Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/at-the-crossroad-of-care-new-advances-in-diabetic-kidney-disease/12092/

Released: 01/29/2021
Valid until: 01/28/2022
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

At the Crossroad of Care: New Advances in Diabetic Kidney Disease

Announcer:
Welcome to CME on ReachMD. This activity, entitled “At the Crossroad of Care: New Advances in Diabetic Kidney Disease” was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC., and is supported by an educational grant from Bayer HealthCare Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Lilly USA, LLC.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Dr. Russell:
Type 2 diabetes represents the main cause of chronic kidney disease and end-stage renal disease. At least half of patients with Type 2 diabetes will develop diabetic kidney disease. Diabetic kidney disease is the single strongest predictor of morbidity and premature mortality in patients with diabetes. Even mild increases in albuminuria or GFR decline are associated with a considerably increased risk of cardiovascular disease and increased healthcare costs. Kidney protection is a critical target in Type 2 diabetes, and new therapeutic agents for prevention of development and progression of diabetic kidney disease are urgently needed. Are newer, anti-hyperglycemic therapies on the horizon? Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD, and I’m Dr. John Russell. Joining me to discuss emerging therapies for diabetic kidney disease is Dr. Janet McGill, Professor of Medicine at Washington University School of Medicine, in St. Louis, Missouri. Dr. McGill, welcome to the program.

Dr. McGill:
Thank you.

Dr. Russell:
So, starting off, and kind of the big picture – the 30,000-foot view – could you tell us the definition of diabetic kidney disease, and how prevalent is it in the United States?

Dr. McGill:
So, diabetic kidney disease is defined as albuminuria, reduced glomerular filtration rate, or both, for three months or more in the setting of diabetes. The prevalence of diabetic kidney disease has remained nearly constant, from the first NHANES survey in 1988-94, where the prevalence was 28.4%, to the most recent survey in 2009-2014, where the prevalence was 26.2% of those with diabetes. So there is some interesting caveats to these prevalence data, and that is the prevalence of albuminuria defined as a urine albumin to creatinine ratio greater than 30 milligrams per gram, has declined over time. So, in 1988-94, it was 20.8%, and in the latest survey, it declined to 15.9%. However, the prevalence of low estimated GFR has increased, and by low we mean less than 60 milliliters per minute per 1.73 meters squared. So it’s increased from 9.2 to 14.1%. And these changes have occurred despite overall lowering of A1C, from 8 to 7.4% across the population, from lowering of the systolic blood pressure from 136 to 130 millimeters of mercury, and having a lower LDL from 135 to 100 milligrams per deciliter. So, we’re doing a reasonably good job controlling risk factors for our patients, but it hasn’t put a significant dent in the prevalence of diabetic kidney disease.

Dr. Russell:

So it's certainly prevalent. How does this impact our patients?

Dr. McGill:
The impact is huge. So, the impact diabetic kidney disease is associated with, loss of life years, and, increased risk of cardiovascular death, myocardial infarction, hospitalization for heart failure. So there's a significant increase in cardiovascular disease risk and heart failure risk, and overall, loss of life, and that is before progression to end-stage kidney disease and need for renal replacement therapy.

Dr. Russell:
So what are the pathologic hallmarks to DKD

Dr. McGill:
So diabetic kidney disease comprises both glomerular lesions and tubular changes. Glomerular lesions include thickened basement membrane and fibrosis that is either nodular or diffuse. Tubular changes include interstitial fibrosis and tubular atrophy. Both of these are important in the development and progression of diabetic kidney disease.

Dr. Russell:
I take care of a lot of people with diabetes. Are there things I can do and help my patients prevent progressing to having diabetic kidney disease?

Dr. McGill:
The best way to prevent diabetic kidney disease is early and consistent glucose control. We're not sure that an A1C of 7-7.5%, for example, is actually good enough to prevent the majority of cases of diabetic kidney disease. So this impact of lower blood sugars was shown first in the Diabetes Control and Complications Trial, and in the U.K. PDS studies. As you know, the Diabetes Control and Complications Trial was first published in 1993, and studied about 1,400 patients with Type 1 diabetes. What's fascinating is that intensive therapy for six and a half years, early in the course of Type 1 diabetes reduced the prevalence of impaired GFR 16 years later, so what we now might call metabolic memory or legacy effect. So, very good glucose control early and sustained is really very important for, prevention of, kidney complications. And this has been shown in trials across the board – in ADVANCE, in VADT, and ACCORD, where the differences in A1C were fairly modest, but, all prevented new or worsening nephropathy or incident albuminuria, for example. So, the best thing to do for patients is to control their blood sugars, control it early, and control it consistently.

Dr. Russell:
So we have a lot more tools with regard to medicines for taking care of diabetes. How do they work with regard to prevention of DKD?

Dr. McGill:
So, as I mentioned, we are now entering a phase where, I will call it the "beyond glucose control" phase. So, what we have learned in the past, few years is that the choice of therapy matters also. I will discuss a few studies that address the role of GLP-1 receptor agonists and SGLT2 inhibitors in the prevention of diabetic kidney disease. The first trial is the LEADER trial, that compared liraglutide versus placebo, and tested the time to first renal event. So, these are now called, MAKEs, or major adverse kidney endpoints. The renal events were macroalbuminuria, doubling of serum creatinine, end-stage renal disease, or renal death. And in the LEADER TRIAL, the hazard ratio was 0.78, so a 22% reduction in time to first renal event. Another exciting class of drugs are the SGLT2 inhibitors that block the sodium glucose transporter on the proximal brush border of the renal tubule. Prevents reabsorption of glucose and sodium, and in doing so, limits the traffic of sodium and glucose through the tubule into the distal tubule, and out through the ureter. When this transporter is blocked, sodium is delivered through the tubule and is sensed by the juxtaglomerular apparatus, and contributes to normalization of tubular glomerular feedback, causing arterial or constriction and reducing pressure on the glomerulus or reducing single nephron estimated GFR.

So, the SGLT2 inhibitors have been tested in a number of studies. The first one was EMPA-REG, that compared empagliflozin with placebo on progression of macroalbuminuria, doubling of serum creatinine accompanied by an estimated GFR less than 45, or initiation of renal replacement therapy or death due to renal disease. The hazard ratio was 0.61 for a nearly 40% reduction in these events. The most important aspect of this therapy is the subgroup analysis that showed that empagliflozin was effective regardless of the level of estimated GFR, and regardless of the amount of albumin present in the urine. When hard renal outcomes were looked at, like doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease, the hazard ratio dropped to 0.54, so nearly a 50% reduction in hard renal outcomes. These studies results were confirmed by the CANVAS study, that studied a greater number, about 10,000 participants, and showed about a 40% reduction in estimated GFR, requirement for renal replacement therapy, or death from renal causes. So the composite renal outcome showed a hazard ratio of 0.6. These findings were later confirmed in observational studies done in large cohorts in Sweden, Denmark and Norway, that demonstrated that SGLT2 inhibitors compared to DPP-4 inhibitors slowed progression to renal replacement therapy, renal death or renal-related hospitalization, with a hazard ratio of 0.42. The same group, led by Dr. Pasternak, studied GLP-1 receptor agonists versus DPP-4 inhibitors and found a similar outcome, or reduction of hard

renal outcomes, with a hazard ratio of 0.76.

Dr. Russell:
How do these therapies impact that patient who already has diabetic kidney disease?

Dr. McGill:
So, testing, progression of kidney disease in patients who already have kidney disease has been the focus of a couple of recent studies. I'll first talk about the AWARD-7 study. This study compared dulaglutide versus insulin glargine, with an endpoint of preservation of estimated GFR. In 577 participants with Type 2 diabetes, in stages 3 or 4 chronic kidney disease elevated A1C of 8.6%, and variable albumin to creatinine ratio. So these patients met criteria for DKD, by virtue of their reduced, estimated GFR, and there was kind of an interesting distribution, that 22% did not have albuminuria at all, 34% had 30 to 300 milligrams per gram, which we would call microalbuminuria, and 44% had macroalbuminuria. And in this study, what we see is stabilization of kidney function across 52 weeks with dulaglutide, but declining kidney function across 52 weeks with insulin glargine. That was, highly significant. So, in the glargine group, the decline was 2.9, so about three milliliters, per minute, and in the dulaglutide group, it was about half of that, so, 1.1 to 1.5, depending on the dose. So again, the GLP-1 receptor agonists – in this case, dulaglutide –showed that it could stabilize kidney function in those with a diagnosis of diabetic kidney disease. There are additional studies looking at the SGLT2 inhibitors. We'll first talk about the DAPA-CKD study. The DAPA-CKD study was done in, interestingly, in patients both with and without diabetes, so two-thirds of the patients had diabetes, and one-third did not have diabetes. The primary outcome with decline in GFR of 50%, and that equates pretty closely to a doubling of serum creatinine. Doubling of serum creatinine is a decline of about 57%, so 50% decline is pretty close, so, end-stage kidney disease or death from renal or cardiovascular causes. In DAPA-CKD dapagliflozin was compared to placebo in 4,304 patients. The mean estimated GFR was 43.2. The urine albumin to creatinine ratio was pretty high, at 950 milligrams per gram. One-third of these patients had cardiovascular disease, and 11% had heart failure. What DAPA-CKD found is that dapagliflozin, compared to placebo had a hazard ratio of 0.61, and as you recall, this is the same hazard ratio with empagliflozin – so the hazard ratio of 0.61 for the primary composite outcome. So dapagliflozin reduced the occurrence of this primary outcome of decline in estimated GFR by 50%, end-stage kidney disease or death from cardiac or renal causes, and this was true regardless of age, sex, race, ethnicity. The effect was true regardless of the presence or absence of Type 2 diabetes. The effect held up with estimated GFR greater than 45 or less than 45, and with urine albumin to creatinine ratio greater or less than 1,000 – also, with systolic blood pressure that was either greater or less than 130. So we see in graphical form, and you see the same type of line graph in all of these studies, where there is an initial small dip with the SGLT2 inhibitor, followed by relative stabilization of kidney function. The placebo group has a more rapid decline in kidney function over time.

Dr. Russell:
Heart failure is a risk factor for rapid loss of kidney function. What is the effect of SGLT2 inhibitors on kidney function in persons with heart failure and reduced ejection fraction?

Dr. McGill:
So, this is a very interesting group of patients and, they need, high level of surveillance, and they need very careful management. So we know of two conditions where loss of kidney function occurs rapidly. So what is rapid loss of kidney function? How is it defined? The most common definition is a loss of greater than five milliliters per minute per 1.73 meters squared, per year. And that can occur with an EGFR above 60 or an EGFR below 60. So these are rapid progressors, and these are patients that we need to pay close attention to. One group of rapid progressors are those with macroalbuminuria, so the higher the albumin, the more rapidly they progress. The second group of rapid progressors, as a group, are those with heart failure and reduced ejection fraction. So in a very recent study, with first author Milton Packer, published in the New England Journal of Medicine in 2020, the study was designed to test the effect of empagliflozin on heart failure hospitalization and cardiovascular outcomes and death. That study was positive, but I'm going to tell you about the renal effects. So there were 3,730 patients, but only 50% had Type 2 diabetes, so 50% did not have diabetes. They all had heart failure with reduced ejection fraction, less than 40% – the mean was 27.7. The NT-proBNP was about 1,900, so these patients were pretty sick. The estimated GFR at the onset was 62 milliliters per minute, per 1.73 meters squared, and the composite renal outcome, which is a predefined renal outcome was end-stage kidney disease or transplant, or sustained reduction of estimated GFR greater than 40%, or sustained estimated GFR less than 15, so that's what we would call Stage 5 CKD. The placebo group met what – least one criteria for rapid progression, with a loss of kidney function of 4.21 milliliters per minute per 1.73 meters square. And this is over 124 weeks, so a little bit under, two and a half years. The empagliflozin group declined by 0.93, so this was highly significant. The between-group difference in slope, was significantly preserved in the empagliflozin group, with a P value less than 0.001. We now have evidence that the GLP-1 receptor agonists are useful in prevention and stabilization of estimated GFR in patients with and without chronic kidney disease, also that the SGLT2 inhibitors are effective, to both prevent, renal outcomes in patients with and without diabetes, and with or without the currently accepted definition of, diabetic kidney disease. I mean, this is a new horizon for those of us

who treat patients with diabetes.

Dr. Russell:
What's the future hold? What's coming in the future for patients with diabetic kidney disease?

Dr. McGill:
So thank you for asking the question. We now have an entirely new mechanism to, explore in diabetic kidney disease, which is blocking the mineralocorticoid receptor. So prior studies of dual RAAS blockade either lacked efficacy or had many adverse events. Hyperkalemia was very problematic, also there was more AKI. A new mechanism has been explored for the treatment of patients with diabetic kidney disease. Blocking the mineralocorticoid receptor has been tested in the past, with spironolactone or other steroidal MRAs. However, they either lacked efficacy or had too many adverse events, including hyperkalemia and AKI. We know that blocking the mineralocorticoid receptor has downstream effects that are beneficial in limiting progression of diabetic kidney disease. What is seen pathologically is a reduction of renal inflammatory markers, and fibrosis of the glomerulus. Consequently, glomerular hypertrophy, glomerular sclerosis, and renal injury are limited by blocking this receptor. This mechanism was tested in the FIDELIO-DKD study that compared finerenone versus placebo. Finerenone is a non-steroidal mineralocorticoid receptor blocker. The study had a composite renal and cardiovascular endpoints. Finerenone was shown to reduce albuminuria. It was also shown to reduce the primary renal endpoint of kidney failure, sustained 40% decrease in estimated GFR from baseline, or renal death, with a hazard ratio of 0.82 that was highly significant. So there's excellent rationale for blocking the mineralocorticoid receptor in the management of patients with DKD.

Dr. Russell:
So, is blockade of the MRA effective in reduction of progression of CKD in our patients who were taking an ACE inhibitor or an ARB?

Dr. McGill:
Yes, absolutely. This benefit was an added benefit, with a hazard ratio of 0.82, as mentioned. And all of the patients were taking an ACE or an ARB at the maximum effective dose.

Dr. Russell:
So when our colleagues in cardiology prescribe an SGLT2 inhibitor for the patients with heart failure with reduced ejection fraction, how can we help collaborate with them?

Dr. McGill:
This is very important. SGLT2 inhibitors are now guideline-approved therapy for heart failure with reduced ejection fraction. PCPs and diabetes specialists need to be prepared to either continue these prescriptions and then to make other therapeutic adjustments as needed, for example insulin might need to be adjusted, or perhaps diuretics need to be adjusted. So, these therapies are so important that we need to learn to adjust the other therapies around them, so that we can continue their use.

Dr. Russell:
So we covered a lot of ground today. What are the couple points you'd like our listeners to take away on all the things that we discussed today about diabetic kidney disease?

Dr. McGill:
First of all, patients with diabetes are at risk for diabetic kidney disease. We identify them based on albuminuria and estimated GFR, but all patients are at risk. Optimizing glucose and blood pressure control goes without saying, and early use of an SGLT2 inhibitor and/or a GLP-1 receptor agonist may reduce the onset and progression of chronic kidney disease. The SGLT2 inhibitors are now standard of care for persons with Type 2 diabetes and either albuminuria or HFrEF, to slow progression of these rapid progressive patients, and to reduce hospitalizations for heart failure. The new, nonsteroidal MRA might further benefit patients with diabetic kidney disease.

Dr. Russell:
So those are really some great points for us to keep in mind as we come to the end of today's program. I'd like to thank my guest, Dr. Janet McGill, for helping us to better understand the management of diabetic kidney disease. Dr. McGill, it was great speaking with you today.

Dr. McGill:
Thank you very much.

Announcer:
You have been listening to CME on ReachMD. This activity was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC., and is supported by an educational grant from Bayer HealthCare Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Lilly USA, LLC.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.