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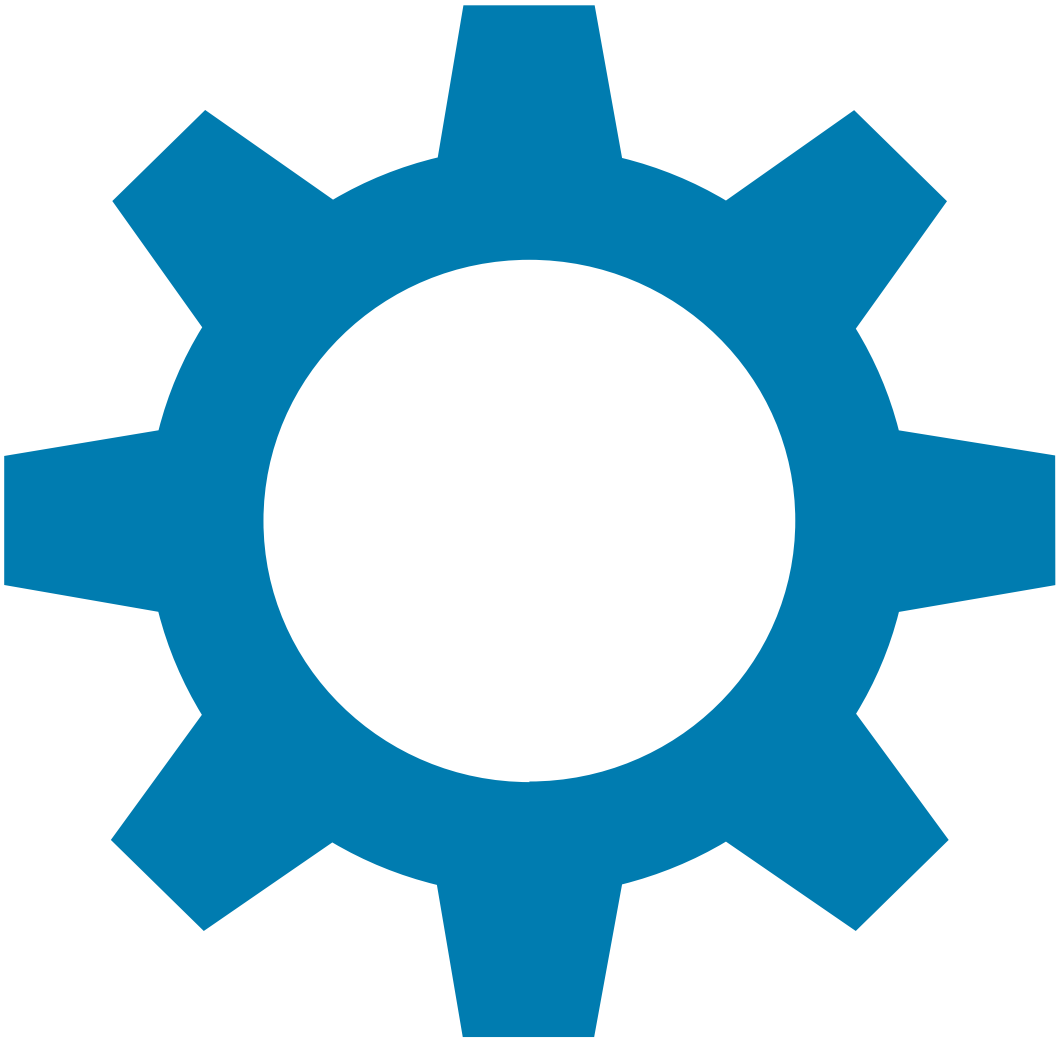
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PARADIGM-HF: MRA and Sacubitril/Valsartan Cut Hyperkalemia Risk

Patrice Wendling

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NEW ORLEANS, LA — A [PARADIGM-HF](#) analysis suggests that use of a mineralocorticoid-receptor antagonist (MRA) with sacubitril/valsartan (*Entresto*, Novartis) rather than the ACE inhibitor enalapril leads to less severe hyperkalemia in patients with chronic heart failure^[1].

Potassium rises were also more common with enalapril and MRA than with sacubitril/valsartan and MRA, although nonsevere hyperkalemia ($K > 5.5$ mEq/L) wasn't statistically different between groups.

Importantly, hypotension, hyperkalemia, and renal impairment were the most common side effects among participants in the pivotal trial treated with sacubitril/valsartan, an angiotensin-receptor-neprilysin inhibitor (ARNI).

The new data suggest neprilysin inhibition, which increases levels of natriuretic peptides, attenuates the risk of hyperkalemia when MRAs are combined with other inhibitors of the renin-angiotensin-aldosterone system (RAAS) system in HF patients, the investigators reported in a poster session at the [American Heart Association \(AHA\) 2016 Scientific Sessions](#). The study was also published online in *JAMA Cardiology*.

"The major clinical implications are that if a physician wishes to use a mineralocorticoid-receptor antagonist in heart failure in conjunction with a RAAS inhibitor, it is safer to do so by combining an MRA with sacubitril/valsartan than with an ACE inhibitor," principal investigator Dr Scott D Solomon (Brigham and Women's Hospital/Harvard Medical School, Boston, MA) told [heartwire](#) from Medscape.

Use of MRAs are recommended to reduce morbidity and mortality in selected patients with symptomatic HF and reduced ejection fraction (HFrEF), but many patients go without in clinical practice because use of MRAs in combination with other RAAS inhibitors increases the risk of hyperkalemia.

In all, 55.6% of the 8399 PARADIGM patients were taking MRAs at baseline, which was consistent with the guidelines for MRA use during the trial, he noted.

PARADIGM randomly assigned patients with NYHA class 2–4 symptoms and an $EF \leq 40\%$ to enalapril 10 mg or sacubitril/valsartan 97 mg/103 mg, both twice-daily, after a run-in period. MRA use was encouraged but left to the discretion of the study investigator.

The 4671 MRA users compared with the nonusers were younger with lower EF,

lower systolic BP, less CAD, greater likelihood of prior HF hospitalizations, and more advanced HF symptoms. Patient characteristics were similar between those allocated to enalapril or sacubitril/valsartan, regardless of MRA use.

Among MRA-treated patients, serum potassium increased more in those treated with enalapril than those receiving sacubitril/valsartan (difference 0.05–0.10 mEq/L). Changes in creatinine over the median 27 months of follow-up were similar.

Rates of severe hyperkalemia ($K > 6.0$ mEq/L) in MRA-treated patients were higher among those receiving enalapril rather than sacubitril/valsartan. This finding persisted after adjustment for baseline characteristics and even after accounting for those newly initiated on MRA during the trial.

Incidence of Hyperkalemia

	No MRA at baseline			MRA at baseline
	Enalapril (n=1812), n (%)	Sacubitril/valsartan (n=1916), n (%)	Adjusted HR* (95% CI), P	Enalapril (n=2400), n (%)
Hyperkalemia	278 (15.3)	288 (15.0)	1.08 (0.91–1.28), 0.39	448 (18.7)
Severe hyperkalemia	90 (5.0)	78 (4.1)	1.30 (0.96–1.78), 0.09	146 (6.1)

*Adjusted for characteristics including known predictors of hyperkalemia such as age, diabetes, renal function, and concomitant medications, as well as potassium levels

Information was not available on diet of the participants, nor did the analysis look at patients who were dose reduced (sacubitril/valsartan 24 mg/26 mg or 49 mg/51 mg).

Since the CV benefits of sacubitril/valsartan are consistent in patients treated and not treated with an MRA, these data further support the rationale for substitution of sacubitril/valsartan for an ACE inhibitor or angiotensin receptor blocker (ARB) in eligible patients, the investigators conclude.



Solomon added, "The US guidelines were pretty clear—patients who have NYHA class 2–3 heart failure and can tolerate being on an ACE inhibitor or an ARB should be switched to sacubitril/valsartan to further reduce morbidity and mortality."

Another [post hoc analysis of PARADIGM](#) recently reported by *heartwire* suggests patients treated with sacubitril/valsartan rather than enalapril were no more and possibly less likely to experience severe hypotensive events, a

concern that may have curbed enthusiasm for the ARNI, formerly known as LCZ369, and initially heralded as one of the great innovations in the management of HF in the past quarter century.

Solomon reports having received research support from or consulted for Novartis. Disclosures for the coauthors are listed in the abstract.

Follow Patrice Wendling on Twitter: [@pwendl](#). For more from [theheart.org](#), follow us on [Twitter](#) and [Facebook](#).



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