THE IMPORTANCE OF RAAS INHIBITOR THERAPY

even when facing hyperkalemia[1]

For many HCPs, RAAS inhibitor down-titration is an initial response to an occurrence of RAAS inhibitor-induced hyperkalemia.[2-4] **But should it be?**

THE BENEFICIAL EFFECTS OF RAAS INHIBITORS ARE MANY[3]

Renin-angiotensin-aldosterone system inhibitors treat hypertension and slow progression of diabetic kidney disease.[3,5] They also reduce both CKD progression and the risks of morbidity and mortality due to heart failure.[3]

"Given the integral role of RAAS inhibitor therapy in reducing CV risk and slowing the progression of CKD, the use of new K^+ binders to lower serum K^+ and thereby maintain optimal RAAS inhibitor therapy is expected to improve long-term clinical outcomes in patients with CKD."[5]

– *Mayo Clinic Proceedings*

FOR PATIENTS WITH CKD, HF, OR DIABETES, RAAS INHIBITOR THERAPY MAKES A DIFFERENCE[6-11]

The following outcomes, derived from various studies of patients on RAAS inhibitors, informed guideline recommendations[6,7,10]

31% reduction in risk of kidney failure in patients with nondiabetic kidney disease treated with ACEi*[6,8]

~50% risk reduction in progression of CKD in patients with diabetic kidney disease treated with ACEi or ARB†[7,9]

~17% and ~30% relative risk reduction in mortality for patients with heart failure/HFrEF on an ACEi or ARB, or on an MRA, respectively‡[10,11]

*From a meta-analysis of patient-level data (N=1860) across 11 randomized, controlled trials comparing antihypertensive treatments that included ACEi to those without an ACEi in patients with predominantly nondiabetic CKD. Mean duration of follow-up was 2.2 years. Kidney failure was defined as ESRD requiring the initiation of long-term dialysis. Results may have been impacted by high withdrawal rate in some trials, errors in clinical test measurements, and use of relatively short-term studies to infer longer-term effects in chronic disease.[8]

†From the *Cochrane Database of Systematic Reviews*–included trials of at least 6 months duration that compared ACEi (17 studies, 2036 patients) or ARB (3 studies, 761 patients) to placebo/no treatment in reducing the risk of progression from micro- to macroalbuminuria in patients with diabetic kidney disease. Limitations include small study sizes and varying study quality.[9]

‡Data from pooled multiple sources, including landmark trials and meta-analyses, and derived from randomized controlled trials. Estimated risk reductions may not be entirely independent from each other.[11]

RAAS INHIBITOR USE IS GUIDELINE RECOMMENDED FOR A RANGE OF CONDITIONS[3,6,7,10,12]

Multiple studies establish the importance of RAAS inhibitors for patients with diabetes with albuminuria, HF, and CKD.[6,7,10,12]

Guidelines call for the optimal* RAAS inhibitor dosing that is tolerated.[6,7,10,12]

Guideline	RAAS inhibitor recommendation	Scenario	Additional information	Class/ Grade	LOE
American Diabetes Association[13]	ACEi or ARB	Diabetes and hypertension	UACR 30-299 mg/g	–	B†
			UACR ≥300 mg/g	–	A†
Kidney Disease: Improving Global Outcomes[6,7]	ACEi or ARB[7]	Albuminuria + diabetes + hypertension	–	I‡	B‡
	ACEi or ARB[6]	High BP + CKD + moderately increased albuminuria without diabetes	AER 30-300 mg/24 h	II‡	C‡
		High BP + CKD + moderately-to-severely increased albuminuria + diabetes	AER ≥30 mg/24 h	I‡	B‡
American College of Cardiology, American Heart Association, Heart Failure Society of America[10]	ACEi or ARB (if intolerant to ACEi)	Chronic HFrEF	In conjunction with evidence-based beta blockers and aldosterone antagonists in select patients	I§	A§
	ARNi (tolerant to ACEi/ARB)	Chronic symptomatic HFrEF (NYHA class II-III)	In conjunction with evidence-based beta blockers and aldosterone antagonists in select patients	I§	B-R§
	Aldosterone antagonists (MRAs)	Appropriately selected patients with HFpEF	Consider use in patients with EF ≥45%, elevated BNP levels or HF admission within 1-year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L	IIb§	B-R§

The table represents select highlights from the guidelines and does not constitute a full description of guideline recommendations. Please refer to the guidelines themselves for additional context and details.

*Medications are generally titrated to achieve optimal clinical effect. Initial and maximum dosing differ depending on the medication used.
†A=Clear evidence from well-conducted, generalizable randomized controlled trials; B=Supportive evidence from well-conducted cohort studies.
‡Grade 1=Recommended, Grade 2=Suggested; B=Moderate, C=Low.
§Class I=Strong recommendation; Class IIb=Weak recommendation; A=High-quality evidence based on randomized controlled trial(s); B-R=Moderate quality of evidence based on randomized controlled trial(s).

HYPERKALEMIA ASSOCIATED WITH RASi CAN BE MANAGED WITHOUT DOWN-TITRATING RASi THERAPY[6,7]

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease states:[6]

- RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses. It is felt that patients would put a large value on the cardiovascular and renoprotective benefits of RASi
- Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum K^+ levels rather than decreasing the dose or stopping RASi
  - Strategies to control chronic hyperkalemia include dietary K^+ restriction; discontinuation of K^+ supplements, certain salt substitutes, and hyperkalemic drugs; adding potassium-wasting diuretics; and oral K^+ binders
  - **In CKD patients receiving RASi who develop hyperkalemia, the latter can be controlled with newer oral K^+ binders in many patients, with the effect that RASi can be continued at the recommended dose**

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease states:[7]

- In patients with diabetes, hypertension, and albuminuria, ACEi or ARB treatment should be initiated and titrated to the maximum approved dose that is tolerated
- ACEi or ARB treatment should only be reduced or discontinued if serum K^+ levels cannot be otherwise managed or if there is a greater than 30% increase in serum creatinine
- Recommendations to manage hyperkalemia include review concurrent drugs, moderate K^+ intake, initiate diuretics or oral sodium bicarbonate in appropriate patients, and use of a gastrointestinal cation exchanger such as a K^+ binder
- **K^+ binders should be considered to decrease serum K^+ levels after other measures have failed, rather than decreasing or discontinuing ACEi or ARB treatment**

HYPERKALEMIA FREQUENTLY LEADS TO DOWN-TITRATION OR DISCONTINUATION OF RAAS INHIBITOR THERAPY...

In a study of electronic health records of approximately 67,000 patients, those on a maximum dose of a RAAS inhibitor were down-titrated to a submaximum dose or discontinued **47%** of the time after a moderate-to-severe hyperkalemia event, and **38%** of the time following a mild hyperkalemia event.*[3]

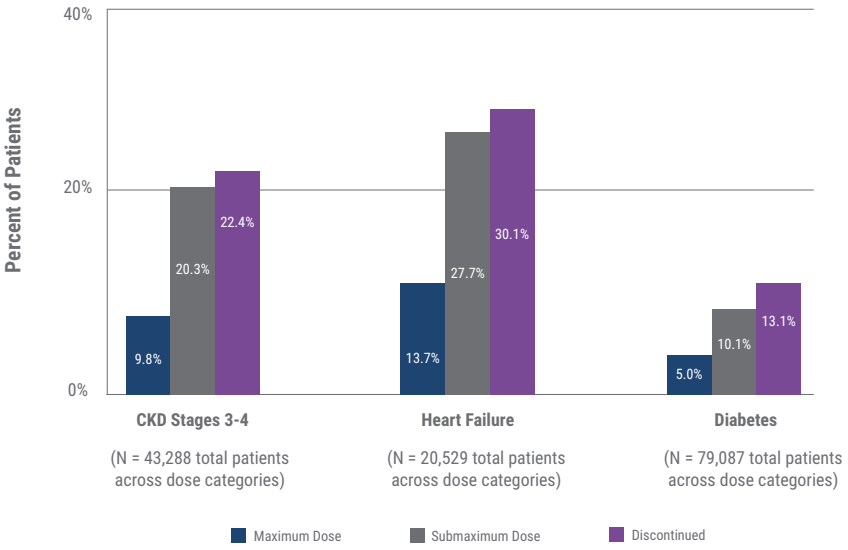
As reported in the *Journal of the American College of Cardiology,* **76%** of patients who discontinued MRA therapy after developing hyperkalemia **did not restart it** within the following year.†[2,4]

*Based on data from an analysis of medical records from the Humedica database that included 205,108 patients 5 years and older with at least 2 serum K^+ measurements, 12 months of data, and at least 1 outpatient RAAS inhibitor prescription, including ACE inhibitors, ARBs, direct renin inhibitors, and select MRAs. Maximum was defined as the labeled dose and submaximum was defined as any dose lower than the labeled dose. A total of 66,862 (33%) patients experienced one or more hyperkalemia events (serum K^+ >5.0 mEq/L). A mild hyperkalemia event was defined as serum K^+ 5.1 mEq/L-5.4 mEq/L and moderate-to-severe was defined as serum K^+ ≥5.5 mEq/L. Causality between hyperkalemia events and RAAS inhibitor dose change was not evaluated.[3]

†This was an observational study of 13,726 adults who initiated an MRA between January 1, 2007, and December 31, 2010. The index date was the date of incident hyperkalemia (serum K^+ >5.0 mEq/L). Following MRA initiation, 2536 patients experienced ≥1 episode of hyperkalemia, and 1761 were still on MRA therapy at the time of hyperkalemia event and were evaluable for changes in prescriptions. After a hyperkalemia event, 47% (827/1761) discontinued MRA therapy and 23% (282/1220) also discontinued their ACEi or ARB therapy. Hyperkalemia causation was not evaluated and results may be an underestimation of actual hyperkalemia incidence.[4]

...WHICH IS ASSOCIATED WITH AN INCREASE IN ALL-CAUSE MORTALITY[3]

Mortality in patients on submaximum dose or discontinued RAAS inhibitor treatment*[3]



"Patients on submaximum dose or who discontinued RAAS inhibitors **died twice as frequently** as patients on maximum dose irrespective of comorbidity status."*[3]

– American Journal of Managed Care

*Based on data from an analysis of medical records of patients 5 years and older with at least 2 serum K^+ measurements from the Humedica database. Patients with ESRD at the index date were excluded from outcomes analyses. Patients were included if they had at least 1 outpatient prescription for a RAAS inhibitor, including ACE inhibitors, ARBs, direct renin inhibitors, and select MRAs. Patients were categorized by their last RAAS inhibitor dose level for the analysis of mortality, where maximum was defined as the labeled dose and submaximum was defined as any dose lower than the labeled dose. Mortality rates for the overall population (N=201,655) during the 12-month period were 4.1% for patients on maximum RAAS inhibitor dose, 8.2% for patients on submaximum dose, and 11.0% for patients who discontinued RAAS inhibitor therapy. Causality between RAAS inhibitor dose and adverse outcomes was not evaluated.[3]

K^+ BINDERS MAY HELP REMOVE A BARRIER TO OPTIMAL RAAS INHIBITOR TREATMENT[2,5]

Key benefits of some K^+ binders:

Studies have shown that some **K^+ binders allow patients to keep potassium controlled long term.*** What's more, they may **help patients continue to stay on their optimal dose of RAAS inhibitors.**[5]

Patients consuming a heart-healthy, plant-based diet **may not need additional dietary K^+ restriction** when using K^+ binders for the treatment of hyperkalemia, although additional studies are needed.[14]

Hyperkalemia can be a **recurrent condition**, but some K^+ binders can help patients **maintain normokalemia** on a long-term* basis, with continued therapy.[15]

*Long term refers to studies done for up to 1 year.[5]

K^+ binders have not been shown to improve outcomes.

ABBREVIATIONS AND REFERENCES

Abbreviations: ACEi=angiotensin-converting enzyme inhibitor; AER=albumin excretion ratio; ARB=angiotensin II receptor blocker; ARNi=angiotensin receptor-neprilysin inhibitor; BNP=brain natriuretic peptide; BP=blood pressure; CKD=chronic kidney disease; CV=cardiovascular; DKD=diabetic kidney disease; EF=ejection factor; ESRD=end stage renal disease; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; K^+=potassium; KDIGO=Kidney Disease Improving Global Outcomes; LOE=level of evidence; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; RAAS=renin-angiotensin-aldosterone system; RASi=renin-angiotensin system inhibitors; UACR=urine albumin-to-creatinine ratio.

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DON'T LET HYPERKALEMIA DEPRIVE YOUR PATIENTS OF OPTIMAL RAAS INHIBITOR DOSING

RAAS inhibitor therapies are important medications across several chronic conditions.[3] However, their use increases the risk of developing hyperkalemia, which can lead to their discontinuation or dose reduction.[4]

CONCLUSION: Guidelines state that RAAS inhibitor therapy should be administered using the highest approved dose that is tolerated. Hyperkalemia associated with the use of RASi therapy can often be managed by measures to reduce serum K^+ levels, like K^+ binders, rather than decreasing the dose or stopping RASi.[6,7] Some K^+ binders can help patients maintain normokalemia on a long-term* basis, and may enable patients to stay on their guideline-recommended RAS inhibitor therapy.[2,4,6,7] Discontinuing or down-titrating these life-saving medications for the management of hyperkalemia should be a last resort.[2,6,7]

*Long term refers to studies done for up to 1 year.[5]

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