Finerenone reduces risk of serious kidney and heart complications in adults with CKD associated with DM2

Executive summary/Background

Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for 3 or more months, irrespective of the cause.[1] The 3 months wait time is essential to distinguish this entity from acute kidney injury.

The burden of CKD is substantial. In the United States, more than 1 in 7 adults, that is 15% of US adults or 37 million people, are estimated to have CKD.

Moreover, as many as 9 in 10 adults with CKD do not know they have CKD and about 2 in 5 adults with severe CKD do not know they have CKD.[2]

The markers used to determine the presence of kidney damage include albuminuria > 30 mg/g of creatinine, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation; or the presence of glomerular filtration rate (GFR) < 60 mL/min/1.73m^2.[3] CKD almost always begins as an acute insult to the kidney. This insult can irreversibly damage a certain number of nephrons. The remaining nephrons then have to adapt to compensate for the damaged ones. This process is called adaptive hyperfiltration. On the surface and in the short term, adaptive hyperfiltration is advantageous. However, in the long run, it is associated with proteinuria and progression to CKD.

CKD is a strong risk factor for cardiovascular mortality and progression to end stage kidney disease (ESKD) requiring dialysis or renal transplantation. In patients with CKD, the risk of death associated with cardiovascular disease is even greater than requiring dialysis.

Keeping in mind the serious complications associated with CKD, it is very important that every effort should be made to control the risk factors involved in disease pathogenesis. One of the most significant risk factors is controlling any underlying diabetes mellitus. Diabetic kidney disease is a major cause of CKD and the most frequent cause of ESKD. Globally, the age-standardized incidence of diabetic kidney disease decreased by approximately 10% from 1990 to 2017; however, mortality increased by 10% over this period.[4]

Diabetes exerts harmful effects on the kidneys by several mechanisms. These include the activation of renin-angiotensin aldosterone system (RAAS) which triggers the kidney to undergo hypertrophy, increasing renal blood flow and causing an abnormally elevated GFR.[5] At a tubular level, diabetes increases glucose and sodium reabsorption in the proximal tubule, which reduces sodium chloride delivery to macula densa, which causes further dilation of the afferent arteriole leading to more increases in GFR. This glomerular hyperfiltration is directly linked to albuminuria and CKD progression.[6]

The current treatment modalities available for DKD include blood pressure control with either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). If combination therapy is required, a dihydropyridine calcium channel blocker is added.[7] Tight glycemic control targeting a hemoglobin A_1c of 7% or less is also advised.[8] In recent years, sodium-glucose co-transporter 2 inhibitors (SGLT2i) have emerged as potent agents in the armamentarium of drugs to treat DKD. These drugs can prevent important kidney endpoints, including ESKD.[9,10]

In July of 2021, finerenone, the first nonsteroidal selective mineralocorticoid receptor antagonist (MRA) received FDA approval. Finerenone use is associated with reduction of albuminuria, and it has a smaller effect on serum potassium than other MRAs.[11,12]

“Chronic kidney disease associated with type 2 diabetes can have such a debilitating impact on patients’ lives. Unfortunately, this disease is far reaching, as up to 40 percent of all patients with type 2 diabetes develop chronic kidney disease,” said Kevin Longino, CEO of the National Kidney Foundation, and a kidney transplant patient. “It is important for physicians and patients to have new treatment options that can slow chronic kidney disease progression.”

Earlier, the FDA had approved dapagliflozin on April 30, 2021. This drug slows the rate of decline in kidney function in adults who are at risk of kidney disease progression.[13] Recently, the FDA has also approved empagliflozin. This drug was found to reduce the risk of cardiovascular death or hospitalization for heart failure in patients who have heart failure with reduced ejection fraction. Almost half of the trial population had diabetes and CKD.[14]

Educational Analysis

Gap#1: Clinicians may be unaware of the latest KDIGO 2020 Clinical Practice Guideline for diabetes management in CKD.

Learning Objective #1: Evaluate KDIGO 2020 Clinical Practice Guideline for diabetes management in CKD and incorporate recommendations to direct patient care to improve outcomes.

In October 2020, KDIGO published new guidelines for the management of diabetic patients with CKD. These guidelines encourage physicians to adopt a comprehensive approach to this problem. All patients with diabetes and CKD will require risk factor modification including smoking cessation, blood pressure and glycemic control, lipid and nutrition management, and incorporation of exercise into their lifestyle.[15]

All patients who have hypertension, diabetes and albuminuria should be placed on an ACEI or ARB, and the dose must be titrated up to the highest approved dose that is tolerated. A consequent creatinine rise of up to 30% within 4 weeks does not warrant any reduction or discontinuation of therapy. If the patient develops hyperkalemia, drugs to reduce potassium levels should be employed, and ACEI or ARB therapy should be continued as much as possible.[15]

Glycemic targets are now individualized to achieve a hemoglobin A_1c between 6.5% and 8%. This is important because it is now recognized that tighter glycemic control in patients with multiple comorbidities, short life expectancy, severe macrovascular complications and a high propensity of the treatment to cause hypoglycemia may be associated with worse outcomes.[15]

For patients with type 2 diabetes and CKD, first line drug therapy now includes metformin and SGLT2i therapy provided the eGFR is ≥ 30 mL/min/1.73 m^2. If an additional drug needs to be added, glucagon-like peptide-1 receptor agonist (GLP-1 RA) is preferred.[15]

Nutritional management includes maintaining a protein intake of 0.8 g protein/kg/day for DKD patients not on dialysis. These patients are also recommended to have a daily sodium intake < 2 g. They should be encouraged to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes/week. If they are unable to achieve this, they should target the highest level compatible with their cardiovascular and physical tolerance.[15]

Gap#2: Clinicians may be unaware of FDA's approval of finerenone and the additional benefits this drug can provide in the treatment of DKD.

Learning Objective#2: Compare safety and efficacy data for MRAs in patients with DKD.

Finerenone is the first nonsteroidal mineralocorticoid receptor antagonist drug ever developed. Two clinical trials led to its approval by the FDA. In the Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes trial (FIGARO-DKD), investigators randomized patients with type 2 diabetes and CKD with an eGFR ≥ 25 mL/min/1.73 m^2 and a urinary albumin/creatinine ratio of 30-300 mg/g or an eGFR ≥ 60 mL/min/1.73 m^2 and a urinary albumin/creatinine ratio of 300-5000 mg/g to receive either finerenone or placebo. These patients were already on a maximum dose of RAAS blockade.[16]

In the Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes Trial (FIDELIO-DKD), investigators randomized patients with type 2 diabetes and CKD to receive either finerenone or placebo. Patients either had an eGFR 25-60 mL/min/1.73 m^2 with a urinary albumin/creatinine ratio of 30-300 mg/g and diabetic retinopathy, or an eGFR 25-75 mL/min/1.73 m^2 and a urinary albumin/creatinine ratio of 300-5000 mg/g. Both groups of patients were on maximally tolerated doses of RAAS blockers.[17]

In both studies, the results showed a definite benefit to the addition of finerenone to RAAS blockade. There was a reduction in both cardiovascular and renal endpoints. In the FIGARO-DKD trial, both cardiovascular and renal endpoints were decreased by 13% each[16], whereas in the FIDELIO-DKD trial, cardiovascular endpoints were decreased by 14% and renal endpoints were decreased by 18%.[17] The incidence of hyperkalemia related discontinuation of the trial regimen was understandably higher with finerenone than placebo.

Also, the use of finerenone at a dose of 10 mg once daily resulted in a much lower incidence of hyperkalemia than with spironolactone therapy at a dose of 25 to 50 mg once daily as per the results of Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS).[18]

During the course of these trials, the recommended care for the patients with type 2 diabetes and CKD evolved with the addition of SGLT-2i and GLP-1 RA therapies. It was notable to see that the cardiovascular benefits of finerenone therapy were seen independent of and in combination with either of these two drugs. This also means that adding finerenone on top of RAAS blockers and SGLT2i may provide additional cardiovascular benefits. We now have three drugs in our arsenal to help these patients.

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