CKD, T2D: Why RAASi isn't enough for cardiorenal protection?

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Managing cardiorenal disease in patients with type 2 diabetes has long relied on optimising blood glucose, blood pressure, and lipid levels. But a significant residual risk of cardiovascular events and kidney disease progression persists, even with aggressive standard-of-care regimens. This unmet need has driven the development of novel therapeutic strategies, including non-steroidal mineralocorticoid receptor antagonists (MRAs).
These newer MRAs offer a distinct pharmacological profile compared to their steroidal predecessors, aiming to provide cardiorenal benefits with a reduced risk of hyperkalaemia and other adverse effects that have historically limited MRA use in vulnerable populations. The focus is on interrupting the deleterious effects of mineralocorticoid receptor overactivation, which contributes to inflammation and fibrosis in the heart and kidneys.

KEY TAKEAWAYS

- The Pivot: Non-steroidal MRAs offer cardiorenal protection by targeting inflammation and fibrosis, addressing residual risk in patients with chronic kidney disease and type 2 diabetes.
- The Data: These agents demonstrate efficacy in reducing cardiovascular events and kidney disease progression in specific high-risk populations.
- The Action: Clinicians should consider non-steroidal MRAs for patients with type 2 diabetes and chronic kidney disease who remain at risk despite optimised standard therapies.

The conventional approach to cardiorenal protection in patients with type 2 diabetes and chronic kidney disease (CKD) has centred on renin-angiotensin-aldosterone system (RAAS) inhibitors, such as ACE inhibitors and angiotensin receptor blockers (ARBs). These agents effectively reduce proteinuria and slow the decline in glomerular filtration rate (GFR), but they do not fully eliminate the risk of adverse cardiorenal outcomes. This persistent risk is partly attributed to ongoing mineralocorticoid receptor (MR) overactivation, even when RAAS is blocked, a phenomenon known as aldosterone escape.

Aldosterone, a key hormone in the RAAS, promotes sodium and water retention, but also contributes to inflammation, fibrosis, and oxidative stress in the heart and kidneys. Steroidal MRAs, like spironolactone and eplerenone, have been used for decades, primarily in heart failure with reduced ejection fraction. But their widespread use in CKD, particularly in patients with type 2 diabetes, has been limited by concerns over hyperkalaemia and worsening renal function, especially when combined with RAAS inhibitors. This is where the non-steroidal MRAs enter the clinical picture, designed to offer a more targeted and potentially safer approach.

A New Approach to Mineralocorticoid Receptor Antagonism

Non-steroidal MRAs represent a significant evolution in targeting the mineralocorticoid receptor. Unlike their steroidal counterparts, these agents are highly selective for the MR and possess a distinct chemical structure that influences their binding kinetics and tissue distribution. This selectivity translates into a different safety profile, particularly regarding potassium homeostasis, which has been a major barrier to broader MRA use in patients with compromised kidney function.

The mechanism of action involves blocking the binding of aldosterone to the mineralocorticoid receptor, thereby mitigating the downstream effects of MR activation. These effects include reducing inflammation, decreasing fibrosis, and improving endothelial function in cardiorenal tissues. The goal is to interrupt the pathological remodelling and damage that contribute to the progression of both heart failure and CKD, especially in the context of type 2 diabetes.

The development of these agents stems from a deeper understanding of the role of MR overactivation in disease pathogenesis, even when the RAAS is otherwise well-controlled. This persistent activation drives a cycle of damage that traditional therapies have not fully addressed. By specifically targeting the MR with a non-steroidal compound, clinicians aim to add another layer of protection without incurring the same level of risk seen with older agents. For a deeper dive into diabetes management, clinicians may find the Oxford Handbook of Endocrinology and Diabetes a useful reference.

The distinction between steroidal and non-steroidal MRAs is not merely academic. It directly impacts clinical applicability. Steroidal MRAs can cause significant hyperkalaemia and anti-androgenic side effects, limiting their use in patients already on RAAS inhibitors or those with moderate to severe CKD. Non-steroidal MRAs, by design, aim to minimise these off-target effects, making them a more viable option for a broader population of patients at high cardiorenal risk.

The Clinical Evidence for Cardiorenal Benefit

The clinical development programs for non-steroidal MRAs have focused on populations with type 2 diabetes and CKD, a group notoriously difficult to manage due to their high burden of cardiovascular and renal complications. These trials have typically evaluated composite endpoints, combining cardiovascular events (such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure) with renal outcomes (such as sustained decline in eGFR, end-stage kidney disease, or renal death).

The patient populations in these studies often include individuals with an eGFR as low as 25 mL/min/1.73 m2 and albuminuria, indicating significant kidney damage. Many are already receiving maximum tolerated doses of RAAS inhibitors, highlighting the need for additional therapies to address residual risk. The primary objective has been to demonstrate that adding a non-steroidal MRA to existing standard care can further reduce the incidence of these critical cardiorenal events.

These trials have consistently shown a reduction in the composite primary endpoint, indicating a dual benefit on both cardiovascular and renal outcomes. The effect on renal endpoints, specifically, has been a key differentiator, demonstrating a slowing of CKD progression. This is particularly relevant given the increasing prevalence of CKD globally and the limited therapeutic options available to halt its advance. The reduction in albuminuria, a strong prognostic marker for CKD progression, has also been a consistent finding.

Safety analyses have paid close attention to hyperkalaemia, the Achilles' heel of steroidal MRAs. While an increase

in hyperkalaemia rates has been observed with non-steroidal MRAs compared to placebo, these events are generally manageable and do not lead to a significant increase in study drug discontinuation or life-threatening events. This improved safety profile, particularly in patients with CKD, is a critical advantage, allowing for the use of MR antagonism in a population that previously had limited access to this therapeutic class. For more insights into managing diabetes with technology, consider our previous coverage on Omnipod 5 and CGM metrics.

Integrating Non-Steroidal MRAs into Practice

The introduction of non-steroidal MRAs necessitates a re-evaluation of current treatment algorithms for patients with type 2 diabetes and CKD. Current guidelines already recommend RAAS inhibitors as foundational therapy, alongside SGLT2 inhibitors, which have also demonstrated significant cardiorenal benefits. The question now becomes where non-steroidal MRAs fit into this evolving therapeutic trial pipeline.

These agents are generally considered for patients who remain at high risk despite optimised therapy with RAAS inhibitors and SGLT2 inhibitors. This typically includes individuals with persistent albuminuria, indicating ongoing kidney damage and a heightened risk of progression. The decision to initiate a non-steroidal MRA requires careful patient selection, monitoring of serum potassium, and regular assessment of renal function.

But the benefits extend beyond diabetes. The underlying mechanisms of inflammation and fibrosis driven by MR overactivation are relevant in other cardiorenal conditions, suggesting a broader potential for these agents. Research is ongoing to explore their utility in patients with heart failure with preserved ejection fraction (HFpEF) and other forms of CKD without diabetes, where similar pathological processes are at play. This expansion of indications could significantly broaden the impact of this drug class.

The practical implementation involves balancing the demonstrated benefits against the risk of hyperkalaemia. While less pronounced than with steroidal MRAs, hyperkalaemia still requires vigilance, especially in patients with lower eGFRs or those on other potassium-sparing medications. Regular monitoring, particularly after initiation and dose titration, is essential to ensure patient safety and maximise therapeutic benefit. Clinicians should also be mindful of the potential for drug interactions. Our article on Metformin and Exercise also highlights complex drug interactions in diabetes care.

The long-term implications of non-steroidal MRA use are still being fully elucidated, but the initial data are compelling. They offer a much-needed additional tool in the armamentarium against progressive cardiorenal disease, particularly in a high-risk population that has historically faced limited options. The challenge lies in appropriate patient identification and careful management to ensure the benefits outweigh the risks. The ongoing research into broader applications will further define the role of these agents in comprehensive cardiorenal care.

> **CLINICAL IMPLICATIONS**
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> The arrival of non-steroidal MRAs marks a genuine expansion of our therapeutic options for patients with type 2 diabetes and chronic kidney disease. For too long, clinicians have been constrained by the hyperkalaemia risk associated with steroidal MRAs, leaving a significant residual risk unaddressed. These newer agents provide a pathway to mitigate inflammation and fibrosis, critical drivers of cardiorenal progression, without the same potassium burden.
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> GPs and specialists alike should now be considering these agents for their high-risk patients who are already on optimal RAAS inhibition and SGLT2 inhibitors but continue to show signs of kidney damage, particularly

> persistent albuminuria. This isn't a replacement for existing therapies; it's an additive strategy that targets a distinct pathological pathway. The initial investment in careful monitoring for hyperkalaemia is a small price for the demonstrated reductions in cardiovascular events and kidney failure.
> The industry's focus on developing more selective MRAs has paid off, offering a targeted approach to an old problem. But the onus is now on clinicians to integrate these therapies thoughtfully, understanding their place in a complex polypharmacy regimen. Simply adding another pill without careful patient selection and monitoring will undermine the potential benefits and could lead to avoidable adverse events.
> The broader implications for patients are clear: a reduced risk of heart attacks, strokes, and the need for dialysis. This translates to improved quality of life and extended survival. It is a reminder that even with significant advances in diabetes and kidney care, there remain opportunities to further refine treatment and provide more comprehensive protection against the devastating consequences of cardiorenal disease.

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