Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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Next-Generation Aldosterone Pathway Inhibitors

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The next-generation aldosterone pathway inhibitors primarily comprise two distinct classes: Non-Steroidal Mineralocorticoid Receptor Antagonists (nsMRAs) and Aldosterone Synthase Inhibitors (ASIs). nsMRAs offer higher selectivity. Unlike older steroidal MRAs, nsMRAs do not cross-react with androgen or progesterone receptors. This eliminates side effects like gynecomastia or menstrual irregularities. When the receptor is blocked, the body often responds by increasing renin and subsequent aldosterone production (aldosterone breakthrough). While the receptor is occupied by the drug, high levels of circulating aldosterone can theoretically compete for binding or activate non-genomic pathways. Finerenone is a representative drug of this class. Finerenone has been approved and is widely used with rapidly expanding indications. The named as “CONFIDENCE” was a double-blind, randomized, active-controlled trial of finerenone alone, empagliflozin alone, or the combination of the two therapies in persons with chronic kidney disease with albuminuria and type 2 diabetes. The trial was remarkable for recruiting many Asians and showed that initial therapy with finerenone plus empagliflozin led to a greater reduction in the urinary albumin-to-creatinine ratio than either treatment alone among persons with both chronic kidney disease and type 2 diabetes. ASIs are considered the innovative "next-generation" agents. Unlike MRAs, which block the receptor, ASIs prevent the production of aldosterone itself by inhibiting the enzyme CYP11B2. The primary challenge has been selectivity, as CYP11B2 is 93% identical to the cortisol-producing enzyme CYP11B1. Next-generation ASIs have achieved high selectivity, minimizing the risk of adrenal insufficiency. Because ASIs inhibit the synthesis itself, they effectively bypass the "aldosterone breakthrough" issue. The Oxford group is running an international, multi-center, randomized double-blind placebo-controlled trial named as

"EASi-KIDNEY". This trial will assess whether a new drug called vicadrostat, also known as BI 690517, reduces the risk of kidney disease progression, hospitalization for heart failure or death from cardiovascular disease in people with chronic kidney disease when it is added to standard care including empagliflozin.

Keywords: chronic kidney disease, diabetic kidney disease, aldosterone