Clinical Brief: "Challenges and Advances in Diabetic Kidney Disease: Tackling the Drivers of CKD Progression in T2DM"

PROCEEDINGS OF A PRIMETIME CME SYMPOSIUM

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Activity Overview

This clinical brief was developed from a primetime symposium at the 2021 CMHC Annual Congress. The Primetime CME Symposium, "Challenges and Advances in Diabetic Kidney Disease: Tackling the Drivers of CKD Progression in T2DM," was jointly provided by the Postgraduate Institute for Medicine and the Cardiometabolic Health Congress and supported by an educational grant from Bayer Health Care Pharmaceuticals, Inc.

Moderated by Dr. Bakris, the symposium highlighted the importance of and the challenges in managing renal disease in patients with diabetes. The panel also gave a thorough background on the development of a non-steroidal mineralocorticoid receptor antagonist, a new drug class that shows promising results in tackling inflammation and fibrosis in patients with diabetes and renal disease.

Introduction

Diabetes mellitus, mainly type 2 (T2DM), is one of the fastest growing health challenges with an estimated global prevalence of 9.3% (537 million people) in adults (20–79 years).[1] Diabetic kidney disease (DKD) is the leading cause of dialysis-dependent chronic kidney disease (CKD) and end-stage renal disease (ESRD),[2-4] and it is estimated that 40% of patients with diabetes develop DKD.[5] In addition, patients with T2DM and CKD are at an increased risk of overall premature mortality and at an increased risk for cardiovascular disease (CVD) morbidity and mortality.[4, 6, 7]

The pathophysiology for the development of CKD in patients with diabetes is complex. In addition to diabetes, other contributors to renal dysfunction such as hypertension, dyslipidemia, obesity, intrarenal vascular disease, acute kidney injury, glomerular atherosclerosis, renal ischemia, and aging-related nephron-loss are usually also present in these patients.[8] Various pathways that contribute to the development of DKD have been described.[8, 9] The hemodynamic and metabolic pathways were primarily attributed to the effects of hyperglycemia.[9] In patients with diabetes, the endothelial cells lining the vasculature are chronically exposed to high plasma glucose levels. These cells cannot downregulate their glucose transport resulting in extremely high intracellular glucose levels.[8, 10] In turn, the excess intracellular glucose leads to the activation of downstream pathways such as the generation of reactive oxygen species,[11-14] and the activation of the protein kinase C (PKC) pathway.[15, 16] However, it is increasingly evident that inflammation, reduced autophagy, and upregulated SGLT2 expression also contribute to DKD.[9]

Patients with diabetes have higher rates of advanced CKD (stage 4 or 5) and higher levels of albuminuria or proteinuria than patients with prediabetes. The most commonly-prescribed antihyperglycemic agents for patients with diabetes and CKD are insulin (10%), metformin (7.9%), and sulfonylureas (4.4%). In comparison, SGLT2is were prescribed only to 0.093% of patients between 2014 and 2017.[17]

Major gaps between the knowledge of effective treatments for CKD and the delivery of evidence-based therapies to patients have been documented.[17-19] Strategies shown to improve CKD patient outcomes include lowering blood pressure,[20, 21] reduction of proteinuria,[21, 22] use of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs),[23] use of statins to reduce atherosclerotic events,[24, 25] and glycemic control for people with diabetes.[26, 27] The inclusion of SGLT2is has additional benefits such as reducing albuminuria, cardiovascular events, and CKD progression in diabetes.[28-31]

Worryingly, considering the link between CKD and CVD mortality, a study found that potentially nephrotoxic nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs) were prescribed to 33.7% of patients with CKD and 50.5% of patients at risk for developing CKD. Conversely, ACE inhib-

itors and ARBs were prescribed to only 20.5% of adults with CKD and 25.9% of adults with CKD and hypertension.[17] In other words, potentially nephrotoxic medications were prescribed at a higher rate than reno-protective drugs for patients with or at risk of developing CKD. Additionally, the use of cardiovascular disease preventive agents, such as statins and aspirin, is also low in this cohort.[17]

Comprehensive management of patients with diabetes and CKD includes lifestyle interventions and managements of risk factors as a foundation, with additional pharmacotherapy in selected patients.[32] However, the management of these patients presents multiple challenges and often requires a multidisciplinary approach.[33] These challenges have been recognized by many professional societies in clinical practice guidelines and consensus statements.[28, 32, 34-39] Despite the release of these guidelines, care for DKD patients remains suboptimal.[19] In fact, even with the development and approval of new therapies for these patients, such as the sodium-glucose contransporter-2 (SGLT2) inhibitors, residual morbidity and mortality remains.[40, 41] This highlights the need for additional strategies to slow kidney disease progression, particularly strategies that address inflammation and fibrosis as a contributing factor to CKD progression.[40, 41]

Background and Future of DKD

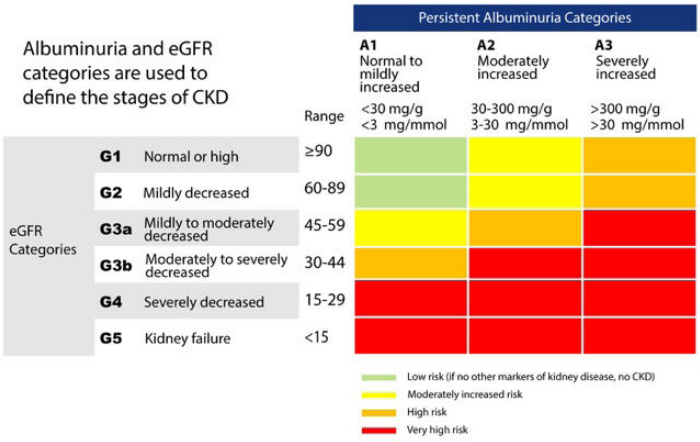
RISING PREVALENCE OF DKD

George L. Bakris, MD, FASN, FAHA, a Professor of Medicine and Director of the American Heart Association Comprehensive Hypertension Center, at the University of Chicago, discussed the background and future of DKD. Dr. Bakris emphasized that the number of people receiving renal replacement therapy is projected to double by 2030, from a baseline in 2010.[42] That is, in just 20 years. This doubling will be accompanied by with rapid increases expected for Asia, Africa, and Latin America and the Caribbean.[42]

CKD CLASSIFICATION

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for the management of CKD in diabetes acknowledge that optimal management of these patients is a complex, multidisciplinary, and a cross-functional team effort that involves various specialists.[28] KDIGO defines CKD as the presence of abnormal kidney structure or function persisting for more than 3 months.[28] This includes an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, albuminuria (urine albumin ≥30 mg per 24 hours or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), abnormalities in urine sediment, histology or imaging, renal tubular disorders, or history of kidney transplantation.[28] Additionally, CKD staging is based on eGFR category (G1–G5), albuminuria category (A1–A3), and the cause.[28]

The relationship between the eGFR and albuminuria categories and how these translate to risk is illustrated in the following heat-map:



"You need to understand this heat map. In fact, I show this heat map to patients. I don't tell them they have kidney disease; I give them the numbers and I ask them to tell me where they fit on the map," said Dr. Bakris. In his experience, the more patients understand their risk of renal replacement therapy (dialysis), the more likely they are to adhere to treatment. Dr. Bakris also explained that most of what we know about kidney disease is from studies done in people with large amounts of albuminuria. While there have been advances in our knowledge recently, it is still limited.

It is important to point out that CKD is a silent disease and patient awareness is very low. Almost all (96%) patients with kidney damage (persistent albuminuria categories A2 or A3) but only mildly reduced kidney function (G1 or G2) remain unaware, and about half (48%) of patients with severely reduced kidney function (G3a, G3b, and G4) but not on dialysis remain unaware that they have kidney disease.[43]

CKD AND CV HEALTH

An analysis of data from a large, integrated health system, including 1 120 295 patients, who had not undergone dialysis or kidney transplantation at baseline, and had serum creatinine measured between 1996 and 2000, found that after a median follow-up of 2.84 years, the risk of cardiovascular events and death increased significantly with worsening renal function, with a substantial increase in risk once eGFR dropped below 45 mL/min/1.73 m^2.[44] Dr. Bakris emphasized the results from this study, "if your eGFR is below 45 mL/min/1.73 m^2, you have almost a 5 fold higher risk of all-cause mortality. If you have stage G4 kidney disease, with eGFR below 30 mL/min/1.73 m^2, it jumps to almost 11.5 times. If you look at the cardiovascular events, even if you're at stage G3a, with an eGFR of 50 mL/min/1.73 m^2, your cardiovascular risk has gone up 3.6 fold."

> "The CKD stages are not just about the kidney; they are about the heart. The heart and the kidney are married."
>
> *George L. Bakris, MD, FASN, FAHA, Professor of Medicine, Director Am. Heart Assoc. Comprehensive Hypertension Center, University of Chicago*

A retrospective cohort study was conducted to assess the risk of hospitalization for heart failure (HF) in relation eGFR in patients with T2DM. Of the 54 486 patients with T2DM included, 5936 (10.4%) had a primary or secondary diagnosis of hospitalization for HF during a median follow-up of 7 years. The study showed that the risk of developing HF and being hospitalized increases considerably as renal insufficiency worsens in patients with T2DM and DKD. Specifically, the risk of hospitalization for patients with an eGFR between 45 and 60 mL/min/1.73 m^2 increased by 25–35%, and it was 2–2.5 times higher in those with an eGFR lower than 30 mL/min/1.73 m^2.[45]

"As the kidney fails, the heart is not ignoring it," said Dr. Bakris. "For people in stage G3b CKD or higher, the incidence of HF is through the roof. That is your biggest problem. When you're treating these patients, don't just focus on blood pressure (BP), focus on therapy that is going to protect the heart and the kidney."

HF is one of the leading cardiovascular conditions in patients with impaired renal function, and several factors explain the relationship between eGFR and HF.[46, 47] These factors are correlated with the degree of tubulointerstitial damage, and include the renin–angiotensin system (RAS), activation of the sympathetic nervous system, increased retention of sodium and fluid, anemia, underuse of diuretics in some patients, underdiagnosis and undertreatment of ischemia, endothelin production, endothelial dysfunction, inflammation, oxidative stress, hypercoagulation, and others.[46]

DKD IS NOT ALWAYS RECOGNIZED IN PATIENTS WITH T2DM

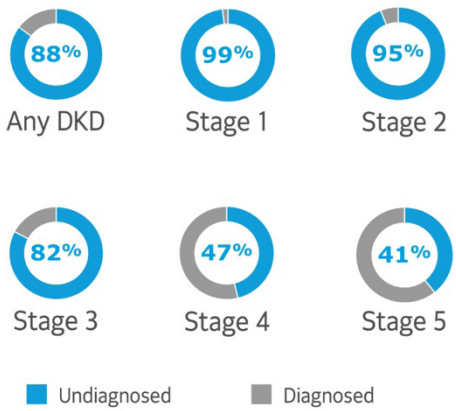
Originally, DKD was described as a progressive disease that starts with the loss of small amounts of albumin in urine, albuminuria, which increase gradually and eventually leads to renal impairment and ESRD.[8, 48] However, between 40% and 50% of patients with diabetes and an eGFR <60 mL/min/1.73 m^2 do not have albuminuria and treatment-induced and spontaneous remission of albuminuria are common,[49-53] suggesting that there may be different mechanisms at play. In fact, two new phenotypes have been described, non-albuminuric renal impairment and progressive renal decline.[54, 55]

Interestingly, DKD presentation in adult patients with diabetes has changed in the last 3 decades with a decrease in the prevalence of albuminuria and an increase in the prevalence of low (<60 mL/min/1.73 m^2) and severely reduced (<30 mL/min/1.73 m^2) eGFR.[2] Moreover, an autopsy study found that histopathologic changes characteristic of DKD were present in a significant proportion of patients who did not have albuminuria or low eGFR throughout life, suggesting that DKD is underdiagnosed.[56] These studies demonstrate that it can be difficult to diagnose DKD.

Many patients with CKD are asymptomatic and most (up to 90%) are not aware of having the disease.[57-59] Therefore, it is not surprising that CKD is often underrecognized by patients and clinicians.[60-63]

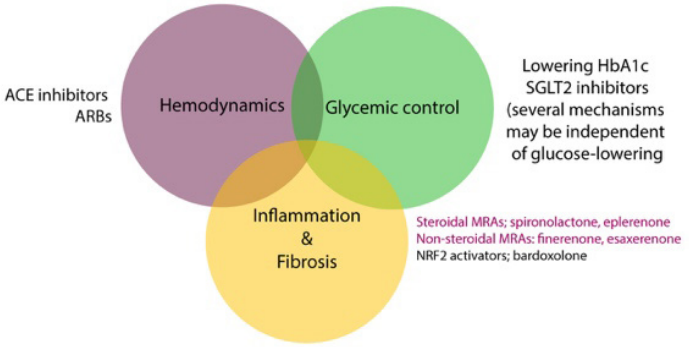
A database (Veteran Affairs [VA] and Medicare) analysis of secondary data from 1999 to 2000 revealed that administrative records failed to identify more than 50% of individuals with diabetes who had comorbid DKD (as defined by eGFR criteria).[64] Similarly, a recent registry-based cohort study found that approximately half of the cases of CKD were unrecognized by healthcare providers by 2017.[17] Furthermore, the study also found that evaluations rates for albuminuria and proteinuria were low for patients with CKD and those at risk of developing the disease, including patients with diabetes or prediabetes.[17]

The Awareness, Detection, and Drug Therapy in Type 2 Diabetes study was a US, multicenter, 15-month (from 2011 to 2012) retrospective review of 9339 adult patients with T2DM. The study assessed the CKD prevalence in this population and characterized the proportion of detected and undiagnosed CKD in the primary care setting. The CKD prevalence, assessed by laboratory data, in this population was 54.1% (5036 patients). Overall, the rates of undiagnosed CKD were very high and, as expected, decreased as the stage of CKD worsened. In patients with laboratory evidence of CKD, the rates of undiagnosed disease were as following[65]:



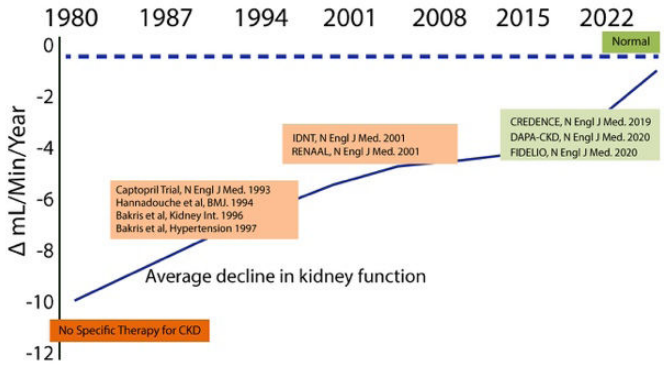
This was further confirmed in a recent retrospective (2010–2017) observational study of 123 169 patients with lab-positive T2DM and DKD. This study showed that 57% of patients with GFR stage G3a (eGFR 45-59 mL/min/1.73 m^2), and 30% with GFR stage G3b (eGFR 30-44 mL/min/1.73 m^2) remained undiagnosed.[66]

Dr. Bakris emphasized the importance of these results by asking how can we expect patients to be adherent and reduce their risks if they don't even know that they have CKD? "It's a big deal," he said.



Strategies for Slowing DKD Progression

Over the last 40 years there has been a trend towards a slowing of CKD progression associated with T2DM, with the average decline in kidney function steadily rising from a loss of 10 mL/min/year in 1980, when no specific therapy for CKD existed, to a loss of 2 mL/min/year in 2020.[67] Dr. Bakris reviewed this timeline pointing out how different studies affected eGFR volume changes over time[67]:



Summarizing the figure, Dr. Bakris said that in 1980 we did not have any therapies, there were no ACE inhibitors or any other agents available. People with diabetes were losing about 10 mL/min/year. Then, the introduction of captopril, an ACE inhibitor, in the 1990s, and results from other smaller studies, slowed things down a little bit, but patients were still losing 6–7 mL/min/year. In the early 2000s the ARB trials showed better BP control and translated to a loss of about 5 mL/min/year. This is still a significant annual loss of kidney function. The 3 more recent trials, with different classes of drugs, all showed significant benefit and all with a loss of 2–2.5 mL/min/year. This is much better, but it is still below normal decline in eGFR, 0.8 mL/min/year. So, Dr. Bakris concluded, we're not there yet.

These therapeutic agents can be organized into three strategies (hemodynamics, glycemic control, and inflammation and fibrosis) used to slow the progression of CKD:

ACE inhibitors and ARBs help control hemodynamics and have been in use for the past 20 plus years.[67] Although these agents effectively reduce the progression of advanced albuminuria in DKD, they do not slow the progression of ESRD.[68] This may be because these agents do not inhibit aldosterone, which has known detrimental effects to kidney function.[69]

The second pillar of CKD management is glycemic control. This is achieved by antidiabetic drugs, such as insulin and metformin, which lower hemoglobin A1c (HbA1c) levels.[70] In the last few years, sodium–glucose cotransporter 2 (SGLT2) inhibitors were also added. Later studies showed that SGLT2 inhibitors protect the kidney via several mechanisms that may be independent of their glucose-lowering effect. Another antidiabetic agent class that has reno-protective functions are the glucagon-like peptide 1 (GLP-1) receptor agonists.[67]

Inflammation and fibrosis, independently of hemodynamics and glycemic control, are the third pillar in managing DKD progression, and are not affected by the agents described above.[71] The latest clinical trials are trying to address the residual risk that remains after optimal hemodynamic and glycemic control; that is, addressing the issue of inflammation and fibrosis.

Steroidal and Non-Steroidal MRAs for the Treatment of CKD in Type 2 Diabetes

Rajiv Agarwal, MD, MS, a Professor of Medicine at the Indiana University School of Medicine, and the VA Medical Center in Indianapolis, discussed emerging advances in treatment of DKD, with a review of the history of mineralocorticoid receptor (MR) activation, the development of non-steroidal MR antagonists (MRAs), and the studies of finerenone in patients with CKD and T2DM.

MR OVERACTIVATION

The MR, a nuclear receptor that binds to aldosterone and cortisol, is expressed in many tissues and cell types including the kidney, heart, immune cells, and fibroblasts. MRs are involved

in fluid, electrolyte, and hemodynamic homeostasis, as well as tissue repair.[72] MR activation by agonists such as aldosterone leads to organ damage caused by inflammation and progressive fibrosis.[73]

Dr. Agarwal started by saying that "we have known for a long time that MR overactivation causes inflammation and fibrosis in the kidney, heart, and elsewhere." In 1943, Hans Selye showed that when you treat animals with desoxycorticosterone acetate, a MR activator, they develop heart hypertrophy, kidney fibrosis, vascular stiffness, and pancreatic edema.[74] That is, not only was there an increase in blood pressure and sodium retention, but also fibrosis in multiple organs.

The RALES trial, published in 1999, 56 years after the publication of Selye's work, established the lifesaving role of spironolactone, a steroidal MRA, in patients with severe HF.[75] Spironolactone was the first MRA approved by the FDA as a diuretic for the management of edematous conditions and essential hypertension.[76] Five years after the publication of the RALES trial, a report in NEJM drew attention to the link between the publication of the trial and the increasing rates of hyperkalemia.[77] Eplerenone was developed as more selective version of spironolactone.[41] However, despite its demonstrated efficacy and safety, its use in patients with CKD is limited as there is an associated hyperkalemia risk, as well as a counterindication for the use in patients with hypertension and T2D with microalbuminuria.[78, 79]

"Now we know that there are several contraindications for the use of eplerenone and spironolactone," said Dr. Agarwal. "In particular, the eplerenone label states that people with type 2 diabetes and microalbuminuria cannot use this drug, especially when they have kidney impairment. Yet people continue to use it."

> "Hyperkalemia is the Achilles heel of MRAs. Patients with CKD and those with a higher baseline serum potassium concentration are particularly likely to develop hyperkalemia with these drugs."
>
> *Rajiv Agarwal, MD, MS, Professor of Medicine, Indiana University School of Medicine, VA Medical Center in Indianapolis*

In 2009, a metanalysis of 11 clinical trials, with a total of 991 patients with CKD, compared optimized ACE inhibitor and ARB therapy with or without spironolactone. These trials showed that the use of a steroidal MRA can reduce proteinuria (24-hour reduction of 0.8 g; 7 trials, n = 372) and improve BP (systolic and diastolic by 3.4/1.8 mmHg; 7 trials, n = 372), but the risk for hyperkalemia goes up dramatically with both spironolactone (relative risk increase of 3.06; 8 trials) and eplerenone (relative risk increase of 1.62; 2 trials).[79]

CAN WE BLOCK THE MR WITHOUT CAUSING HYPERKALEMIA?

Dr. Agarwal reviewed a clever laboratory experiment done by investigators in Australia, which helped us understand the importance of the MR in various tissues. They selectively blocked the MR using molecular techniques in myeloid cells (white blood cells) and in podocytes (kidney cells). To simulate CKD, the animals had a form of experimental glomerulonephritis induced. They showed that when the MR is knocked out in the myeloid cells, it protects the kidney; and when it is knocked out in the podocytes, it doesn't have any effect on the kidney. Moreover, when knocked out in the myeloid cells, it doesn't produce hyperkalemia, unlike using eplerenone.[80]

So, Dr. Agarwal said, "it was a nice proof of concept that you can knock out the MR in the myeloid cells and produce kidney protection without provoking hyperkalemia." These experiments provide hope that drugs can be developed that improve the therapeutic ratio. What if we moved away from the steroidal molecules and developed drugs that were non-steroidal in nature? Would they be able to improve the therapeutic ratio?

Soon, a race began to develop drugs that could do just that, said Dr. Agarwal. These new molecules, which they called non-steroidal MRAs, didn't share the steroidal structure of eplerenone or spironolactone, the cyclopentanoperhydrophenanthrenes ring, which is the classical cholesterol nucleus.

In the US, Eli Lilly and Pfizer developed non-steroidal molecules and performed some human studies.[81] Outside the US, the interest was even greater. In fact, esaxerenone, a drug developed by Daiichi Sankyo, is already approved for the treatment of hypertension in Japan. Apararenone, developed by Mitsubishi Tanabe, has also shown some success in phase 2 trials. Finerenone, a non-steroidal MRA developed by Bayer, is in the most advanced stage of development.[81-83]

In preclinical models, finerenone had more potent antiinflammatory and antifibrotic effects than steroidal MRAs.[41, 71, 84, 85] Animal studies showed that an equal amount of urinary sodium was lost with 10 mg of finerenone as 100 mg eplerenone. Next, animals were treated with equinatriuretic doses of eplerenone and finerenone. The results indicated that finerenone treated

animals had less proteinuria and better histology, suggesting that the drug protects the kidney more.[85] A similar experiment was designed to study heart protection in mice with the injection of isoproterenol, a non-selective β adrenoreceptor agonist that causes subendocardial fibrosis and inflammation. Compared to eplerenone, finerenone caused less cardiac fibrosis and inflammation, and animals had better cardiac function as assessed by echocardiograms.[84] So, concluded Dr. Agarwal, head to head studies in animals comparing steroidal versus non-steroidal MRAs, showed that finerenone gave better structural and functional protection, which led to subsequent phase 3 studies.

FIDELIO-DKD

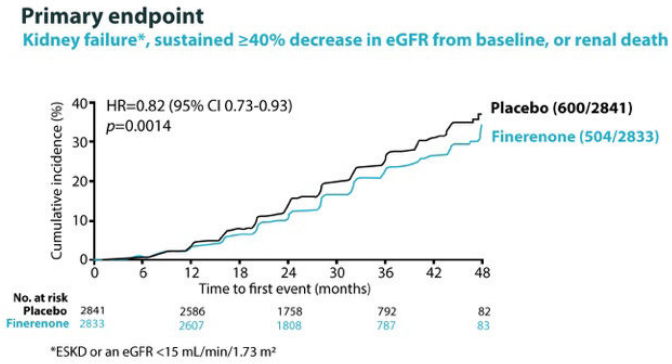
The first phase 3 trial published was the FIDELIO-DKD study (ClinicalTrials.gov number, NCT02540993).[86] Dr. Agarwal explained that the hypothesis was that inhibiting the MR receptor with finerenone would block inflammation and fibrosis in the kidney and the heart and therefore, produce clinical benefits. Eligible patients were adults (≥18 years of age) with CKD and T2DM and optimized ACE inhibitor or ARB therapy for four weeks or more. Additionally, participants had to have serum potassium levels of 4.8 mmol/L or less at the screening and run-in visit. People who had renal artery stenosis (RAS), another non-diabetic kidney disease, or were symptomatic for CVD (HF or uncontrolled BP) or diabetes (HbA1c >12%), were excluded.[86]

More than 5700 patients were randomized to either finerenone or placebo with a median follow-up of 2.6 years. The primary outcome was a composite of kidney failure, time to a sustained decrease of 40% or more in eGFR from baseline or over a period of 4 weeks, or kidney death.[86]

This was a very well treated, older population (mean age, about 65 years), and 70% were males. Glycemia (mean HbA1c, 7.7%) and BP (138/76 mmHg) were reasonably controlled, and all patients were being treated with either an ACE inhibitor or an ARB. About 70% were also on statins and 5% on SGLT2 inhibitors. As for their renal function, the mean eGFR was quite impaired (44 mL/min/1.73 m2), and the median UACR was 850 mg/g. That is, nearly 90% had microalbuminuria.[86]

There was a nice reduction (31%; least-squares mean ratio to baseline, 0.69 [0.66–0.71]) in UACR at four months, said Dr. Agarwal, "which is what we saw in the phase 2 trials, but not much change in BP and HbA1c." There was a drop of about 3–3.5 mmHg in BP at four months and no change in HbA1c, compared to placebo.[86]

"If we look at the primary endpoint of kidney failure," said Dr. Agarwal, "there was an 18% relative risk reduction favoring finerenone" (hazard ratio [HR], 0.82; 95% confidence interval



Likewise, the components of the primary kidney-specific composite endpoint all favor finerenone, suggesting that finerenone is improving kidney failure outcomes.[86]

A key secondary endpoint was the cardiovascular composite, which included time to cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for HF. There was a 14% reduction in the cardiovascular composite risk with finerenone (HR, 0.86; 95% CI, 0.75–0.99; $p = .0339$).[86] However, the differences in all-cause mortality and hospitalizations were not significant.[86]

There was a 24% reduction in the secondary kidney failure endpoint, the doubling of serum creatinine, starting dialysis, or dying of kidney failure.[86] Dr. Agarwal explained that "this is the more traditional end-point we use in kidney failure trials, and that was going from 18% to 24%. You have 50% more benefit if you use a more difficult hurdle to surmount, which is the 57% drop in eGFR."

The number needed to treat (NNT) analysis showed that you need to treat 29 patients for about three years to prevent one kidney failure endpoint and 42 patients to prevent a cardiovascular endpoint. There was a modest effect on blood pressure, consistent effects on the components of the primary endpoint and across key subgroups, including eGFR and UACR at baseline.[86]

There were slightly more adverse effects leading to treatment discontinuation in the finerenone group, and these were mostly due to hyperkalemia. There were about 64 increased blood potassium events in the finerenone group compared to 25 in placebo.[86] Dr. Agarwal reminded that this was a trial of more than 5700 patients and that less than 40 patients (64 in the finerenone group minus 25 in the placebo group) were inconvenienced by using finerenone. So, said Dr. Agarwal, you would have to write 71 prescriptions before one patient permanently discontinued the drug because of hyperkalemia.

Mean serum potassium did go up, about 0.23 mmol/L at month

4. However, there were no deaths because of hyperkalemia, there were very few hospitalizations due to hyperkalemia, and there were very few people who discontinued the drug because of hyperkalemia.[86] Similarly, there were not many cases of acute kidney injury (AKI),[86] which are common in people who are treated with spironolactone, explained Dr Agarwal.

Dr. Agarwal summarized the study saying that the drug was well tolerated with no serious side effects, but serum potassium does go up, and there are some discontinuations because of hyperkalemia.

However, these effects were much lower compared to what was seen in other trials such as ALTITUDE (aliskiren + ACE inhibitor/ARB) or VA NEPHRON-D (ACE inhibitor + ARB).[87, 88] The incidence of hyperkalemia with the combination therapy in VA NEPHRON-D, was nearly 10% compared to 2.3% percent in the FIDELIO-DKD trial.[88] ALTITUDE likewise was more than twice as much.[87] In the AMBER trial (patiromer + spironolactone + ACE inhibitor/ARB), 23% of patients who had impaired kidney function had to stop spironolactone in 12 weeks, compared to 2.3% in 2.6 years in the FIDELIO-DKD trial.[89] So, concluded Dr. Agarwal, the ability of finerenone to cause hyperkalemia is very different to that of spironolactone.

Cardiovascular and Renal Outcomes from FIGARO-DKD and FIDELITY

Bertram Pitt, MD, a Professor Emeritus of Medicine, at the University of Michigan, School of Medicine, in Ann Arbor, presented the recently published results from the FIGARO-DKD and FIDELITY trials.

Dr. Pitt started by explaining that in comparison to the old steroidal MRAs, spironolactone and eplerenone, finerenone has different binding characteristics when it blocks the MR. Furthermore, in addition to blocking some of the same genes that the steroidal MRAs block, it also blocks other genes.

Finerenone is more effective at reducing inflammation and fibrosis and is more tolerable than the steroidal MRAs, especially spironolactone, with less hyperkalemia.[86] Dr. Pitt said that "we think that's partially because the distribution is different." The steroidal MRAs distribute mainly to the kidney and less to the heart, whereas the non-steroidal finerenone is more evenly distributed. That may not be the only reason for the better tolerability, but it may be an important one. Finerenone has recently been approved by the FDA for treatment of adult patients with CKD associated with T2DM. It is indicated to slow CDK progression by reducing the risk of eGFR decline, and to reduce the risk of ESKD, non-fatal MI, HF hospitalization, and cardiovascular death.[90, 91]

FIGARO-DKD

The eligible population for the FIGARO-DKD trial (ClinicalTrials.gov number, NCT02545049) had an overlap with the FIDELIO-DKD trial, but it included patients with a normal eGFR and microalbuminuria. It also included some patients with more severe disease with a reduction in eGFR.[92]

As in the FIDELIO-DKD trial, in FIGARO-DKD there was a run-in enrollment period where ACE inhibitors and ARBs were optimized, with almost all patients being on these medications. After screening and stabilization, patients were randomized to finerenone, 10 or 20 mg a day, or placebo. Follow-up is at a median of about 3.4 years.[92]

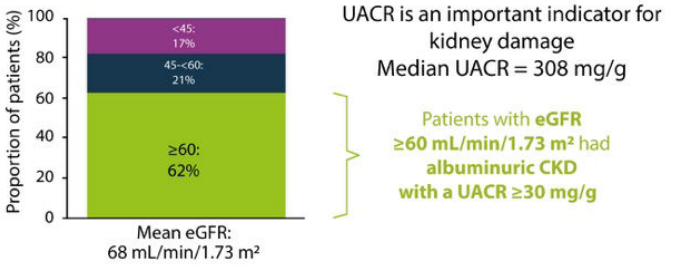
The inclusion and exclusion criteria were very similar to FIDELIO-DKD. In summary, eGFR had to be greater than 25 mL/min/1.73 m^2, and the UACR greater than 30 mg/g. Patients with HF, a reduced ejection fraction, and uncontrolled hypertension were excluded. People with a serum potassium level higher than 4.8 mmol/L were also excluded to avoid hyperkalemia.[92]

The primary outcome was a cardiovascular composite including cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for HF. The secondary outcomes were greater than 40% and 57% reduction in eGFR. The study also looked at progression to ESRD.[92]

Dr. Pitt explained that "one of the reasons that a reduction of 40% in eGFR was taken is that when these trials were planned, several years ago, there was information from both the EMA and the FDA that this was a pretty good renal outcome." Since then, we have realized that 40% reduction is not very sensitive, and 57% is more robust and more sensitive and it's equivalent to about a doubling of serum creatinine.

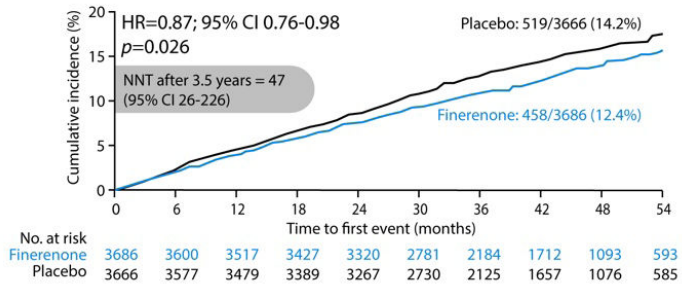
There were almost 7400 patients, 7352, and the mean age was 64 years. BP was well controlled (136/77 mmHg). A little less than half of the patients had cardiovascular disease, and about 8% had HF, but these were likely very mild cases. All patients were on either an ACE inhibitor or an ARB. Additionally, some patients were on statins and beta blockers. All patients were also well treated for diabetes. Dr. Pitt pointed out that about 8% had an SGLT2 inhibitor or a GLP-1 receptor agonist.[92]

It is also important to point out that 62% of the patients in the FIGARO-DKD trial had an eGFR greater than 60 mL/min/1,73 m^2, but they also had an increase in UACR greater than 30 mg/mg[92]:



Dr. Pitt emphasized that patients with albuminuric CKD with preserved kidney function were a very important group and they were a very large component of the FIGARO-DKD trial.[92] He further commented that diabetologists routinely screen the urine of patients with diabetes, but other specialists do not do it when the patient has a normal eGFR. However, Dr. Pitt stressed, if a diabetes patient has albuminuria, even with a normal eGFR, they have an increased cardiovascular risk. In other words, the risk goes up if eGFR falls, but it also goes up independently with an increase in UACR. Now that there are effective agents to treat these patients, such as SGLT2 inhibitors and finerenone, it's really important to check UACR levels so that treatment can be initiated, said Dr. Pitt.

There was a significant reduction of the primary outcome (HR, 0.87; 95% CI, 0.76–0.98; $p=.026$) that was primarily driven by a reduction in HF (29%)[92]:



There was not a significant reduction in cardiovascular mortality.[92] However, previous studies have shown that there is an increased risk of cardiovascular death following HF hospitalization, said Dr. Pitt. Therefore, even though the reduction in cardiovascular death in this trial was not significant, we expect there will be a significant reduction in the long-term.

> "If you can stop HF hospitalizations, you certainly can reduce cardiovascular death."
>
> *Bertram Pitt, MD, Professor Emeritus of Medicine, University of Michigan, School of Medicine, Ann Arbor*

There was no reduction in MI or stroke.[92] Dr. Pitt pointed out that SGLT2s also did not have any reduction in stroke, they had a slight reduction in MI, not due to any direct effects on thrombosis, but because they reduce preload.

In terms of the renal outcomes, the trend in the 40% eGFR reduction tended to favor finerenone, but it was not significant (HR, 0.87; 95% CI, 0.76–1.01; $p=.069$).[92] On the other hand, there was a significant reduction in the 57% decrease in eGFR from baseline (HR, 0.77; 95% CI, 0.60–0.99; $p=.041$),[92] and this is the most important for patients with ESRD. That is, the need for dialysis, what our patients really care about, was really reduced explained Dr. Pitt.

Given that finerenone is an MRA, hyperkalemia was expected. There was twice as much hyperkalemia compared to placebo, "but what was striking is that the number of people who had to stop the drug was less than 1% in this study," said Dr. Pitt. As in the FIDELIO-DKD study, there were no deaths related to hyperkalemia.[92] So, finerenone "was really well tolerated and was much better than what we've ever seen with the steroidal MRAs, like spironolactone," said Dr. Pitt.

On the other hand, there was also significantly less hypokalemia.[92] Dr. Pitt commented that there is a lot of concern regarding hyperkalemia with MRAs and that many people choose not to start an MRA because they are concerned about hyperkalemia. However, there's increasing data suggesting that hyperkalemia is more of a risk marker, rather than a risk factor for death. That it is the underlying renal disease that is really critical. Meanwhile, hypokalemia is both a risk marker and a risk factor. So, said Dr. Pitt, "I think we should certainly pay attention to hyperkalemia, but I think we may have caused more harm than good by withholding MRAs and not using them or stopping them prematurely." Because the HF evidence suggests that patients who do not get an MRA or who stop it are at a tremendously high risk compared to those people who persist on the drug.

Dr. Pitt concluded by saying that finerenone is an agent that is very well tolerated, but that patients should be monitored for hyperkalemia.

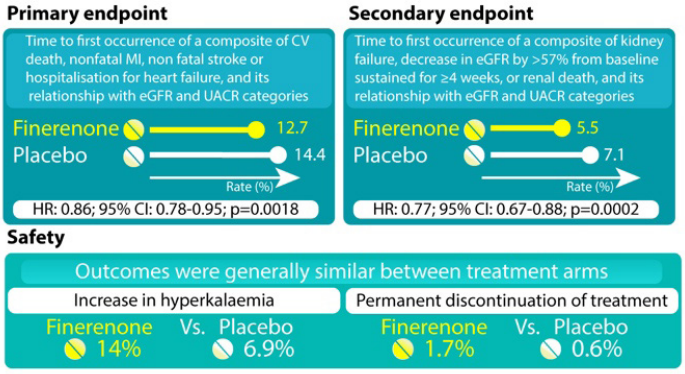
FIDELITY

The FIDELITY pooled analysis combined data from the FIDELIO-DKD and the FIGARO-DKD trials, including 13 000 patients across a broad spectrum of renal disease, both with a reduced eGFR and a normal eGFR but with increased albuminuria.[93]

The primary outcome was the same as that for the FIGARO-DKD trial, significantly reduced cardiovascular outcomes including time to cardiovascular death, non-fatal MI, non-fatal stroke, and hospitalization for HF. There was a 14% reduction in the risk of the cardiovascular composite outcome (HR, 0.86; 95% CI, 0.78–0.95; p=.0018).[93] Once again, the major driver of this is reduction in hospitalization for HF (HR, 0.78; 95% CI, 0.66–0.92; p =.0030),[93] "which is really important in the long run for reducing cardiovascular death," re-iterated Dr. Pitt.

The pre-specified primary renal outcome in the FIDELITY analysis was the effect on the greater than 57% eGFR reduction from baseline. There was a significant difference between the groups with finerenone being favored (HR, 0.77; 95% CI, 0.67–0.88; p =.0002).[93] There was also a significant reduction in ESRD (HR, 0.80; 95% CI, 0.64–0.99; p=.04).[93]

So, concluded Dr. Pitt, this analysis of over 13 000 patients showed a reduction in cardiovascular and renal events[93]:



"I think we're pretty confident that finerenone is really working to reduce cardiovascular and renal events across the entire spectrum of diabetic kidney disease. So, I think this is really a major new advance," said Dr. Pitt.

About 8% of the participants in the FIGARO-DKD trial were taking an SGLT2 inhibitor, and a lot of people are interested in how these two drugs work together. Dr. Pitt said that all we can say at the moment, from these trials, is that finerenone seems to work just as well when it is combined with an SGLT2 inhibitor as when it is not. The same goes for combinations with a GLP-1 receptor agonist. However, an animal model study found that the combination of finerenone and empagliflozin, an SGLT2 inhibitor, had additive synergistic effects.[94] So, it is possible that, in the future, the optimal therapeutic regimen is going to be a combination of a non-steroidal MRA, such as finerenone, and an SGLT2 inhibitor; or maybe finerenone and a GLP-1 receptor agonist, because finerenone and SGLT2 inhibitors do not reduce stroke or MI, GLP-1 receptor agonists do. Since stroke is a concern for patients with diabetes, that may be a good combination for the future. But right now, we certainly have evidence that finerenone works across the entire spectrum of renal disease and it's a new tool to help our patients, concluded Dr. Pitt.

Conclusion

Compared to either condition alone, when T2DM and CKD coexist in patients, it significantly exacerbates the cardiovascular and renal morbidity and mortality. Although new therapies have been developed and approved in the past few decades, many patients with DKD progress to kidney failure and have significant cardiovascular adverse events. Therefore, the current strategies to address cardiorenal risk in these patients are inadequate.

A major focus for the development of new treatments has been to target kidney-specific mechanisms such as glomerular hyperfiltration, inflammation, and fibrosis. By targeting MR overactivation, a key pathophysiological driver of DKD, the recent development of the non-steroidal MRA, finerenone, has started to address some of these gaps. Finerenone, recently approved by the FDA, is well tolerated, despite causing an increase in serum potassium levels, and effectively reduces cardiovascular and renal outcomes in diabetic patients with CKD. Questions remain about how to optimally integrate these agents into the current treatment landscape.

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