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Physicians own judgment must remain central in the selection of a therapy options for their patient's specific medical conditions. The following is supported in part by the Ohio State University Wexner Medical Center and Arthur G, James Cancer Hospital and Solove Research Institute. Updates in nephrology, that's today's presentation, with the following distinguished faculty from the Ohio State University Wexner Medical Center, and Arthur G, James Cancer Hospital and Solove Research Institute.

And now, filling in for our moderator, Dr. Jim Allen.

>> I'm Dr. Jim Allen. I'll be guest hosting MedNet for the next few weeks while Dr. Jing Jing is off. To start off the season, we're going to be discussing the current state-of-the-art in the management of patients with chronic kidney disease.

This is an especially important topic since this year marks the 80th anniversary of the invention of dialysis. The first dialysis machine was cobbled together using sausage casings, orange juice cans, and a washing machine. Needless to say, dialysis has come a long, long way in the decades since. But even more important, are recent developments in tactics to prevent progression of renal failure in patients with chronic kidney disease, thus avoiding or delaying the need for dialysis.

Well, many of these new preventative concepts have only emerged in the past three to four years. consequently, most of us did not learn them during medical school and residency. So today, we are going to update you on the management of chronic kidney disease, and to do it, I'm pleased to welcome back Dr. Rima Kang.

I've been Nephrologist and Assistant Professor of Ventral Medicine at the Ohio State University. Rima, it's great to have you with us today.

>> Thank you so much Jim, it's great to be back.

>> Well, it seems like, as recent, as just a few years ago, we define chronic kidney disease by the BUN and creatinine.

If those values were elevated, then the patient had chronic renal failure. Is this still

the way that we diagnose patients with chronic kidney disease?

>> Well, we should certainly still look at the BUN and creatinine, of course, but it's important for us to note that this is not the most accurate way to diagnose chronic kidney disease.

In fact, if we keep using BUN and creatinine, we're gonna miss a lot of early CKD that goes underdiagnosed. So we need to use alternative equations and methods to estimate the GFR and help delay progression of chronic kidney disease earlier on when we can actually make a difference in progression.

>> In the past about all we could do to slow the progression of chronic kidney disease was treat hypertension, do we have more effective options today?

>> Absolutely, so speaking from a medication standpoint, we now have a three-pronged approach to delaying progression of chronic kidney disease, with medication management.

However, there are a lot of lifestyle modifications we can make, and of course, treating hypertension, and diabetes, and underlying disorders of kidney disease.

>> Well, thanks Rima. Broadview viewing who are new to MedNet. We broadcast 40 programs each year from the WOSU TV studios here at the Ohio State University campus.

Each week, we feature different faculty members to update you on the latest developments in medicine. You can view this and all 120 of our current MedNet webcasts by going to ccme.osu.edu on your web browser. And if you prefer to get your continuing medical education by podcast, just go to your podcast app and search OSU MedNet21.

Also, if you have questions about chronic kidney disease you can contact Dr. King by using the Ask a Question icon at the bottom of the MedNet web page. Now, let's get started with today's webcast, Rima.

>> All right, so, we'll start off today by discussing the objectives, what we want to learn in today's discussion.

And number 1 is how to diagnose chronic kidney disease, and number 2 is how to assess progression in chronic kidney disease. And then lastly, the bulk of the talk will be the management of chronic kidney disease, including the target blood pressure, renal protective medications, metabolic acidosis, and diet.

The definition of chronic kidney disease includes the abnormality in kidney structure or function for more than three months. And this means, a sustained decrease in GFR less than 60. The presence of albuminuria, and what that means is either a urinary albumin-to-creatinine ratio of 30 mg per gram, or an albumin excretion rate of 30 mg in 24 hours.

But the definition also includes abnormalities on urine sediment, histology, or imaging, electrolyte abnormalities due to tubular disorders, or a prior history of kidney transplant. It is important for us to recognize changes on urine sediment or imaging because this can help us diagnose those early cases of chronic kidney disease, especially if there's no albumin area or a drop in the GFR.

So, who should we screen? Of course, universal screening should be for all patients with hypertension, diabetes, or cardiovascular disease. We should take an individualized approach for patients with other clinical or genetic risk factors. So if we know that a patient comes from a family of, let's say, polycystic kidney disease, which we know that we should screen those patients for polycystic kidney disease, for example.

If you have a patient who's had prior history of acute kidney injury, those are probably individuals who are appropriate for screening for CKD. The screening for CKD involves checking a urinary albumin to creatinine ratio. The creatinine and or cystatin C depending on the clinical situation. And I would add a full urinalysis as well, just to ensure that we're detecting any abnormalities on urine sediments such as hematuria.

And then once we diagnose CKD based on those measures, for patient safety, including all patients, we should counsel our patients to avoid the non-steroidal anti-inflammatory medications. And I counsel all patients with CKD in terms of the sick day rules, as we would say. So, if they are ill and not eating or drinking very well, just ensuring that they're holding their ACE inhibitors, their ARBs, their diuretics, just to avoid any type of pre-renal injury.

Furthermore, I would advise them to let their physician know that they do have chronic kidney disease and to dose all medications appropriately. As well as, if they ever need IV contrast, just ensuring that we're taking the proper precautions with regards to chronic kidney disease and adequate hydration in those cases.

Once the GFR is 45 to 59, same precautions exist. When the GFR is 30 to 44, we wanna be sure to decrease doses of metformin. And once the GFR is much lower, dropping below 30, we know that we're in advanced CKD, stage 4 and stage 5. In those cases, we really need to be aware of dosing our medications, avoiding things like bisphosphonates, of course, the NSAIDs, and then PICC line placement to preserve the vasculature up the of the upper extremities.

Because once we establish that the patient has advanced CKD stage 4 or stage 5, we know that they're approaching dialysis and we really should be preserving the vasculature in the upper extremities. The bulk of this talk will focus on slowing CKD progression and reducing the complications, and so we'll get to this.

And then lastly, reduction of cardiovascular complications. So ensuring that our patients are on statin therapy, especially if they've been diagnosed with chronic kidney disease above the age of 50. If they fall into the category of age 18 to 49 with chronic kidney disease, if they have preexisting coronary artery disease, they've had a prior stroke, if they're diabetic, those individuals should also be on statin therapy.

And then, of course, controlling blood pressure adequately to ensure we're reducing cardiovascular risk. So when do we refer to a nephrologist? And here's a list of some of those indications. If a patient has acute kidney injury or abrupt drop in GFR that's sustained, a GFR less than 30, albuminuria greater than 300 milligrams per gram, progression of CKD, urinary red cell casts, which isn't always detected, but in case it is, that would be an indication to refer.

CKD with resistant hypertension, persistent electrolyte abnormalities, recurrent kidney stones, hereditary kidney disease, or suspected glomerular disease, and any patient with chronic kidney disease who may become pregnant We'll start off with our first case, and keep this one in the back of your mind because we will come back

to this.

We have a 72-year-old female with long-standing diabetes and hypertension, coronary artery disease, right lower extremity amputation, who sees you for follow up. She has a creatinine of 1.28 and her urinary albumin to creatinine ratio is 780 milligrams per gram. You are considering adding a sodium-glucose cotransporter to inhibitor.

What method should we use for GFR measurement? Is it iohexol plasma clearance, 24-hour urine for creatinine clearance, GFR by cystatin C or GFR by creatinine, or a combination of both creatinine and cystatin C. And we'll get back to that question. When we talk about assessment of kidney function, it's important for us to recognize that creatinine and GFR vary by time of day, diet, exercise, body size, drugs, and hemodynamics.

In this chart, we'll look at some of the pros and cons of looking at creatinine and GFR. So the pro is that this is a direct measure of kidney function. We can do this with ease. It's just a routine blood test that we can do. The GFR decrease is correlated with decreased endocrine and metabolic functions.

So we can start focusing on those renal protective medications and start our therapies for delaying progression. The GFR is reduced before the onset of symptoms, so it's important for us to really check the routine lab work, because symptoms of chronic kidney disease don't appear until it's too late in the disease course.

Cons include the accurate measurements are difficult to perform, it can be biased and imprecise, and it can be insensitive for detection of early kidney disease. You may note that when you're checking labs, the GFR may not be detectable as abnormal until that GFR is actually below 60. And we know that there's a substantial drop in GFR already by that point.

So here are some methods by which we assess kidney function. And in the nephrology space, we switched to the CKD-EPI equation in 2021. And so our labs started to use this equation to estimate GFR. And it's important to note that race was dropped from the equation in estimating GFR.

And this is important because it includes a larger population of the African-American population that weren't otherwise being diagnosed with chronic kidney disease. So now we're reaching more individuals with chronic kidney disease earlier on. Cystatin C is a protein biomarker that we can use to estimate kidney function. It is not secreted, so it is somewhat of a good measure to use in conjunction with the CKD-EPI equation if needed.

However, no one method is actually precise, and so we suggest increased research funding to optimize that GFR estimation. Of course, the most accurate measure would be an exogenous substance that is neither secreted nor reabsorbed, but it's not practical to do in everyday practice. So when we're looking at both creatinine and cystatin C, it's important for us to recognize that there are limitations to both.

So when it comes to body composition, we know that creatinine can be inaccurate at the extremes of muscle mass, whereas cystatin C can be affected by obesity. Chronic severe illness or frailty can affect your creatinine levels. Inflammation, thyroid disease, or smoking can affect cystatin C. And then it's important to recognize that high protein diets or creatine supplements can affect their creatinine

level as well.

So for example, if you have a younger male patient who works out a lot, they're taking creatine supplements and a very high protein intake, they may have a higher creatinine level, but that may not actually represent chronic kidney disease. And then, of course, in non-steady states such as acute kidney injury, dialysis, or edematous states where both creatinine and cystatin C could be affected.

So getting back to our case, the correct answer is actually a combination of creatinine and cystatin C that is recommended by the Kidney Disease: Improving Global Outcomes guidelines. So this is helpful because we know that there are limitations to both. So we can use a combination of both to get a better idea of what the actual GFR may be, and that'll help dose medications as well.

Looking at albumin area really helps us assess progression of kidney disease. So in this next section here, we'll talk about how we know which individuals will progress quickly. So this is an adaptation of the chronic kidney disease heat map, as we call it. Towards the left, we have a breakdown of chronic kidney disease by stage, NGFR, and across the top, a breakdown of albuminuria by degree of albuminuria.

And by and large, we can see that the more advanced stages of chronic kidney disease by GFR, regardless of degree of albuminuria, those are gonna be higher risk to progress. But even in a stage 1 patient with GFR greater than 90, the higher the degree of albuminuria, the higher the risk is for CKD progression.

So targeting albuminuria really should be a focus of treating chronic kidney disease. We'll just take a look in this table for more risk factors for chronic kidney disease progression. So of course, there are sociodemographic, behavioral, genetic, cardiovascular, metabolic, and novel biomarkers that help us assess for risk of progression.

And in red, we have some of the items that we can focus and counsel our patient on, for example, smoking cessation. High dietary animal protein intake is another important one. We should be counseling our patients to Limit dietary animal protein intake, and suggest plant-based protein. And the reason for this is because plant-based protein tends to be more alkaline.

So these patients develop less metabolic acidosis, there's less production of uremic toxins, and it actually has a positive hemodynamic effect in the kidney as well. So this is an important one to emphasize and something that from a lifestyle perspective, we should be counseling patients. Poor self-management can be a reason for CKD to progress.

And I always counsel patients, to take an active role in their management, because there's a lot that we can be doing from a lifestyle perspective, that will slow CKD progression. For example, switching to plant-based protein intake. Some of the genetic risk factors, and I'll touch on the APOL1 gene variants, because this has been described as one of those gene variants that we know leads to progression.

There was a cohort of patients in the chronic renal insufficiency cohort, which was greater than 3,000 patients. And those individuals with the ApoL1 gene variants were noted to have worsening proteinuria and decline in GFR, and their CKD progressed at a much faster rate. Regardless of whether or not those patients had diabetes.

So we know that the ApoL1 gene variant plays a role. And this is important for the future because at some point there may be alternative targets that we can look at to delay CKD progression. From a cardiovascular standpoint, we know controlling blood pressure is important to delay CKD, ,making sure that our patients are on the appropriate heart failure medications.

And that appropriate goal-directed medical therapy. From a metabolic standpoint, treating low serum bicarbonate. We know that metabolic acidosis can also lead to progression of chronic kidney disease. So this is another important thing to focus on. I'll briefly touch on the increased uric acid because recently this has sort of, our practice has changed.

We know that increased uric acid can lead to chronic kidney disease progression, however, there have been studies looking at uric acid lowering therapies. Which were actually shown not to slow progression. There was no change in, progression of chronic kidney disease regardless of whether or not uric acid was treated to a normal level.

So regardless of the level itself, treating it doesn't really delay progression of kidney disease. And some of the novel biomarkers such as NT-proBNP, urinary Ngal, and inflammatory marker CXCL 12. We know that these are elevated, in patients who are progressing quickly. So, those factors are known to be associated with high risk for progression, as well.

This diagram is a representation of all the factors that lead to chronic kidney disease progression. So there's a lot that we can be doing outside of just medications to slow the CKD progression, much of which we've already touched on. But of course, some other factors such as anemia, genetics, obesity, environmental factors, inflammation, dyslipidemia.

All of these things that we can be focusing on, in addition to the medical therapies that we'll talk about. So the first step in the management of chronic kidney disease, in every patient we should be addressing hypertension. This is the leading risk factor for progression of chronic kidney disease and has a higher prevalence in the advancing stages of kidney disease.

Because of salt retention and worsening hypertension. This leads to the development of cardiovascular disease, so it certainly is something that we should focus on, because we know that patients with chronic kidney disease have a high rate of cardiovascular disease. And this is the leading cause for mortality in this group of patients.

So the next case is, regarding blood pressure, which is true regarding reduction of blood pressure to less than 120 systolic. Is it a reduction in all cause mortality? Does it slow CKD progression? Lower the incidence of renal replacement therapy? Or lower the incidence of kidney transplant? And the next case is a 55 year old patient with CKD stage three, A3, due to diabetic nephropathy.

The average home blood pressures are 140s over 80s, on the center April 20 milligrams CT valladon 50 milligrams and M Lupien 10 milligrams. The urinary albumin to creatinine ratio is 800 milligrams per gram. What is the next appropriate next step in management? Should we add Lozart into the current regimen, stop lisinopril and add spermolactone, increase lisinopril dose, or change Clothaladone to Firocimide.

So we'll keep these questions in the back of our minds and get back to them once we discuss hypertension in a little bit more detail. 30 to 60% of hypertension is actually heritable. So we are diagnosing a lot more genetic related hypertension, through more genetic testing in these patients.

CKD patients of course are predisposed to salt sensitivity and this process is just. It keeps going because the excess salt actually leads to monocytes and T helper cells which further exacerbate salt retention as well. So the process just keeps going. And the key mechanism is an inappropriate renin-angiotensin-aldosterone system activation.

Environmental factors such as. Drinking alcohol, obesity, and smoking account for about 40% of hypertension. So again, we can't discount, counseling our patients on those lifestyle measurements as well. I'll briefly touch on secondary hypertension, because I think it's important to recognize, especially in the chronic kidney disease population, and when we have resistant hypertension.

It has been shown that we're probably under diagnosing aldosteronism in a lot of these patients. Some of the clinical clues include, hyperkalemia, metabolic alkalosis, or an adrenal nodule. You may have one or none of these findings, and so when you do have resistant hypertension, it is important to screen for primary aldosteronism.

And depending on clinical clues, maybe some of these other secondary causes. And of course, the diagnostic testing for primary aldosteronism is an aldosterone to renin ratio. And if that is confirmed as elevated, then we can do confirmatory testing from there. Renovascular disease is highly prevalent in the chronic kidney disease population.

It leads to progressive CKD, asymmetric kidneys, may be a clinical clue, or if the patient has a history of atherosclerosis, coronary artery disease, or just vascular disease in general. And of course the diagnostic testing includes a duplex ultrasound, CT angiography, or MR angiography. And the rest of the secondary causes are listed here as well, just as a point of reference.

So lets' take a look next at the KDIGO guidelines for blood pressure management. Interestingly, the target systolic blood pressure is actually less than 120 millimeters mercury based on standardised office blood pressure measurements. This target is the same regardless of albuminuria diabetes or older age. So across the board, the KDIGO does recommend a systolic blood pressure less than 120.

Kidney transplant recipients should have a target blood pressure less than 130, or diastolic blood pressure less than 80. I'll just touch on some of the implications for hypertension management. As per the Kdigo guideline. So we're talking about less than 120 for that systolic blood pressure. 69.5% of US adults with CKD are eligible for blood pressure lowering.

So we're clearly not treating blood pressure adequately as per the Kdigo guideline. And among those with albuminuria, and this is according to an enhanced study of about 1700 patients, 78.2% are eligible, but only 39.1% take angiotensin converting enzyme inhibitors, or the ARBs. So it's really important for us to recognize these cases, and ensure that our patients with albuminuria are getting treated appropriately with the first line therapy which will include inhibitors.

These of course are missed opportunities to improve blood pressure control. And adhere to guidelines. So, looking at the pathophysiology of hypertension in chronic

kidney disease, if we start with reduced nephron mass, this is going to lead to intraglomerular hypertension, increase in filtration pressure, which subsequently worsens proteinuria. And downstream, we're activating pro-inflammatory mediators, which eventually leads to fibrosis.

And then of course another component is the vasoactive signaling, angiotensin II and aldosterone. As we know, angiotensin II is a potent vasoconstrictor, and so that's a potential target for treatment for blood pressure. Anti-hypertensive therapy is important of course, because it reduces intraglomerular hypertension, and of course downstream we'd reduce filtration pressure, and improve proteinuria.

But the last antagonist should be first line because we're having a direct effect on intraglomerular hypertension, filtration pressure, improvement of proteinuria. But it also has a positive effect when it comes to Inhibiting those pro-inflammatory mediators, and of course inhibiting that angiotensin II, which is that potent vasoconstrictor. And that works in the efferent arteriole.

So, when we are using RAS antagonists, we are going to dilate the efferent arteriole and drop the intraglomerular pressure. And so subsequently that leads to improved renal hemodynamics. The KDIGO guidelines for blood pressure management came from the systolic blood pressure intervention trial, which was a sprint trial. This was a landmark trial in studying blood pressure.

It included 9,361 patients greater than 50 years old. The patients were assigned to a systolic blood pressure less than 120 versus less than 140. So there was an intense treatment group, and there was a less intense treatment group. The lower blood pressure group had a lower risk for cardiovascular events in all-cause mortality.

And this is the reason why the KDIGO guidelines changed, because, again, we know that patients with chronic kidney disease have higher risk of cardiovascular events. .So, lowering that blood pressure target helps us control those, or at least help reduce the risk of those cardiovascular events. There was no difference in chronic kidney disease progression.

I will mention that there was higher incidence of hypotension, syncope, electrolyte abnormalities, and acute kidney injury in the intense treatment group. However, these effects were mitigated at least within a year. So, in the long run, at the post-intervention period, there was no difference in CKD progression. So, here's our approach to the management of hypertension.

Again, as per the KDGO guidelines, regardless of whether or not the patient has albuminuria or diabetes, we should be starting therapy with RAS inhibitors, so ACE inhibitors, ARBs. And as per the ACCHA guidelines from 2017, the treatment with RAASi is reasonable for patients with hypertension and GFR less than 60, with a urinary albumin creatinine ratio greater than 300.

So, long story short, I think we still have to take somewhat of an individualized approach to blood pressure management when it comes to chronic kidney disease. In general, I try and adopt the lower the better policy. However, we need to take it into consideration when we have elderly patients who already have issues with dizziness or syncope, or a patient with bad vascular disease who may need to maintain higher blood pressure for perfusion issues.

So again, case-by-case basis, but especially in most individuals, try and get as low as possible. I'll briefly touch on continuation of the renin-angiotensin system inhibitors

in advanced CKD. The current recommendation is to continue this therapy, if the creatinine change is less than 30% in the first month after initiation of therapy.

Continuation of the RAAS inhibitors is associated with lower risk of major adverse cardiac events and overall mortality. But the risk to progression to end stage kidney disease is still unclear. There was actually a large Swedish trial of about 10,000 patients that looked at discontinuation of RAAS inhibitors in more advanced kidney disease.

And there, of course, was a lower risk for major adverse cardiac events, and in this trial as well, there was a higher risk for development of end-stage kidney disease. However, in a United States study, there was less risk for adverse cardiac events, and no change in development of end-stage kidney disease in those who continued versus those who discontinued RAAS inhibitors.

So again, the risks of progression to end stage kidney disease is somewhat unclear. But the recommendation as of now is to continue those RAAS inhibitors even if a patient has advanced CKD. We know that there are many anti-inflammatory effects as well. So, there are multiple ways by which these agents can be helpful in chronic kidney disease.

Here is an example of a resistant hypertension algorithm. Resistant hypertension, of course, is defined as a blood pressure greater than 130 over 80, with more than three medications at maximal doses, and one of those has to be a diuretic. So what do we do when the patient is still hypertensive despite these measures?

So we obviously already have to focus on those lifestyle modifications. The next step in management would be evaluating for chronic kidney disease, and screening for those secondary causes, as we'd mentioned. And then lastly, changing the diuretic to chlorthalidone. Most of these individuals will be on a thiazide diuretic, like hydrochlorothiazide.

Chlorthalidone, it has a bit of a more potent effect when it comes to blood pressure management. There is a little bit more risk for hypokalemia as opposed to hydrochlorothiazide, but anecdotally, it does have better blood pressure effect. If the GFR is less than 30, we can then add a loop diuretic to the thiazide, and titrate to dry weight.

After that, mineralocorticoid receptor antagonists can be helpful. In fact, as I'd mentioned earlier, a lot of these patients with chronic kidney disease do have some degree of hyperaldosteronism, so these agents can be very helpful in resistant hypertension. Lastly, if the heart rate is above 70, we can add a beta blocker, and if still uncontrolled, we can refer to a hypertension specialist.

Next, I'll touch on the non-steroidal mineralocorticoid receptor antagonists. These are more selective for the mineralocorticoid receptor, and they have less anti androgenic and progestogenic side effects. There's also a lower risk for hyperkalemia. The specific nonsteroidal that was approved in 2021 was finerenone. It suppresses the expression of pro-inflammatory and pro-fibrotic genes in the presence or absence of aldosterone.

So finerenone was also shown to slow the progression of kidney disease, and also have a positive effect with regards to albuminuria. If you have a patient with resistant hypertension, finerenone may not be the optimal therapy. The non-steroidal MRAs really only have a modest effect on blood pressure. So, if you need a

better blood pressure effect, we can use our traditional agents like spironolactone or eplerenone.

But if you need additional renal protective therapy, in a patient who otherwise has relatively well controlled blood pressure, finerenoneis another great option. So, getting back to our cases, case two, what is true regarding the reduction of blood pressure to less than 120? We know that it shows a reduction in all-cause mortality, but has no effect on CKD progression.

In case 3, in this patient with CKD stage 3, who's on lisinopril 20 mg, chlorothalidone 50 mg, and amlodipine 10 mg, with an elevated urinary albumin to creatinine ratio, we should really focus on maximizing the RAS inhibitor first. After that we can consider changing the other medications or adding medications to the current regimen.

There's no evidence to support dual ACE inhibitor and ARB therapy, and in fact, there's a higher risk for hyperkalemia. RAS inhibitors are first line so we should not stop this therapy. So B choice B is incorrect. And for choice D, there's no indication that we have to change chlorthalidone to furosemide in this patient, we can use her pre existing medications and maximize her rest inhibition.

So next we'll move on to another case. And again, we'll keep this in the back of our minds as we get into further discussion. You have a 48 year old male patient with diabetes type 2 and CKD stage 3 a A2 with retinopathy and hypertension.His medications include Losartan 100 milligrams, metoprolol 75 milligrams, bid twice a day, Metformin 500 milligrams bid.

His blood pressure is under acceptable control. But you note that his albuminuria has been steadily worsening to a thousand milligrams per gram in the past year. What is the next best step? Should we start SGLT2 inhibitors to reduce albuminuria, start SGLT2 to reach A1C less than 7, add finaranone, or stop the metformin?

So next we'll talk about the biggest buzz in nephrology in the recent years. And these are the sodium-glucose cotransporter inhibitors. They inhibit the primary glucose transporter in the proximal tubule, and this inhibits proximal tubule sodium reabsorption. So from a mechanism standpoint, when we're reducing that reabsorption of both sodium and glucose, we have increased distal tubule delivery of sodium, and so the macula densa senses that and restores that tubular glomerular feedback, and in return, this will lead to the afferent arterial vasoconstriction.

And that'll reduce pressure across the glomerulus. And again, that increased distal sodium delivery also leads to naturesis and decreases circulating volume with improved blood pressure and improved cardiac preload. So of course, there are both cardiovascular and renal benefits to the sodium glucose co-transporter inhibitors. And furthermore, there are also anti-inflammatory effects.

Looking at the pathophysiology of SGLT2 inhibitors and how it affects renal hemodynamics, we see a normal glomerulus with an afferent and efferent arterioles at the top. In untreated diabetes we have a dilated efferent arterial, which will increase the filtration pressure and of course, Affect the renal hemodynamics and worsen per proteinuria over time.

As I had mentioned, the SDLT two inhibitors, will restore that tubule, glomerular feedback, and eventually lead to, vasoconstriction of the ary arterial. So that'll reduce pressure across the glomerulus. In conjunction with the RAS inhibitors which

will dilate the efferent arterial by inhibiting angiotensin, the two of those agents in conjunction will truly Improve renal hemodynamics.

Looking at some of the SGLT2 trials, this is just a few of them, of course at this point there are many SGLT2 trials, but looking at the overall theme here is that regardless of which type of SGLT2 inhibitor, there was a slower progression in chronic kidney disease there was less risk for major adverse cardiac events and there was an a positive effect on reducing albuminuria as well I'd like to focus on two particular trials with regards to chronic kidney disease.

DAPA-CKD is looked at DAPA glufosin, which is an important study because it actually studied patients with chronic kidney disease due to IgA nephropathy, FSGS, and causes other than just diabetes. These patients included had a GFR of 25 to 75 and urinary albumin to creatinine ratio of two 200 to 5000 milligrams per gram.

They were randomized to depo flows in versus placebo, and there was overwhelming efficacy. It reduced the primary outcome of sustained decline in GFR by greater than 50%. Reduced the risk of death from renal or cardiovascular event by 50%. And the benefits were shown across all stages of chronic kidney disease, degrees of albuminuria, presence or absence of diabetes.

The EMPA-KIDNEY trials studied empagliflozin which was a study of 6609 patients with a GFR of at least 20 but less than 45. So, now we're looking into more advanced stages of chronic kidney disease. And these individuals It didn't necessarily have to have albuminuria, and it also included patients with GFRs that were a bit higher, so greater than 45, but less than 90, with a urinary albumin creatinine ratio of at least 200.

The primary outcome was looking at progression of kidney disease or death from cardiovascular causes. By and large, across a wide range of GFRs and levels of albuminuria or causes of chronic kidney disease, there was 28% less risk for progression of kidney disease or death from cardiovascular cause on empagliflozin.

So, if we have to take anything from any of the SGLT2 trials. It's that regardless of the cause of chronic kidney disease or regardless of the degree of albuminuria, the SDLT II inhibitors are beneficial with regards to preventing those major adverse cardiac events, slowing progression of chronic kidney disease, and it also has those anti-inflammatory effects as well.

So again, looking at a summary, we know that at reduced renal events, these agents reduce cardiovascular events and the risk of hospitalization for heart failure. So when we're initiating SGLT2 inhibitors in diabetes and chronic kidney disease Towards the left here in this flow chart. These are pretty much slam dunk cases for starting SGLT2 inhibitors if you have a patient whose GFR is greater than 30 a urinary albumin creatinine ratio greater than 200 heart failure, these individuals should absolutely be on SGLT2 inhibitors.

They can certainly be considered in other individuals and of course as we know may be beneficial even in the more advanced stages of chronic kidney disease. But again, these are sort of those slam-dunk cases where we can initiate a low-dose SGLT2 inhibitor. On follow-up, we need to ensure to assess for any of those adverse events and also anticipating an acute decline in GFR.

So if there's a decline in GFR, anything less than 30% decline in GFR is acceptable for SGLT-2 inhibitors. And of course the benefit certainly outweighs the risk of a

small decline in GFR with these agents. So getting back to case four of our 48 year old male patient with diabetes and CKD on Losartan metoprolol foreman and worsening albuminuria.

We should start this patient on an SGLT2 inhibitor to reduce albuminuria. Regarding starting an SGLT2 inhibitor to reach A1C targets, SGLT2 inhibitors have somewhat of a modest effect on glucose control. So if we're really focusing on tight control of glucose, we may need to use alternative agents. Adding Finerenone wouldn't necessarily be indicated yet in this patient, but certainly could be considered third line for renal protective medications.

So, this slide focuses on a summary of the chronic kidney disease therapeutics that we've discussed today. So, of course, we have the mineralocorticoid receptor antagonists, the RAS inhibitors, and the SGLT2 inhibitors. And all of these agents have a positive effect on the renal hemodynamics and restoring tubular glomerular feedback and dropping the pressure across the glomerulus, which we know will slow CKD progression and slow that development of proteinuria.

Lastly, we'll touch a bit on the lifestyle modifications in chronic kidney disease. There was a recent meta-analysis showing that a diet consisting of fruits, vegetables, whole grains and fiber, plus a lower intake of sodium, red meat and sugar was associated with 30% reduced odds of kidney damage. Exercise and weight loss are important for chronic kidney disease patients, smoking cessation as we'd mentioned.

Smoking has been associated with higher prevalence of coronary artery calcification in chronic kidney disease. So certainly important to focus on this. And as we'd mentioned before with protein intake, it is important to counsel our patients to change their diet to a plant-based protein. Discussing a little bit about metabolic acidosis, we know that western diets, because they're high in protein, cause a higher acid load.

CKD leads to decreased acid excretion because they're unable. These patients are unable to synthesize ammonia and excrete those hydrogen ions. Metabolic acidosis can also lead to bone disease, which we know is important for chronic kidney disease patients. An increased risk for cardiovascular disease and a decline in GFR.

So the classic waste to treat would include sodium bicarbonate, sodium citrate and a diet high in fruits and vegetables. Our goal is to raise the serum bicarbonate to greater than 22. The key points in diabetic kidney disease, just to touch on this for a little bit, because we know that a large proportion of our patients have diabetic related kidney disease.

We should treat patients with diabetes and chronic kidney disease with GFR greater than 20 with an SGLT2 inhibitor. So this has very good evidence. So we should be routinely doing this, practicing this in chronic kidney disease. And the earlier the better, so that we have the most time of renal protection with these agents.

Adding nonsteroidal MRAs in diabetes with a GFR greater than 25 if normal serum creatinine and albuminuria greater than 30 despite max rest inhibitor therapy. And lastly a target a one C ranging from less than 6.5 to less than 8 in patients with diabetes and chronic kidney disease not yet on dialysis.

>> Well, thanks Rima You talked about the three classes of drugs we should be using, but what are some of the common medications that we should be avoiding in

patients with chronic kidney disease?

>> Yes, exactly. So one of the most common classes of medications we should certainly avoid are the non-steroidal anti-inflammatories.

A lot of times we really don't know whether or not patients are taking these, so we really have to take a good history and ensure that we're asking our patients. I routinely ask them if they have any joint pains, aches, and pains here and there, because by and large a lot of patients may be taking them even if not daily, at least multiple times a day every other day.

This can still lead to chronic kidney disease progression. But more than just that just being aware of any other over-the-counter medications they may be taking such as herbal supplementations, creatine supplements and things like that.

>> Well, our goal is to avoid dialysis, but for many of our patients, dialysis does ultimately become necessary.

Once more there was an article in the New England Journal of Medicine showing some advantages of hemodiafiltration over conventional hemodialysis. Hemodiafiltration is a new concept for me, what is it and is it currently an option for our patients.

>> Sure, so I'll start with your second question. Hemodiafiltration is not currently an option for our dialysis patients.

At present, we just have hemodialysis as a modality. Hemodialysis utilizes diffusion for clearance. So, in general, it's very good at the smaller solute clearance, but not necessarily for those larger molecules. Hemodiafiltration utilizes both convection and diffusion so we have a better ability to be able to remove those middle to larger molecules.

It's a bit tough even based on this study that was just published to generalize this to the population. And furthermore, we don't know that removing some of these larger molecules, maybe we would be removing some proteins that are necessary. And so we certainly need more research behind whether or not hemodiafiltration would be beneficial.

In some of the studies that have been done as of yet, there is some improvement in mortality but I think we still just need a little bit more evidence at this point and logistically it's still a little bit difficult because hemodiafiltration utilizes both a dialysis solution and a replacement solution.

So it is a lot of cleansing solution that is required. That is not otherwise necessary with hemodialysis. There are some higher flux filters that can be utilized and that clear middle molecules better. So I think there are a lot of ways, that we can certainly improve clearance in these patients and we're not quite there but hopefully soon we'll come up with these high-capacity dialyzers that could accomplish the same.

>> Yeah, one of the consequences of chronic kidney disease is hyperkalemia and hyperphosphatemia. What's your current approach to managing the electrolyte abnormalities that are attended to chronic kidney disease?

>> This is a great question. So hyperphosphatemia is generally encountered more

in the advanced stages of chronic kidney disease.

And a lot of this requires counseling and dietary education on what are those high phosphorus foods. But otherwise there are many phosphorus binders that we could be using to help bind up phosphorus in the GI tract for these patients. Hyperkalemia is an important one to mention because classically our renoprotective medications can cause hyperkalemia, right?

So our RAS inhibitors, our mineralocorticoid receptor antagonists, these are great agents for renal protection, but they have the unintended side effect of hyperkalemia. So for us to be able to continue these agents, it's been very helpful in the recent years that we have the arrival of new potassium-binding resins like sodium zirconium psychosilicate or localma and Pityrimer otherwise, Veltassa.

I generally utilize glaucoma a little bit more because it, it exchanges potassium for sodium, whereas Pityrimer can affect calcium and magnesium levels and cause hypocalcemia and hypomagnesemia. So these are very effective agents that our patients can be on long term and still continue those rest inhibitors and the MRA is, so great class of medications.

>> It's beginning of your talk, you mentioned some of the reasons to refer patients to an allergy specialist. What about some of the reversible causes of worsening renal function that you do see as neurologist? Are there any that we should be particularly on the lookout for? Right, so as I mentioned, some of those over-the-counter medications that can cause AKI or chronic kidney disease, just again, taking that history and being aware that your patient could be on creatine.

Let's stop that and recheck the labs and see how the kidney function looks. And in certain cases where we have a patient with let's say a history of lupus, we should be doing the routine screening with your analysis, so that we can catch those cases early. Which before there's any change in GFR.

So those patients could be referred to a nephrologist early on when there may be some hematuria of the urinalysis. And so, that may be potentially reversible and much earlier than if we would detect it otherwise.

>> Lipid abnormalities are very common in patients with impaired renal function. What's your general approach to evaluating and managing lipids in patients with chronic kidney disease?

>> Yes, so as we know, these patients have a high risk for cardiovascular disease, so any patient with chronic kidney disease and a GFR, excuse me, over the age of 50, they should all be on statins. We should check the lipid panel and if indicated they should be on statins.

If they are below that age, but they have those cardiovascular risks, or they've already had cardiovascular events, coronary artery disease, a prior stroke, or if they're diabetic, they should be on statins as well.

>> Another issue in chronic kidney disease is bone health. What are the common causes of bone disorders in chronic kidney disease and how do you clinically manage them?

>> Bone disease is a large topic in chronic kidney disease. There's a lot of ways to actually diagnose it, but most cases that we deal with in chronic kidney disease are

cases of secondary hyperparathyroidism with high bone turnover. So one of the earliest findings that we see is phosphate retention, which may not always be reflected on the labs, but we know that there's an increase in FGF-23, which downstream inhibits calcitriol synthesis and will affect our PTH levels.

So the PTH levels start to get high and so we're routinely treating both the phosphorus and our vitamin D levels. And if the PTH is continuously getting higher, there's no specific KD go recommendation as for the actual number that we go for. But as the PTH is steadily increasing, we should be treating that with those vitamin D analogs.

>> Well, patients with chronic kidney disease are also at risk for some infections. What are your recommendations regarding vaccinations?

>> Yes, so this the population of CKD patients they're obviously at high risk for infection, and they actually don't always have a robust response to immunizations as well. In general, we do recommend typically adult recommended vaccinations, but in addition to that, the pneumococcal vaccine, influenza, and lastly, the Hepatitis B series.

It's a bit unclear as to when to start the Hepatitis B series, but Hepatitis B is still a concern in dialysis units. So we generally make sure that our patients are immunized, at least in stage four or five chronic kidney disease.

>> The SGLT2 inhibitors are a new class of drugs for many of our physicians who are viewing, and I think a lot of us are not as familiar with them as they are some of the other drugs used in nephrology.

What are some of the common side effects of this class of drugs that we should be on the lookout for?

>> Right, I think one of the most common would be those urogenital infections. So really counseling our patients on this may be a possibility, UTIs, and just kind of giving them that history, especially if they've had prior UTIs or history of Fournier's gangrene, which is pretty rare, but just to be aware of those severe side effects.

>> Do you have a personal preference of which of these drugs you actually start within this category?

>> I don't necessarily, it's mostly, whatever we can get approved. But the SGLT2 inhibitors across the board have been shown to be beneficial in chronic kidney disease, so I don't necessarily have a preference.

>> When it comes to the RAS inhibitors, we have our choice between the ACE inhibitors and the ARBs. And as a pulmonologist, for me it was always easy cuz I would get patients coming in with a chronic cough, they'd be on lisinopril. So I would change them to losartan.

Do you have a preference between ACE inhibitors versus an ARB in initial choice of drug?

>> I generally start ACE inhibitors first, and if not well tolerated, I switch to ARBs, but that's generally my practice. I don't know that there's necessarily a rhyme or reason to that but that's my general practice.

>> Is one ACE inhibitor better than another?

>> Not necessarily.

>> The last question is in patients with declining renal function, I think often many of us want to order some kind of a test to evaluate it. What's the indication for doing an ultrasound of the urinary tract system in patients with declining renal function?

>> Every patient should have a renal ultrasound. Anytime I get a consult for chronic kidney disease, I ensure to get a renal ultrasound to make sure that we're not missing any urinary tract abnormalities. And it's also helpful because if we see the features of the cortex is thin or there's increased echogenicity, we know that there is some chronic component to the CKD and this is not just a case of acute kidney injury.

>> Well, thanks, Rima. We're gonna finish up with a final key point about chronic kidney disease, Rima?

>> Thank you. What I'd like to us to all take away from today is if we're using medication management for chronic kidney disease, delaying chronic kidney disease. I'd like us to utilize the three pronged approach and, of course, starting all of our patients on RAS inhibitors, SGLT2 inhibitors and mineralocorticoid receptor antagonists.

>> Rima, thanks again for joining us today. And for all of you viewing, don't forget that you can get American Board of Internal Medicine Maintenance certification points for viewing Mednet, and then taking the post-test questions following the webcast. And joining me next week will be gynecologic reconstructive surgeon Dr. Lisa Hickman to discuss postpartum pelvic floor dysfunction.

We'll see you then.