[MUSIC PLAYING]

MANISHA JHAMB: Hello. My name is Dr. Manisha Jhamb. I'm an Associate Professor of Nephrology at the University of Pittsburgh. Today, I will be talking to you about updates in chronic kidney disease management. The objectives for today's talk are to understand the role of SGLT2 inhibitors in the management of chronic kidney disease. We will also discuss the role of GLP-1 receptor agonist in the management of chronic kidney disease. And lastly, we'll talk about safety concerns and safe prescribing practices for these medications.

So just to start off with a little bit of background, diabetes and chronic kidney disease commonly coexist. Diabetic kidney disease occurs in about 30% of patients with type 1 diabetes and in about 40% of those with type 2 diabetes. And the most common cause of death in patients who have diabetes and chronic kidney disease are atherosclerotic cardiovascular disease and heart failure.

So let's first talk about sodium glucose co-transporter 2 inhibitors, or SGLT2 inhibitors. As the name suggests, these medications act on the SGLT2 transporter, which is located in the proximal tubule of the nephron. And there, they inhibit the reabsorption of glucose and sodium. As a result, this causes glucosuria and natriuresis.

These medications reduce HbA1C. Although, their glucose lowering effects are only modest, especially in people with advanced kidney disease. These medications also act as diuretics and reduce blood pressure as a result. But their effect on blood pressure is also quite modest with a reduction of 2 to 5 millimeters in systolic and 1 to 2 millimeters in diastolic blood pressure. These medications can also cause 1 to 2 of weight loss.

One of the first trials that came out with SGLT2 inhibitors looked at the effect of these medications on cardiovascular outcomes and mortality in patients with type 2 diabetes. The EMPA-REG trial came out in *New England Journal of Medicine* in 2015. This was a large trial. It enrolled 7,000 participants who had a prior history of cardiovascular disease. These patients were already on ACE and ARB inhibitors and statins for the most part.

What this trial found that-- was that there was a very beneficial effect of SGLT2 inhibitors on the primary outcome, which was a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. The hazard ratio was 0.86, suggesting a relative risk reduction of about 14% with these-- with this medication. Also, to note, the reduction in A1C was about 0.5%. And the reduction in systolic blood pressure was about 5 millimeters.

Subsequent to this EMPA-REG trial, a number of trials came out which looked at different medications in the same drug class, the SGLT2 inhibitors, and again reinforced this very positive and beneficial effect of SGLT2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes. Subsequently, there was a very growing interest based on some of the analysis in these prior trials to really look at what happens with these medications on renal outcomes in these patients.

And the CREDENCE trial was looking at that. This was designed to look at renal outcomes in patients with type 2 diabetes and nephropathy. The CREDENCE trial enrolled about 4,400 patients with chronic kidney disease. These patients had eGFR of 57, so CKD stage 3, and have pretty significant urine albuminuria of about 900 milligrams per gram. These patients were required to be on stable-- on stable maximally tolerated doses of RAS inhibitors for about four weeks before they were randomized to either canagliflozin or the placebo arm.

And what this trial showed was about a 30% relative risk reduction in the occurrence of the primary outcome, which was largely a renal outcome which is doubling of serum creatinine, end stage kidney disease, and also had mortality due to cardiovascular or kidney disease. And the number needed to treat was 21.

When they looked at end stage kidney disease as a secondary outcome, again, very impressive risk reduction in the occurrence of end stage kidney disease in patients who received canagliflozin. Thus, this was a very important outcome. And it shed new light on the effect of this class of medications in patients with diabetic nephropathy and showed the beneficial effect on retarding the progression of CKD in these patients.

It was interesting to note, there was no increased risk of amputations or fractures in this trial. There had been a signal for increased amputations in a prior trial of canagliflozin. And this was importantly not seen in this trial.

Again, looking at some of the results from the CREDENCE trial, the renal specific composite outcome. Very nice separation between the canagliflozin and the placebo arm. And very impressive reduction in the relative risk of developing renal adverse events in patients with diabetic nephropathy at baseline. Similarly, reduction in mortality from cardiovascular causes in patients who received canagliflozin was very impressive.

What was also important to note in this trial that the benefits of SGLT2 inhibitors were largely independent of glycemic control. And the efficacy and safety of these medications did not differ by baseline HbA1C. So these top two things here, they show the efficacy on the primary composite outcome and end stage kidney disease by varying levels of HbA1C. And in these different subgroups of A1C, there was no difference in the effect. And in all these subgroups, there was a favorable effect of canagliflozin on the-- on these outcomes.

It was also important to note the safety of these medications. So looking at hypoglycemia, there was no difference within the placebo or the canagliflozin group. For all these, the confidence intervals cross the 1, which means the safety was equal in both these groups. And similarly for acute kidney injury, there was no safety concern for patients who received canagliflozin.

Subsequently, there were a number of trials which looked at the renal outcomes. And this is a nice summary. It's a systematic review and meta-analysis of about 7,000 participants that were included in these trials with a baseline eGFR of less than 60 mLs per minute. And this meta-analysis showed that there was a beneficial effect of SGLT2 inhibitors on cardiovascular outcomes, hospitalization for heart failure, eGFR slope, and renal composite outcomes in patients with diabetic nephropathy.

And these were maintained when we looked at these effects stratified by eGFR. So when we look at patients with eGFR of at least 90, 60 to 90, 45 to less than 60, or less than 45 mLs per minute-- for all these subgroups, the effects favor the SGLT2 inhibitors and are more pronounced with patients with more preserved kidney function.

Similarly, the effect of SGLT2 inhibitors on regional outcomes is similar across different levels of proteinuria-- so patients who have a urine albumin creatinine ratio of less than 30 milligrams per gram or normal proteinuria, patients who have microalbuminuria or urine ACR of 30 to 300 milligrams per gram, or those with macroalbuminuria with a urine ACR of greater than 300 milligrams per gram. In all these subgroups, the effects favor SGLT2 inhibitors.

The mechanism for renal protection of SGLT2 inhibitors is not entirely clear. They may restore tubuloglomerular feedback. We know that these agents have an effect on glomerular hemodynamics. And as a result, the eGFR may initially fall by about 5 mLs per minute. But this is generally reversible. And these medications also may reduce inflammation and fibrosis within the nephrons.

Because of the overwhelming data of SGLT2 inhibitors and really showing their efficacy and safety in patients with diabetic kidney disease, the FDA came out with this approval in September of 2019 where they approved canagliflozin to treat diabetic kidney disease and reduce the risk of heart failure hospitalizations in patients with type 2 diabetes.

Subsequently, there have been a number of associations that have come out with revised guidelines in 2019 and 2020 for patients with type 2 diabetes. The American Diabetes Association, Kidney Disease Improving Global Outcomes or the KDIGO guidelines, American Heart Association guidelines, and European Society for Cardiology guidelines now recommend SGLT2 inhibitors for patients with type 2 diabetes who have chronic kidney disease, established or high risk of atherosclerotic cardiovascular disease, or heart failure.

And the KDIGO guidelines have this nice graphic where they discuss management of patients with type 2 diabetes and CKD. So the first and foremost is always lifestyle therapy with physical activity, weight loss, and nutrition management. After this, the first line therapy is metformin plus an SGLT2 inhibitor.

But notably, metformin is not recommended for patients who have a GFR less than 30 or are on dialysis. And even for patients with a GFR of less than 45, a reduced dose is recommended. And SGLT2 inhibitors should be added onto these patients, especially if they need proteinuria and diabetic control.

However, SGLT2 inhibitors are not recommended to be initiated with an eGFR of less than 30 or four patients on dialysis. And after these, additional therapies may be added. GLP-1 receptor agonists are preferred medications. And we will come back to this in later in the talk. And then, there are options for other oral or injectable medications including insulin.

So now, we've seen this overwhelming efficacy and safety of SGLT2 inhibitors in patients with type 2 diabetes. So what about the effects in non-diabetic patients? And this is very interesting data. One of the first studies that looked at non-diabetic patients is the DAPA Heart Failure trial. And this trial was really looking at the effect of dapagliflozin, an SGLT2 inhibitor, on mortality in patients with heart failure and reduced ejection fraction.

This was an international trial, which enrolled about 4,700 patients with an EF less than or equal to 40%. And about 45% of their patients had type 2 diabetes. But the rest did not have diabetes. These patients were randomized to receive either dapagliflozin or the placebo. And what they showed was that there was a beneficial effect of the dapagliflozin on the primary composite outcome, which was worsening heart failure or death from cardiovascular cause. And this was regardless of a patient's diabetic status.

Subsequently, the DAPA-CKD trial evaluated the effect of SGLT2 inhibitors on renal outcomes in patients with diabetic and non-diabetic CKD. And this trial results were published in September of 2020. And this trial was actually stopped early because of overwhelming efficacy.

So just going over some of the highlights of study design. So this trial enrolled participants with an eGFR of 25 to 75 mLs per minute and urine ACR of 200 to 5,000 milligrams per gram. So it enrolled participants with a lower eGFR and a lower urine albuminuria than some of the prior trials.

And in this trial, 68% of the patients were type 2 diabetics. But the rest of the patients, or one third, did not have diabetes. The mean eGFR was 43 mLs per minute, so lower than some of the prior trials. And median urine albuminuria was about 1,000 milligrams per gram. These patients were followed for a median of 2.4 years.

And this trial showed this very impressive, almost 40%, relative risk reduction in the primary endpoint, which was sustained decline in GFR, end stage kidney disease, renal, or cardiovascular death. And you see this very nice separation between the two arms. And the number needed to treat was only 19. So this is very, very impressive and strong data on the efficacy of dapagliflozin. And what was even more impressive, I think, is that this effect was maintained in patients with type 2 diabetes or without type 2 diabetes.

And here, you can see the effects on some of these outcomes individually. So 44% relative risk reduction in the renal outcomes of sustained at least 50% eGFR decline, end stage kidney disease or renal death. About 30% relative risk reduction in cardiovascular death or heart failure hospitalizations. And 30% relative risk reduction in all cause mortality.

And what's important to note is the safety data in this trial. There was no difference in discontinuation of the drug due to adverse event in the dapagliflozin or the placebo arm. The serious adverse events were actually higher in the placebo arm. And then, when you look at major hypoglycemia, these were non-- these were slightly higher in the placebo arm.

And as expected, the volume depletion was higher in patients with dapagliflozin. Although, this doesn't-- did not result in significant acute kidney injury. And the renal related adverse events were similar in the dapagliflozin or the placebo arm. So very reassuring data on the safety of these medications in non-diabetic patients.

So to summarize what I've talked about SGLT2 inhibitor use in chronic kidney disease, there's very compelling data now for the effectiveness of SGLT2 inhibitors in improving renal and cardiovascular outcomes and safety in that not only diabetic but also non-diabetic patients with kidney disease.

However, currently, these medications are only approved for patients in-- with type 2 diabetes. And they're also only approved for use in patients with an eGFR of at least 30 mLs per minute. However, the recent DAPA-CKD trial has shown that these medications are safe in non-diabetic patients. And they may be also safer in patients with a little bit lower eGFR.

There are ongoing studies that are actually evaluating use in patients with eGFR as low as about 20 mLs per minute. So the current recommendations are that once an SGLT2 inhibitor is initiated, it is reasonable to continue it even if eGFR falls less than 30 mLs per minute, unless it is not tolerated or kidney replacement therapy is initiated.

Moving on, I'm going to talk next about some of the safety concerns and side effects of these medications. One of the biggest one that comes to mind is hypoglycemia. But the risk of hypoglycemia is actually very low with these medications. And in patients who are not on insulin or a sulfonylurea or in non-diabetics, essentially, there is no risk of hypoglycemia.

And as GFR falls, their glucose lowering effect is diminished. With an eGFR of less than 45 mLs per minute, essentially, there's no change in A1C. And with an eGFR of 45 to 60, A1C is only lowered by about 0.5%. So the risk of hypoglycemia is very, very low, only in patients who already have their A1C less than 7% or have a history of frequent hypoglycemic episodes. Those are the patients who if they are concurrently on an insulin or a sulfonylurea may need a dose reduction in those medications. And it is recommended to decrease the dose by 10% to 20%.

Another complication from these medications is euglycemic diabete-- diabetic ketoacidosis. This is a very, very rare complication. But it can be very serious and fatal. And we really need to educate our patients about this. This medication should be avoided in patients with type 2 diabetes who have a history of diabetic ketoacidosis. And if a patient is undergoing a major surgery or is acutely ill when they have an increased risk of ketosis, this medication should be held temporarily. And patients should be educated about the sick day rule.

One of the most common side effect of these medications is genital mycotic infections. This is not surprising, because these patients-- these medications cause glucosuria. But these are usually mild, not recurrent, and relatively easy to treat infections and can be treated with topical or systemic antifungals. We want to advise patients to maintain genital hygiene. And only if these infections are recurrent, then we may need to discontinue SGLT2 inhibitors.

The next is urinary tract infections. These are actually not that common. But SGLT2 inhibitors should be avoided in patients who have a history of severe UTIs. So for example, pyelonephritis, or sepsis, or patients who have increased risk of UTIs. For example, a patient who has an indwelling Foley catheter, or has urethral stents, or has significant stone burden. These medications should also be avoided in patients with urinary incontinence or men with prostatic disease and obstructive urinary symptoms, again, because of this increased risk of UTIs in these situations.

Next, let's talk about the diuretic effect. So these are diuretics. And they can cause increased urinary output and frequency. But volume depletion is very rare. And their blood pressure lowering effect is also very modest. So in a majority of patients, we really don't have to worry about this. We want to advise patients to maintain adequate hydration. And very rarely, if a patient is already euvolemic or has borderline blood pressures, those are the patients where you might need to decrease the dose of their other diuretics.

These medications should be avoided in patients who already have hypotension, orthostasis, unexplained syncope, or who are prone to volume depletion. For example, a patient with a high ostomy losses. And patients should be educated about the sick day rule. So if they have an acute illness in which they have poor oral intake or have a GI illness causing diarrhea, they should temporarily stop taking their SGLT2 inhibitors in those situations.

Related to this diuretic effect is this concern about GFR dip and acute kidney injury. But this is actually very rare. Even the volume depletion, it is usually not that significant to cause acute kidney injury. When the SGLT2 inhibitors are first initiated, the GFR may drop by 3 to 5 mLs per minute. But this is entirely due to the hemodynamic effect. And this is reversible and does not indicate kidney injury. And the GFR usually returns to baseline and stabilizes after a few days.

Lastly, I just want to mention there's concern about increased lower limb amputations. This was seen in the Canvas trial with canagliflozin. But that was the only one study that has reported it. None of the other SGLT2 inhibitor trials have reported increased risk of amputation. This was part of the FDA Black Box warning but no longer is. Regardless, we should be cautious about this side effect, especially in patients who have history of severe peripheral artery disease or active foot ulcers. And frequent foot exams should be recommended in all diabetic patients.

So now, I'm going to shift gears a little bit and talk about this other class of drugs. These are the GLP-1 receptor agonists and their use in patients with chronic kidney disease. So these GLP-1 receptor agonists, these stimulate glucose dependent insulin secretion. They slow gastric emptying, regulate postprandial glucagon release, and reduce food intake. We can reduce the HbA1C by about a 0.5% to 1.5%, so a little bit more than what the SGLT2s do. And they can cause weight loss of about 2 to 3 kilos.

There have been a number of trials that have looked at the result-- that have looked at the effect of a GLP-1 receptor agonist on cardiovascular outcomes. I'm just going to show one of them. This is the Trulicity trial which randomized patients to dulaglutide versus placebo. And what it showed was about a 12% relative risk reduction in risk of major adverse cardiovascular events in patients receiving dulaglutide. And this was mainly driven by a reduction in non-fatal stroke among these patients.

Subsequently, a number of trials have evaluated these medications. There is a list of some of the commonly used medications. And as you can see, for a majority of them, no dose adjustment is required for CKD. Side effects from these medications are usually because of their GI side effects.

There have been a number of trials that have looked at the effect of GLP-1 receptor agonists on cardiovascular events and mortality in patients with type 2 diabetes. I'm showing just one of them here. This is the Trulicity trial, which examined the effect of dulaglutide versus placebo among patients with type 2 diabetes. And what it showed was about a 12% relative risk reduction in the risk of major adverse cardiovascular events which is cardiovascular death, non-fatal MI, or non-fatal stroke among patients who received dulaglutide. And this effect was mainly driven by the favorable effect on non-fatal stroke.

Subsequently, a number of trials have come out which have established the cardio protective effect of these medications. And this is a meta-analysis, which looks at all these trials. And there's a beneficial effect on all cause mortality, on hospital admissions for heart failure, and on composite kidney outcomes including macroalbuminuria with a relative risk reduction of about 17% with these medications. Here's a list of some of the commonly available medications in this drug class. And as you can see, for most of these, no adjustment in the doses required for severe CKD.

Next, I'm going to talk about some of the side effects with these medications. So one of the main side effect is the GI side effect. And this can include nausea, vomiting, diarrhea, or abdominal pain. And this is primarily because these medications act by slowing gastric emptying. These effects are usually short term and abate within one to two months of therapy. And these can be minimized by starting with the lowest dose and uptitrating the dose very slowly.

We can advise patients to eat smaller meals and eat slowly, which might help with minimizing these symptoms also. These medications should be avoided in patients who have gastroparesis or follow-- or following bariatric surgery. And again, patients should be educated about the sick day rule. And they should hold these medications temporarily if they have an acute GI illness.

The risk of hypoglycemia with these medications is very low in diabetic patients who are not on insulin or sulfonylurea. Essentially, there is no risk of hypoglycemia. Only in patients whose A1C is already tightly controlled and is less than 7% or patients who have frequent history of hypoglycemic episodes, in those patients, a dose reduction of insulin or sulfonylurea dose by about 10% to 20% might be indicated.

Majority of the medications in this drug class are injectables. And they can cause local injection site reactions, which can be minimized by rotating the injection site. And then very, very rarely, these medications have been reported to cause pancreatitis or gallbladder disease and should be avoided if a patient has history of disease-- of these diseases.

Lastly, these medications should not be used in patients with medullary carcinoma of thyroid or multiple endocrine neoplasia type 2. They should not be used in patients with type 1 diabetes. And these should not be used in combination with DPP-4 inhibitors, which are the gliptins.

So now, I've talked to you about SGLT2 inhibitors and GLP-1 receptor agonists. And I previously showed guidelines that have come out supporting the use of SGLT2 inhibitors in patients with diabetic kidney disease. But where do we stand in terms of which one among these?

So the American Diabetes Association says that patients with type 2 diabetes who have established or are at high risk of atherosclerotic cardiovascular disease who have established kidney disease or heart failure, either of these medications can be used. So SGLT2 inhibitors or GLP-1 receptor agonist is recommended independent of the A1C. And this is Evidence level A, which is the highest level of evidence supporting this recommendation.

The Kidney Disease Improving Global Outcomes or the KDIGO guidelines that came out in 2020 recommend that patients with type 2 diabetes, kidney disease, and who have an eGFR of at least 30 mLs per minute should be treated with an SGLT2 inhibitors. And GLP-1 receptor agonist is recommended in patients who have not achieved individual glycemic targets despite the use of metformin and SGLT2 inhibitors. So it is an add-on therapy after the SGLT2 inhibitors or in patients who are unable to use any of these medications, especially the SGLT2 inhibitors. Then, a GLP-1 receptor agonists is recommended.

I like this nice algorithm for using SGLT2 inhibitors or GLP-1 receptor agonists in diabetic kidney disease. So the one thing I want to point out first is that patients with a GFR that is less than 30 mLs per minute, in those patients, SGLT2 inhibitors initiation is currently contraindicated. Although, there are ongoing studies and a recent study, the DAPA-CKD, which showed that it might be safe. But per the FDA, we should not be initiating SGLT2 inhibitors in these patients. So for these patients, GLP-1 receptor agonists, such as dulaglutide, is preferred.

For patients who have any level of proteinuria, micro or macro albuminuria, and have a GFR of more than 60 or 30 to 60 mLs per minute, an SGLT2 inhibitor is always preferred and should be initiated as the first line. A GLP-1 receptor can be added as an add-on therapy or can be added if a patient cannot tolerate SGLT2 inhibitor or an SGLT2 inhibitor is contraindicated in that patient. For patients who have a GFR of more than 60 mLs and have no proteinuria, then either SGLT2 inhibitor or GLP-1 receptor agonist can be used.

So just to summarize some take-home points, we have this newer class of drugs, the SGLT2 inhibitors and GLP-1 receptor agonists which have shown this incredible data on improving adverse cardiovascular and renal outcomes and mortality in patients with type 2 diabetes and CKD.

There's emerging evidence showing cardiorenal benefits and safety of SGLT2 inhibitors even in non-diabetic patients who have chronic kidney disease. And the risk of adverse events with these medications is quite low, including hypoglycemia. So these medications should be used in the management of majority of our patients with chronic kidney disease. Thank you.