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Case-Based Learning and Future Directions

Dr. Lam:
So here's our case discussion, a 73-year-old female with long-standing type 2 diabetes, obesity, proteinuria, and hyperlipidemia. This is the physical exam. Blood pressure is 110/60, heart rate 67, BMI 37, and current meds: rosuvastatin, metformin, furosemide, carvedilol, and losartan.

So, I think, a pretty familiar patient to us, I think. And if you don't mind me asking, therefore, Dr. Vaduganathan, you seem to be ready to hop on now. So are we going to go straight into management? Do we need more information? How do you approach a patient like that?

Dr. Vaduganathan:
So I fully agree. This is a very common patient we see in clinical practice. Often, a patient that is otherwise feeling well, may even be asymptomatic and may present to your practice, and we review their medications, we review their blood pressure and say most of the risk factors seem reasonable, see you in 6 months, or see you in a year. However, underlying this normal blood pressure, normal heart rate, some medications that are cardioprotective, is this large unmet risk that is unattenuated. She has presence of albuminuric kidney disease. She has type 2 diabetes. And that combination has been shown to dramatically increase cardiovascular events. And many of these patients, even at the age of 70, who have lived their lives, may experience important kidney events such as developing substantial declines of their kidney function or even going on and requiring dialysis. So I think this is an early opportunity to halt the train of inertia and start therapies that we know are evidence based for patients with type 2 diabetes and chronic kidney disease.

Dr. Lam:
Yeah, if I may, Dr. Floege, I mean, we're cardiologists here, and from the nephrology point of view, is this also a common patient? And do you see things any different?

Dr. Floege:
So, very clearly, it's a common patient, even though a BMI of 37 is somewhat unusual in Germany; it would be more likely 30. But what I'm really missing here is GFR. What is estimated GFR? And how was it measured? We're coming to the problem of determining GFR based on muscle mass. We have no idea what this 73-year-old female is doing. If she's sedentary, she may not have muscle mass. I would love to know a cystatin-based GFR measurement.

Dr. Lam:
This is so humbling. You see, it's very, very interesting. That's not the first question that came to my mind, either. But you are so right that we certainly need more information, I think, to adequately characterize this patient. And so if you don't mind, this KDIGO map, could you break it down for us simple cardiologists, Dr. Floege?

Dr. Floege:
Well, she's stage yellow here, which doesn't look that bad, but the risk is already increasing quite significantly. And as I said, look at this creatinine; it's a pediatric creatinine in a 73-year-old lady. I would love to see her eGFR based on a cystatin C. It's not that expensive. And you're often very surprised how much difference you see when you estimate GFR based on creatinine as opposed to cystatin. Cystatin isn't free of problems, but it's clearly not related to muscle mass. But what is certain is she has quite an elevated uACR, which

places her in a significant risk category. And sort of confirmatory is her BNP. I was struck by the low blood pressure of this lady. Normally, as a diabetic 73-year-old, she should have a highish blood pressure even though she's on medication. I agree. But the medication was not that intense. I agree.

Dr. Vaduganathan:
And to have a NT-proBNP level of 320 pg/mL despite a BMI of 37 should strike you. And that really does suggest underlying risk. As you know, adiposity expresses adipose tissue, adipose cells express neprilysin, and so circulating levels of natriuretic peptides are cleaved in the periphery. And so natriuretic peptide levels are constitutively low in patients who are obese. So here, we would have expected normal or even low level of natriuretic peptides. This really does suggest that there is underlying cardiovascular risk, especially for subclinical heart failure.

Dr. Lam:
You know, I love this, because I can pit the 2 gentlemen against themselves. Because if I were to ask you, Dr. Floege, I mean, like, why can't we say the NT-proBNP is from the kidneys? Her GFR isn't that –

Dr. Floege:
Well, the GFR is, formally speaking, it's still highish for a 73-year-old. By the way, even if you simply adjust for her age – see, she's 73, so most of us will see a loss of a mil per minute in GFR starting at the age of 40, so I'm way downhill already. I would have expected a GFR around 70 to be age adequate. So this really makes me wonder whether the estimation is adequate.

Dr. Lam:
I see. I see. And Muthu is, of course, just going, "Oh, mine must be pediatric then, and I'm starting to worry." But there you go.

So, Muthu, if you could give us also – so the NT-proBNP, you immediately said, yeah, I notice the obesity. But what numbers do you keep in your mind when you sort of assess, especially that impacts what you're thinking about, is this CKM? Is there subclinical? What stage is this? Do you use the NT-proBNP? Do you use something else to think about is there subclinical disease already?

Dr. Vaduganathan:
So I think NT-proBNP is a very useful clinical marker and, like all markers, should be interpreted in the context of the patient and the clinical risk factors. For instance, we know that certain factors increase levels of natriuretic peptides, like age and poor kidney function, but many things may reduce the levels of natriuretic peptides, at least taken at the population level, for instance, obesity or Black race. And so when estimating natriuretic peptides and measuring it in an individual patient, we have to integrate all those factors. But in general, I think, as a population-level strategy and one that we can share with our own colleagues, single thresholds can be useful. And an NT-proBNP above 125 pg/mL does identify patients at high risk for progression to symptomatic heart failure. And that cutoff is embraced, that single cutoff is embraced in the universal definition of heart failure in identifying those with so-called preclinical heart failure, or stage B. So that would be the cutoff, in my mind, that would say perhaps something is going on. I think it does deserve a thorough history and physical for subclinical or clinical signs of congestion.

Dr. Lam:
Now that's brilliant, and it also helps to answer one of these questions, or rather brings on one of the questions. Thank you for the audience who wrote that. What about echo, symptoms and signs, physical activity? And that's what you were saying about a more in-depth evaluation of could she possible have subclinical or mild, already, clinical disease.

Yes? Dr. Floege, were you about to add something? Yes?

Dr. Floege:
No, no. It's basic rule number 23, which I teach to all my medical students. If you measure a creatinine, you have to look at your patient. And I guess the same is true for the BNP here. If you find edema in this patient, if she's short of breath, then you have your diagnosis.

Dr. Vaduganathan:
I have far fewer rules than 23.

Dr. Lam:
Fabulous. So how would we manage her? First, let's assume she got started on an SGLT2 inhibitor, 2 weeks later develops a urinary tract infection which is treated, and 4 weeks later develops a genital mycotic infection which is treated, and she discontinues her medication. So, first, common scenario or not? And how would you manage?

Dr. Floege:
Well, it's common. UTIs are common in this type of patient anyway. Whether this is related or not is uncertain. Actually, the discussion is still not really resolved whether the gliflozins do cause an increase in UTI. But certainly, the genital mycotic infection is very suggestive

of an adverse event. And yes, it happens. Most of the patients do continue the medication, but I've seen this happen, so it's unfortunate. I would have loved to see her on empagliflozin or dapagliflozin, but if she doesn't want to take it, c'est la vie.

Dr. Lam:
Excellent. Excellent point about UTI versus genital mycotic infection. Now, for those of us who didn't really catch that, there is a difference. We do not or we're not sure about the additional risk of urosepsis or UTI per se. We're very sure of the increased risk of genital mycotic infections, and they are different things for an SGLT2 inhibitor.

Muthu, could you tell us, perhaps, a little bit about the data behind why are we so enthusiastic about the SGLT2 inhibitor in such a patient?

Dr. Vaduganathan:
Yeah, so SGLT2 inhibitors have been studied in exactly this patient profile of type 2 diabetes with concomitant chronic kidney disease, as evidenced by her proteinuria. This has been studied in multiple randomized clinical trials with multiple different SGLT2 inhibitors, including the CREDENCE trial, the DAPA-CKD trial, the EMPA-KIDNEY trial, and the SCORED trial. And each of the 4 showed a delay or slowing in kidney disease progression. But for us as cardiologists, even in that patient with CKD type 2 diabetes, you may be wondering, well, why are they seeing me as a cardiologist? That is an opportunity to reduce cardiovascular events, and some of these trials even demonstrated a reduction in cardiovascular death or even all-cause mortality.

So CKD has not traditionally been one of the check marks that we move through when we assess a patient like her, like blood pressure, like lipid management, but CKD should be, because it is as much, if not more, important of a prognosticator of future outcomes.

Dr. Lam:
Nice. And if I could, Dr. Floege, that was a very nice question here from Dr. Bongarts. With increased uACR, would you advise a 24-hour urinalysis, with the added benefit of getting a more accurate GFR and some insight into natriuresis? And if that answer is yes, at which level of uACR would you start to do a 24-hour urinalysis?

Dr. Floege:
Very good point. The tricky issue is that in a 73-year-old lady who is that obese, it's not trivial, collecting 24-hour urines. Currently, we believe the gold standard would be an attempted 24-hour collection and then determine a uACR in that specimen. Thereby you eliminate sampling errors, because it's not relevant whether this is a complete collection or not. But in real life, a spot check will be reasonably reliable as long as she is outside of a UTI. That is a confounder that we have to take into account, of course. So if you find a high albuminuria, do repeat it and do confirm it and be certain that she has no UTI.

Dr. Lam:
Interesting. Great. We're learning all the time. Thank you very much.

But, Muthu, is there any other medications you would start and consider in this lady? And based on what evidence?

Dr. Vaduganathan:
Yeah, so I think that there are additional pillars that we can certainly consider. So the GLP-1 receptor agonists have been shown to be beneficial in this population, specifically studied in the FLOW trial. The FLOW trial was a large trial of patients with chronic kidney disease and type 2 diabetes. This was with low-dose semaglutide. And while there was only modest weight reduction in this trial, there was outsized benefits on cardiovascular events, kidney events, and mortality outcomes. So GLP-1 receptor agonists certainly not only can help with her weight management but can also help reduce her risk. Similarly, the nonsteroidal MRA finerenone has been studied in populations like herself in these trials of the FIDELITY program and, again, has been shown to reduce risk. So these are additional therapeutic options, even beyond an SGLT2 inhibitor, and should be added to her losartan, which still remains foundational.

Dr. Lam:
Thank you. Do I see any difference of opinion here, Dr. Floege?

Dr. Floege:
Nope. No, absolutely no. It's a pity she is not on an SGLT2 inhibitor, because that would mitigate the risk, for example, for acute kidney injury in this patient. The surprising thing in the landmark trials with SGLT2 inhibitors were that if you give them in a CKD patient with heart failure, your AKI risk decreases. It decreases by 50%. And that is a super common situation, that you dehydrate these patients, and an SGLT2 inhibitor has a mild diuretic effect, and they go into acute kidney injury. It's a pity she doesn't tolerate that, but such is life, and we have to live with it. So I would do the same in this patient.

Dr. Lam:

Well, if I may, though, I think I would have tried to persist with the SGLT2 inhibitor in this lady. As I said, elderly ladies, we can get a urinary tract infection for other reasons. But with the mycotic infections, I would love to know if she has already been educated on the preventive measures that can be taken, basically genital hygiene, and I would try to persist in it. Would you not?

Dr. Floege:
Yeah, very good. Yeah, sure.

Dr. Lam:
And then, now, here's a very tricky question here, but it's asked quite a few times so I don't want to seem like it's avoiding especially when Dr. Nik Halmey goes, “Hey, Carolyn,” so thank you. I don't know where Nik is. In a resource-limited setting, is it acceptable to use spironolactone instead of finerenone as one of the treatments for this CKM syndrome?

Dr. Vaduganathan:
It's a very important question. Spironolactone, of course, has been around for decades. We all have great familiarity with the use of spironolactone. Spironolactone's use has generally been limited because of its risks of hyperkalemia. Fortunately, we don't have any outcomes trials of spironolactone in patients with CKD. We know spironolactone can reduce levels of albuminuria, but we have no definitive evidence, or actually, no randomized trial has ever been conducted to show that it actually slows kidney disease progression, so we do need to rely on the evidence-based strategy that is with finerenone in this patient population.

But as clinicians, I think we all recognize that there are going to be limits to our own practice because of external factors such as economic or financial restraints of the patient. And as such, I think we need to lean on what we may believe should still be considered true in that same patient population.

And in this case, I think it seems reasonable that spironolactone should provide some degree of kidney disease protection in this population.

That said, my own perspective is, I would prioritize the therapies that are evidence based, are affordable, and that can be implemented first. And then when thinking of some of these substitution options, then we use our best judgment as clinicians.

Dr. Lam:
Dr. Floege?

Dr. Floege:
I will never forget the figure in *The New England Journal* that occurred after the RALES data came out, and that figure showed the massive increase in hospitalizations for hyperkalemia when spironolactone became popular among cardiologists. We don't know the head-to-head comparison between finerenone and spironolactone in terms of hyperkalemia risk, but we do have some data suggesting that it's considerably higher with spironolactone, so you need to watch it. You need to adjust it. And don't forget, if you're in advanced kidney failure, spironolactone can have a half-life of 8 days. So once you have hyperkalemia, you’ll have it for a really long time.

Dr. Lam:
Thank you. Now, could we switch tracks a bit? And a very hot topic is, of course, the obesity. And how would you incorporate, say, data such as SURMOUNT-2 of tirzepatide in type 2 diabetes and obesity? Would we think about that as well? I mean, she has a BMI of 37, and tirzepatide, the combined GLP-1 and GIP dual agonist, has indeed been shown to have very efficacious and safe weight loss in this patient population. What do you think?

Dr. Vaduganathan:
Yeah, we live in a remarkable time in which there has been almost a race to the bottom in terms of weight loss. A number of incretin-based therapies are being tested in various disease populations, whether obesity at large or obesity with certain comorbidities. The only definitive evidence we have that the incretin-based therapies reduce kidney disease progression in a dedicated trial is the FLOW trial with semaglutide. And so my own perspective is I would use semaglutide in a patient like this, because she fits the patient profile of that trial. That said, this field is going to move at a very, very rapid pace. And I think even at ESC 2025, I think we might have a number of different options to combat kidney disease progression.

Dr. Lam:
I absolutely agree with that. And we will not be able to talk about the future or future guidelines in this session, but it is such a hot field that is moving so quickly. And I think this discussion already illustrates how we may have a bit of siloed thinking, because when it comes to initiating the semaglutide or initiating tirzepatide, have we ever seen it as our tasks as cardiologists for weight loss and for obesity? Our tasks as cardiologists or our tasks as nephrologists? Or is that the endocrinologist’s job? Or someone else's job? And I think this really illustrates why thinking about the whole thing as CKM syndrome is really, really trying to get us to manage the patient holistically.

Dr. Floege, you were going to add one last point, I think, and then we're running out of time.

Dr. Floege:
Nope, I totally agree. This is one of the most exciting areas. In FLOW, it was so interesting to see that the benefit from semaglutide was mitigated when you were on an SGLT2 inhibitor, which certainly is much cheaper. So it's a shame this lady is not taking one, but we'll have to see this. As you say, next year, we'll be much smarter and see whether it makes sense.

Dr. Lam:
Wonderful. Well, thank you, everyone. I think this really, really summarizes that we put the patient in the center. It is one patient that has all 3 systems involved in this systemic syndrome. So thank you for learning with us about the CKM syndrome.

Thank you.