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Diuretics should be used as the second-line agent in combination with RAS inhibitors in proteinuric patients with CKD

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To the Editor: The Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension (GUARD) study,[1] showed that combination of an angiotensin-converting enzyme inhibitor (ACEi) with a diuretic significantly reduced albuminuria more than combination with a calcium channel blocker in patients with type 2 diabetes. As blood pressure (BP) is lowered more in combining an ACEi with a calcium channel blocker, the marked antiproteinuric effects of combining an ACEi with a diuretic cannot be explained by BP control. Thus, at least to reduce proteinuria, a diuretic rather than a calcium channel blocker should be combined with an ACEi or inhibitors of the renin–angiotensin system (RAS).

In contrast to albuminuria reduction, the decline in the glomerular filtration rate (GFR) from the baseline to the end of the 1-year GUARD[1] study was much smaller when an ACEi was combined with a calcium channel blocker than with diuretic. Although this finding is often considered unfavorable for diuretics, we think it opposite. Diuretics suppress tubular sodium reabsorption, making urinary sodium excretion greater than intake. As far as BP, glomerular capillary pressure, GFR, and tubular sodium load remain at the baseline levels, and sodium balance continues negative, resulting in fall in BP. Once BP is lowered, glomerular capillary pressure is also lowered, leading to reductions in both GFR and tubular sodium load. Under diuretic administration, a steady state of sodium balance can be achieved only when the GFR and tubular sodium load are reduced.[2] We believe that the decline in GFR in diuretics reflects lowered glomerular capillary pressure as seen with renin–angiotensin system inhibitors,[3] and therefore may suggest long-term renoprotection. Diuretics should be used as the second-line antihypertensive agent for proteinuric patients with chronic kidney disease, in combination with renin–angiotensin system inhibitors to reduce proteinuria and to preserve renal function.

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Response to 'Diuretics should be used as the second-line agent in combination with RAS inhibitors in proteinuric patients with CKD'[1]

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Current guidelines support the notion that patients with proteinuric kidney disease should receive a thiazide diuretic as a second agent, if further blood pressure reduction is needed.[2] There are many studies where addition of a nondihydropyridine calcium antagonist, that is, diltiazem provided similar levels of blood pressure reduction to hydrochlorothiazide. Use of this subclass of calcium antagonists is also recommended by current guidelines to reduce blood pressure and proteinuria.[2–4] However, in patients with low levels of proteinuria, that is, generally less than 1 g/day use of any calcium antagonist in the presence of a blocker of the renin–angiotensin system can reduce proteinuria.[5] The Gauging Albuminuria Reduction With Lotrel in Diabetics With Hypertension (GUARD) Study tested the hypothesis that a fixed-dose combination of amlodipine/benazepril is more efficacious in lowering proteinuria than a benazepril/hydrochlorothiazide combination.[6] Although blood pressure was reduced to a greater extent with amlodipine/benazepril, proteinuria was reduced more by benazepril/hydrochlorothiazide. This study is an example where using a surrogate marker effect is misleading. A careful look at the data demonstrates that a significantly greater fall in glomerular filtration rate resulted in a relatively greater fall in proteinuria in the benazepril/hydrochlorothiazide group. Given the better blood pressure reduction without a fall in glomerular filtration rate in the amlodipine/benazepril group, one would have to argue for a calcium antagonist as a second-line agent unless there was a compelling indication for a diuretic, such as edema or volume overload. In short, both thiazide diuretics and calcium antagonists get blood pressure to goal and reduce proteinuria on background therapy that blocks the renin–angiotensin system, so either is a viable option depending on the clinical circumstance.

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