg volume of both legs at screening and at subsequent prespecified intervals. All measurements should be conducted according to a strict protocol, as detailed previously.[S7] It should be emphasized that this methodology is highly sensitive. In the study by Lund-Johansen *et al.*, even in patients without any clinical evidence of edema, the leg volume change from baseline was significantly higher in patients with symptoms than in patients without symptoms, suggesting that reports of symptoms could be used by clinicians as indicative of subclinical edema, and by inference sodium acquisition. Even if SZC edema is documented to be somewhat greater than proposed, this should not militate against prescribing SZC. Rather, this finding should be perceived as constituting an action item, prompting the clinician to institute concomitant dietary sodium restriction thereby enabling unimpaired RAASI therapy.

Optimizing RAASI therapy to adhere to mandated guidelines in order to achieve cardiorenal benefits constitutes the clinician's therapeutic goal when practicing evidence-based medicine. With the advent of new K^+ binders, affording opportunities to treat hyperkalemia without concomitant increased sodium acquisition may provide clinicians with increasing options to achieve improved cardiorenal outcomes.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References

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