Established and Emerging Strategies in the Treatment of Chronic Kidney Disease

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Summary: Chronic kidney disease (CKD) is a common condition that has become a significant public health concern. The mainstay therapeutic approach to CKD is based on renin-angiotensin system blockade as well as blood pressure and glycemic control. Despite these interventions, the management of CKD remains suboptimal, with a large proportion of the CKD population progressing to end-stage renal disease. Newer strategies for the treatment of CKD have emerged over the past years focusing on decreasing inflammation and delaying the development of fibrosis. Despite promising results in experimental models and small randomized studies, adequately powered randomized trials are required to evaluate the benefits and risks of these therapies in the CKD population. In this review, we discuss the evidence behind, and gaps in our knowledge of, established therapies as well as newer potential strategies for managing CKD, concentrating on interventions that currently are being evaluated in randomized studies.
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Chronic kidney disease (CKD) is a common condition that has become a significant public health concern. The mainstay therapeutic approach to slow progression of CKD is based on renin-angiotensin system (RAS) blockade as well as blood pressure and glycemic control. These interventions slow, but do not stop, the progression of kidney disease. In addition, the benefit of standard therapies varies across stages of CKD.

Newer strategies for the treatment of CKD have emerged over the past years focusing on different factors associated with the progression of renal disease. Medications that target inflammation and delay the development of fibrosis are being investigated in CKD with the purpose of preserving renal function and delaying the progression of this disease.

In this review, we discuss the evidence in support of established therapies as well as newer potential strategies for the management of CKD.

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ESTABLISHED THERAPIES IN THE TREATMENT OF CKD

RAS Blockade

RAS blockade has been the cornerstone of treatment of CKD. Earlier studies showed that RAS blockade affects renal hemodynamics by decreasing glomerular intracapillary pressure and decreasing urine protein excretion. Its benefits on progression of renal disease are independent of its antihypertensive effects.[1,2]

However, RAS blockade is not a one-fits-all strategy for all patients with renal disease. The benefit of RAS blockade with an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-receptor blocker (ARB) has been shown most clearly for individuals with urinary albumin excretion (UAE) greater than 300 mg/g creatinine. In individuals with high levels of proteinuria, RAS blockade slows the decrease of glomerular filtration rate (GFR) and progression to end-stage renal disease (ESRD) by 16% to 56%. The benefit of RAS blockade in individuals with proteinuria has been shown for diabetic kidney disease, hypertensive kidney disease, and glomerular disease.[2–7]

The data in favor of RAS blockade are less strong for individuals with lower levels of albuminuria (30-300 mg/g creatinine), especially for individuals without diabetes. In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study, 590 hypertensive patients with type 2 diabetes and persistent microalbuminuria were randomized to irbesartan 150 mg, irbesartan 300 mg, or placebo daily. The patients were followed up for 2 years to assess the development of overt nephropathy defined by UAE rate 200 μg/min or greater and at least 30% higher than baseline. After adjustment for baseline levels of microalbuminuria and blood pressure, irbesartan decreased the risk for overt proteinuria by 44% and 68% in the

150-mg and 300-mg groups, respectively. Moreover, irbesartan restored normoalbuminuria in more patients compared with placebo.[8] However, there was no difference in loss of kidney function. The Telmisartan Randomised Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease (TRANSCEND) study looked at the renal effects of telmisartan in individuals 55 years or older who could not tolerate ACE-I and who had either documented cardiovascular disease or diabetes complicated by end-organ damage. The incidence of the composite outcome of dialysis or doubling of serum creatinine level was similar across the telmisartan and placebo treatment groups. Although this study was a negative for the primary composite outcome, telmisartan reduced the risk for new microalbuminuria, macroalbuminuria, or both (relative risk, 0.77; 95% confidence interval [CI], 0.67-0.88; $P = .001$) and the progression to macroalbuminuria in patients with baseline microalbuminuria (relative risk, 0.58; 95% CI, 0.36-0.92; $P = .018$). In a subgroup analysis, telmisartan reduced the composite renal outcome of dialysis or doubling of serum creatinine level in patients with microalbuminuria or an eGFR less than 60 mL/min/1.73 m^2.[9] These observations suggest a possible role for RAS blockade in patients with mild levels of albuminuria and CKD.

RAS Blockade and Prevention of CKD

The clinical practice recommendations regarding RAS blockade among individuals with diabetes and hypertension differ across organizations. Many of their guidelines do not differentiate the recommendations by level of albuminuria (Table 1). Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for diabetes and CKD and the American Diabetes Association (ADA) standards of medical care in diabetes 2015 recommend not using ACE-Is or ARBs for the primary prevention of diabetic kidney disease in normotensive normoalbuminuric patients with diabetes.[10,11]

Results of randomized studies evaluating the use of an ACE-I or ARB to prevent the development of microalbuminuria in individuals with diabetes are mixed. The Diabetic Retinopathy Candesartan Trials (DIRECT) program evaluated the use of candesartan versus placebo for the prevention of microalbuminuria in normotensive, normoalbuminuric individuals with type 1 diabetes and in normoalbuminuric individuals with type 2 diabetes regardless of hypertension. The study found that candesartan had no effect on the incidence of microalbuminuria over a median follow-up period of 4.7 years.[12] Mauer et al[13] evaluated the effects of RAS blockade on early renal structural changes from diabetic nephropathy (mesangial fractional volume on renal biopsy) in 285 normotensive patients with type 1 diabetes and normoalbuminuria. In this study, patients were randomized to receive enalapril 20 mg daily, losartan 100 mg daily, or placebo. The study showed no differences in structural changes and similar reductions in GFR in all three groups over a median follow-up period of 5 years.

In contrast, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) compared the effects of trandolapril in combination with verapamil, trandolapril alone, verapamil alone, and placebo on the incidence of microalbuminuria in 1,204 patients with type 2 diabetes, hypertension, and normoalbuminuria. This study found that trandolapril plus verapamil and trandolapril alone reduced the risk of microalbuminuria compared with placebo (5.7% and 6% versus 10%, respectively) independent of blood pressure and diabetes control. Verapamil was no different than placebo (11.9%% versus 10%).[14] Similarly, the Randomized Olmesartan and Diabetes Microalbumin Prevention (ROADMAP) trial found that olmesartan was associated with a delayed onset of microalbuminuria compared with placebo.[15] Olmesartan was more likely to be effective in patients with higher blood pressure, lower hemoglobin A1c (HbA1c) levels, lower levels of renal function, or higher UAE at baseline. However, it was associated with a higher number of cardiovascular deaths, particularly in patients with pre-existing coronary heart disease. In the Heart Outcomes and Prevention Evaluation (HOPE) study, patients with vascular disease or diabetes with at least one other cardiovascular risk factor or evidence of vascular

Table 1. Recommendations for Treatment of Hypertension in Patients With CKD but Without Albuminuria

Guideline	Recommendations
KDIGO hypertension	No specific recommendation regarding use of ACE-I or ARB if UAE <30 mg/g creatinine
KDOQI diabetes	Should be treated with an ACE-I or ARB, usually in combination with a diuretic (CKD stages 1-4, no differentiation by level of albuminuria)
ADA	Use an ACE-I or ARB as first line in all patients with diabetes and hypertension
JNC 8	ACE-I or ARB, regardless of race or diabetes status (CKD defined as eGFR <60 mL/min/1.73 m^2 or by albuminuria > 30 mg/g creatinine)
ACP	Recommend ACE-I or ARB (CKD stages 1-3, do not differentiate by level of albuminuria)

ACP, American College of Physicians; JNC, Joint National Committee; KDIGO, Kidney Disease Improving Global Outcomes.