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

Shifting Gears in Cardio-Renal-Metabolic Care: Harnessing Evidence-Based Therapies to Optimize Patient Outcomes

Announcer:
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Dr. Gluckman:
We are going to now move into our presentations. You are going to see a recurrent theme here. Anne is going to lead things off and we are going to provide some didactic background information. We are then going to go and actually show a patient case, a video, and then again, encourage all of you posing questions to discuss with your neighbors, who you may know or not know, what are the opportunities that may exist? Are these issues that you are facing in your own clinical practice? Then we will pitch things back to Anne and Steve for their perspective as well.

With that, I am going to turn things over to Anne to kick things off for us.

Dr. Peters:
Again, I am an endocrinologist and I love coming to these meetings because I learn so much because, frankly, it is not what I do every day, although really what I do every day involves cardiology and cardiologists.

The other thing that I did not say to begin with is that, for many years, I have been on and off the committees, both in the US and Europe that writes all the guidelines, and I am currently on the ADA PPC Committee for writing the US guidelines and on the CCA committee in Europe.

I roll my eyes a little bit about guideline-directed care, because I know how we write guidelines, and sometimes we do not really have the evidence that we need to support what all of us know that we do clinically that works for patients.

What I am going to try to do is talk about doing guideline-directed therapy in the setting of real patients, of people that we see, because that is where it really matters the most.

Poll 3

This is polling question number three. It is a simple one. How often do you routinely initiate an SGLT2 inhibitor in patients with cardio-kidney-metabolic conditions?

A. Never;
B. Rarely;
C. Sometimes;
D. Often;
E. Almost always; or

F. Always.

Put in your answers, please.

Interesting. We will talk about this as we go.

CKM Syndrome

The next slide is really to describe this syndrome. We all know what it is basically. Frankly, it is something I see every day in most of the patients I see because most of my patients all have diabetes, many have obesity, CKD, CVD, or at least CVD risk. It is incredibly common and it is becoming more common. There is all this overlap with all these syndromes as we are going to discuss.

Instead of just thinking about glucose, I think about all of these things at every visit. I am really pretty rigorous in my own brain about going through my list about what the patient has and what I am trying to do to reduce their risk for progression or occurrence of any of these other comorbidities.

We also know that obesity is one of the big drivers here, and that all of us have real change in our practice since we have had the incretin hormones available for helping people deal with obesity. It is a different world. It is one that I really like existing in, because I can help patients do a lot more and improve a lot more than I used to be able to.

That being said, there is still no magic bullet and I still really believe in lifestyle. If we are all going to be talking about medication, I think lifestyle matters, exercise matters, the quality and quantity of food people eat matters. We really need to think about that as we see our patients.

Prevalence and Overlap of CKM Conditions in US Adults, 2015-2020

This slide basically looks at the prevalence and overlap of all of these subset conditions and then all of them together in US adults. As I said, so many of these conditions exist in the same person. The best drugs that we use in addition to lifestyle are ones that do more than one thing.

As you can imagine, I am pretty glucose-focused, right? I am a diabetologist. Glucose matters. In case you get lost in some of these guidelines, which I will show you, glucose always matters because it increases the risk for retinopathy, nephropathy and neuropathy. We have all seen people with painful neuropathy that we cannot really treat very well. You would really like to prevent that from maintaining people in the normal glucose range, so they do not end up getting the microvascular complications of diabetes.

These drugs do more than one thing. They lower glucose levels, they reduce cardiovascular risk, they help improve renal function. It is really exciting to me to be practicing medicine now, as opposed to back in the day when I first started training. When I first started training, all we had was insulin, non-analog insulin, and sulfonylurea agents.

I did some of the first trials on metformin that got it approved in the United States. I know I do not look that old, but I am just pointing this out.

Future Prevalence of HF and Adverse CV Conditions

We also know that heart failure rates are increasing. When I started training, we did not think all that much about heart failure. Now, really it is a problem that I see a lot. I also see a lot of atrial fibrillation. I have almost no patients actually die of MIs. In my practice, people really do not get myocardial infarctions. I know you cardiologists see this all the time, but I do not. I have a couple thousand patients that I take care of all by myself. It is amazing to me how well we are doing with cardiovascular risk modification if you do it appropriately.

CKM Syndrome: Burden and Care Fragmentation

We also know that all of this increases the risk for our patients doing poorly. It is not just not dying. What we want to do is prevent hospitalizations. These newer therapies help us reduce the risk for heart failure hospitalizations and obviously death.

The very first time I gave a patient empagliflozin and I was all excited about it. I had just come back from the EMPA-REG trial. I had been in Sweden where it was first discussed and the results came out. A patient said to me and I was so excited, this drug is going to lower your sugar and it is going to lower your risk of cardiovascular events and help your kidneys. He said, “How will I know if it is working?”

I said, “You would not be dead. It is a 30% reduction in overall mortality.” He looked at me like I was insane. I possibly am. But it was true. I know in the back of my head that I am using these drugs and reducing the risk for overall mortality, and that is really huge.

Obviously, people do not really notice it because they are alive. But we all want to live a long and healthy life and be active. So it is important to think of what we are really doing. Then obviously, treating obesity is a very helpful tool that we now have in our toolkit to help people avoid developing some of these comorbidities.

One of the problems, though, is that care ends up fragmented. I spend about half my time working in the LA County healthcare system for under-resourced patients. Care is very fragmented there. We have a lot of resource issues. Recently, we are having to roll back use of certain medications because we no longer have the funding we once did. There is a lot that is going on in my patient population in East Los Angeles that breaks my heart.

We do the best that we can. But even on my West Side practice, which is my practice, it is more affluent, I do not feel like I communicate as well with other specialists as I ought to.

Now I am at USC, but almost all the people I work with are at UCLA or Cedars. Even we have Cerner and they have Epic. It makes it even hard for me to communicate in terms of just looking at the EHR.

Sometimes I will see a patient and I will want them to be on an SGLT2 inhibitor, but their eGFR is less than 45. Then it becomes not my drug, right? Because if the eGFR is less than 45, it is not affecting glucose. It is affecting kidney function, it is affecting reducing risk of heart failure. Then it is in the purview of the nephrologist or the cardiologist.

Then that is not right on my part if I say this is not my drug because glucose is not impacted if the eGFR is too low, but it becomes this dance I feel sometimes among specialists about what medications people should be on. It is the more we can communicate with each other and decide who needs what when, the better off we will do.

Then obviously our patients have a lot of medicine they have to take. It is important to really be clear, and you will learn about this or talk about this as we go through this, about how to get patients to really understand what they are taking and why.

SGLT2 Inhibitor Underuse in Patients With HF With or Without Diabetes

Now, SGLT2 inhibitors are underused in patients with heart failure with or without diabetes. Now, these figures actually really surprise me because I think SGLT2 inhibitors are really easy to use because they are a pill, they are once a day. Yes, they have side effects, but they are pretty simple.

It turns out that we do not use them nearly enough. In patients with heart failure who really should be on these drugs, SGLT2 inhibitors were prescribed to about 12% of people with diabetes and only 3.1% without diabetes. That is just way too low. These drugs work, and they should be given to more and more patients. I do not quite know how to get people to use them more, but it is important that we think about this as we are helping advise others treat their patients.

SGLT2 Inhibitor Use for HF in US Ambulatory Setting

This looks at SGLT2 inhibitor use in heart failure in US ambulatory setting. This is a huge retrospective cohort study of over 700,000 people with heart failure. Again, you can see really low rates of people on SGLT2 inhibitors who really should be on them. This should be close to 80% for sure, maybe 100%. But there is always a reason not to be on one of these medicines.

Underuse of GDMT: It Is not Only SGLT2 Inhibitors and HF!

Now I am going to talk about some of the whys for the underuse of these drugs. I do not know that this is any different than some of the whys than any drugs are underused. Partly, it is cost. These are more expensive drugs. It is sometimes a challenge to get people to take them because they simply cannot afford them.

Sometimes it is newness. People do not like drugs that they think are new and have not been well tested. Sometimes it is a fear of side effects. I am going to talk about those in a minute because that that is a real concern here.

Then there is clinical inertia. I do not use the word clinical inertia. I say that I am thinking because I often spend time with the patient thinking about what is the best choice and going with the patient through the options until I actually get to using a drug.

Use of Glucose-Lowering Therapies in T2D Care

That leads me to this, which is our current algorithm for treating people with diabetes. I can criticize this is all I want because I helped build this algorithm.

I want to point out that on the left-hand side of this algorithm basically looks at cardiovascular and kidney risk reduction. Now, personally, that should be across the top of the whole thing because we are always interested in that.

Let us just say you are looking at the left and you are looking at people who have atherosclerotic cardiovascular disease, who are at high risk for it, who have heart failure and who have CKD. All of those people should be on an SGLT2 inhibitor and/or an incretin hormone and/or both, depending on the setting. Then we go through that algorithm.

On the right-hand side, we basically talk about treatment of obesity and hyperglycemia. Now let us just marginalized that little area. We talk about treating weight by using the drugs that are most effective that really is not all that much in terms of guidance. Then we talk about treating glucose levels in diabetes, and we basically give almost no guidance. We say, "Well, you can use metformin and then use whatever else you think is best for the next step." That is hard, because a lot of times it is hard to know the best step. The best step does depend on the environment in which you are practicing and the costs that are incurred from each step.

We all know the drugs that we think would be the next best step for most people and we really want people to individualize how they do that in terms of treating glucose.

Factors Contributing to Clinical Inertia

Now, these are the factors contributing to clinical inertia. I am not going to read all of them to you. They are obviously institutional ones that have to do with cost and how medications are provided to patients. I really think that the interface between patient and provider is really vital, and it is important to know the patient and know the side effects.

In many of these medicines, the SGLT2 inhibitors in particular, you are going to cause potentially a side effect that is an increase in urination that may be quite noticeable to a patient and annoying, but may actually be something worth putting up with until people get adjusted to being on the drug.

I have seen all the side-effects you can think of the SGLT2 inhibitors. I was the person who actually first reported the cases of DKA in patients with type 1 and type 2 diabetes on these drugs. But short of putting people with type 1 diabetes on SGLT2 inhibitors, you really are pretty safe with these.

I am just going to tell you one short personal story, is that my husband who does not mind that I speak about him, has type 2 diabetes. He is 81 years old and he is really stubborn. I have him. Of course, I am not really his doctor, but how it goes. He is on metformin, semaglutide and empagliflozin.

On empagliflozin, that man has more polyuria and nocturia than you can imagine. My entire life seems to me to be about finding the next bathroom. I am not kidding. It is really noticeable. If he has ever gone off the empagliflozin for a week, he goes back to some normal pattern of urination.

Now, it does not help that he drinks non-stop Coke Zero and he loves candy. Every time a sugar goes up, he pees out sugar and he is drinking all this soda, and I get really mad at him, but I try to hold my anger in because I want to keep married to him. But any way, I live with this, and yet it is worth everything to me to have him on empagliflozin. So we put up with it. We are not ending our marriage. I have learned how to shut up.

I am just pointing out that I live this, and I know how important it is for him to be on the SGLT2 inhibitor.

Clinical Inertia and Implementation Delay

These are some of the ways to try to get around all of this. It is really just individualized care. There may be patients where it really is not something you want to do. I really do not want to leave anybody without the right medications. Sometimes I forget to start the SGLT2 inhibitor because the cardiologist is doing it or the nephrologist is doing it.

Again, look at your medication list and be sure that they are on the right medications that are going to really help deal with all of these conditions in an appropriate way.

GDMT in HF Among Hospitalized Patients Who Are Frail

In heart failure patients who are frail, again, these patients do benefit. You just have to have some sense of where a patient is. In these settings, I do a lot about nutrition. I do a lot with physical therapy. I do a lot to think about the whole person and really helping them be healthy. These medications fit as part of that.

Primary HCP-Reported Reason for Not Initiating GDMT in Patients With HF

This is the reasons for not initiating the guideline-directed therapy. It basically is pretty much the same for all these agents. They again call some of the inertia they say here, which I like, is that they say that the patient is clinically stable. When I get the glucose level down to a normal range, the A1c is 5.6, I may not think about bumping up the medication that might lower the glucose level further, but it

actually might have additional benefit in terms of this cardio-renal impact. So I may not do this sometimes.

Unintended Harms of "First, Do No Harm"

I have to always try to be aware of what I may or may not do. We did obviously not hurt our patients, but we could also benefit them if we think more holistically about all of what they are taking.

Patient Barriers in CKM Syndrome Management

This just looks at some of the barriers that we discussed before. I have seen so many barriers in all sorts of ways, particularly in my under-resourced population, to getting adequate medical care. Again, it just breaks my heart sometimes what people cannot access, because people who can access care can do so much better.

Consequences of GDMT Underuse

We are going to move, because I do not want to run out of time, to our first case.

Who Should "Own" the Prescribing of SGLT2 Inhibitors?

This is just who should own the prescribing. I mentioned this earlier. We all own prescribing of SGLT2 inhibitors. Each of us needs to make sure that the other is doing the right thing and the patients are getting prescribed the medications they need.

Pit Stop 1: Joe, a 66-Yr-old Male, Has a Story to Tell!

Then that brings us to Joe. Joe is an AI-generated patient, and he is unusual. He has this voice that will go through this whole thing. Listen to his words because his words are very much the way patients actually think about all this in terms of what they have been through.

Here is Joe.

Joe:
Thank you for letting me speak today. I am not a doctor. I am just someone who has been living with lots of health problems for a long time. I am 66 years old. I have type 2 diabetes, kidney disease and heart failure. I have also had high blood pressure most of my adult life, and I am overweight. I know those risk factors did not come out of nowhere. I worked long hours, did not exercise much, and I did not always understand how serious my conditions were until things started piling up.

I see a lot of doctors. My cardiologist manages my heart failure. My primary care doctor handles my diabetes, and I have seen a kidney specialist a few times. Most visits feel rushed. We focus on numbers, my A1C, my creatinine, my blood pressure, and on adjusting the medicines I have already been taking for years.

No one ever really talked to me about medications that protect more than one organ at the same time. I was not offered an SGLT2 inhibitor until recently. Honestly, I did not even know what that was. Looking back, I think there were a few reasons. My kidney function was not great and there was concern it might get worse. I was already on diuretics and I was told to watch out for dehydration.

I also complained a lot about having to pee a lot, so maybe people did not want to make that worse. From my side, I was hesitant, too. I did not want another pill. I had had a genital infection once before and did not want to repeat that. No one explained clearly how the medication could help my heart and kidneys, even if my blood sugar was not that bad.

Then I ended up back in the hospital with fluid overload. That is when someone finally sat down and explained the bigger picture that this medication was not just for diabetes, and that starting it earlier might have helped prevent what I was going through.

I guess what I want you to hear is this. Sometimes we do not say no. We just do not get asked or we do not understand the question.

Dr. Gluckman:
Anne, I want to thank you for a great presentation. We are now going to actually move into an interactive. I am going to ask Anne and Steve to move down in the audience overall.

Pit Stop 1: Joe, a 66-Yr-old Male, Has a Story to Tell!

These are some of the questions for us to entertain. At your tables, our ask of all of you is:

- To discuss this story;
- Do you see patients like Joe in your clinic; Is it common or is it infrequent;
- What went well thus far with Joe's care; and

- Where did we miss the mark, and are there opportunities.

We are not going to ask you to do this for long, but for a couple of minutes, just discuss with your neighbors, with your colleagues, any of these questions at the bottom. What could have been done better overall?

I am going to ask Steve and Anne just to report back one or two things that they may have heard from the tables as it relates to this. Please talk amongst yourselves.

For those of you that are online, I will tell you that I see patients like this relatively frequently. As we think about opportunities for improving the care for our patients, are we doing everything that we can for someone like Joe? More importantly, are we doing everything we can as quickly as we otherwise can?

Now, as Joe outlined relatively well in his own story, this is an individual who had multiple cardio-metabolic-renal risk factors. Ultimately, at the end of the day, it felt like Joe's care was fragmented because different clinicians were tackling different aspects of Joe's care. Maybe it was not until ultimately that Joe got so bad as to land in the hospital that someone needed to think about intensifying his treatment.

I would just ask you for a moment to reflect on what you, in fact, may see in a patient like Joe, where there are the opportunities, where ultimately the care was correct but could have been sped up and maybe prevented a hospitalization worsening of renal function, improvement in their overall cardiovascular, renal and metabolic picture overall?

For those that are online, we are going to just give this about another 30 seconds. Then we will bring it back with input from our experts in the room here today.

I have already let our online audience know that we got about 30 seconds left. We will have Steve and Anne report out here in about 30 seconds just to give some feedback about this case, Joe.

Steve, I apologize, but I know we could be talking for quite a while about this case. Any clear takeaways about things that you heard from the tables around you?

Dr. Greene:
Yes, Ty. A couple key things. One, I was talking to some people that work primarily in the hospital and they said it really resonated with them how they have people that come in for heart failure or worsening heart failure and were not on an SGLT2 inhibitor. One of the first things they think about is, man, maybe this could have been prevented if we had started the SGLT2 inhibitor in clinic a few weeks ago.

They also highlighted how in-hospital initiation seems like a really great time to start these therapies because again, the patient is like a captive audience. Honestly, maybe we have more time in the hospital. Starting the medicine in the hospital seems to really resonate with patients, like just like our patient case here.

Dr. Gluckman:
Yes. For everybody, we are going to welcome Steve's input about this as it relates to this. It sounds like ultimately the right thing was done. This really could have been done much earlier.

Dr. Greene:
Exactly. A delay.

Dr. Gluckman:
The delay. Okay. Anne, any key takeaways from your perspective as well?

Dr. Peters:
Yes, we talked about health literacy and that we had not really addressed that with this person, Joe, because we had not really understood how much he actually does understand. In this, he seemed to understand a lot. Maybe we failed to teach him earlier about really what he needed to know, and we needed to better assess how he would learn. Then we talked about the problems when in our own practices, we do not have the time to follow up on the blood pressure or follow up on the potassium levels or do that job when we keep punting it to someone else and I am always giving it, “Here, talk to your primary care provider”, but then it does not get done either because nobody had the time. So it is hard to find the time to do a lot of the follow-up that we need in these patients.

Dr. Gluckman:
I love the themes, not because they are good themes, but at least we are calling out some identifiable problems or opportunities is a better way to frame it earlier and more timely initiation of therapy, recognizing the importance of education, literacy that may be important in this patient population that we are all seen on a regular basis with cardiovascular-renal-metabolic syndrome or disease

overall.

It speaks, Anne, a little bit to the fragmentation issue. He even identified the fact that he gets his care from his cardiologist. He gets his care from his primary care clinician. How well are those two communicating overall? I know we are not going to solve all of the problems this evening, but at least highlighting themes that maybe in your own practice you can take back overall.

With that, we are going to move into the next phase. I am going to welcome both of our experts back up on the stage. Steve, I know you are going to be taking us through this next portion. You are going to see a theme for those of you in the room. For those of you that are online, we will visit this with another case after Steve has done. We will break out into the individual group sessions as well, and we will revisit this two more times with Steve's section and then my section as well.

Steve, I will pass things to you.

Shifting Into Gear: Optimizing GDMT in CKM Care With SGLT2 Inhibitors

Dr. Greene:
Thank you, Ty. Shifting Into Gear: Optimizing GDMT and CKM Care With SGLT2 Inhibitors.

Poll 4

Here is our next poll question. Which of the following patients would not be an appropriate candidate for initiation of an SGLT2 inhibitor? You can select more than one.

A. A patient with HFrEF and type 2 diabetes that is stable on GDMT;
B. A patient with HFpEF without diabetes and an eGFR of 45;
C. A patient with CKD and albuminuria, eGFR of 30;
D. A patient with a history of recurrent diabetic ketoacidosis in type 1 diabetes; or
E. A patient with HFrEF and well-controlled blood pressure.

Which would not be an appropriate candidate?

People have spoken. Thanks for voting.

2022 HF Guidelines: 4 Pillars of GDMT for HFrEF

To get into it, I am going to start focusing on heart failure. I am a heart failure cardiologist. Back in 2022, we had the most recent publication of the US Heart Failure Guidelines. Really front and center of these guidelines was the addition of the fourth pillar for HFrEF. This was, of course, the SGLT2 inhibitor. It got a Class I level of evidence A recommendation that for patients with HFrEF, we need to start these therapies to reduce heart failure hospitalization risk and also cardiovascular mortality.

SGLT2 Inhibitors in HFrEF: DAPA-HF/EMPEROR-Reduced

You ask, “Well, Class I level of evidence A recommendation is a really strong recommendation. What is it based on?” It is based on overwhelmingly strong clinical trial evidence. There is two key landmark trials in HFrEF with SGLT2 inhibitors:

- The DAPA-HF trial with dapagliflozin; and
- EMPEROR-Reduced with empagliflozin.

Again, you see a meta-analysis here. Look at the endpoints we are talking about.

For one, we are talking about the endpoint of all endpoints, all-cause death. SGLT2 inhibitors reduce the risk of all-cause mortality by about 13%. 14% reduction in cardiovascular death, 26% relative risk reduction in the composite of CV death or heart failure hospitalization. They reduced the risk of heart failure hospitalization by over 30%. Again, it is not just that these drugs work in HFrEF. They work really well, huge magnitude of benefit, including for all-cause mortality.

What About Heart Failure With an Ejection Fraction >40%?

Okay, but that is HFrEF. What about heart failure with ejection fractions above 40%? So heart failure with mildly reduced or preserved ejection fraction.

SGLT2 Inhibitors: Cornerstone of HFpEF Treatment

For so long in HFpEF, we had struggled without any disease-modifying definitively proven therapy. That was always so troubling to me

because more than half of our heart failure patients actually have ejection fractions above 40%. We for so long, yes, we were celebrating all our pillars in HFrEF and whatnot. That is only less than half of all patients with heart failure. For the majority of patients with heart failure, we had nothing definitively proven to help them.

That all changed with SGLT2 inhibitors. Now we have updated guidance, like here is an expert consensus statement from the ACC. You see when we think about our HFpEF treatment algorithm, at the very top of the algorithm is SGLT2 inhibitors. They have very strong language about SGLT2 inhibitors in HFpEF such that barring contraindication, all patients with HFpEF should be treated with an SGLT2 inhibitor to reduce CV death or heart failure hospitalization and improve health status. Again, at the top of the mountain, when we think about our HFpEF therapy.

EMPEROR-Preserved: Outcomes

This was very well justified being at the top of the mountain, because again we have our first definitively positive trials in HFpEF. After trying for so long, all these various drugs that had worked in HFrEF, we try them in HFpEF. Close, but no cigar sometimes or not even close in some ways.

Here we have EMPEROR-Preserved. Again, the first definitively positive trial. Over 6,000 patients with heart failure with an ejection fraction above 40% with or without diabetes. An overwhelmingly positive clinical trial for the primary endpoint of CV death or heart failure hospitalization, 21% relative risk reduction.

Total heart failure hospitalizations reduced that by 29%. It also was good on the kidney too. Slowed progression of kidney disease, something else that is very convenient when we think about our HFpEF multimorbid patient population.

Meta-analysis: DELIVER and EMPEROR-Preserved

About a year or so after EMPEROR-Preserved came out, we have the second trial with dapagliflozin in HFpEF. This was called DELIVER. Again, you see a mirror image in terms of the endpoint results. Again, consistent benefit on hard clinical outcomes. There is no doubt about it these drugs work and are disease-modifying in our HFpEF patient population.

What Else Should I Know About SGLT2 Inhibitors?

Okay. That is the high level clinical trial data for HFrEF and HFpEF. Many of you in the audience have likely heard of those trials before and know the results. What else should we know about SGLT2 inhibitors that are relevant for our clinical practice?

Key Point

The first key point I want to highlight is that it is not just that these drugs work, but they work quickly. There is clinically and statistically significant benefits with SGLT2 inhibitors appearing early after treatment initiation.

Clinical Benefit Within Days of Initiation

Just as a case example here, you see data from EMPEROR-Reduced. Remember this was empagliflozin in HFrEF. You see it does not take months or years on these drugs for clinical benefits to show up. You see very early separation of event curves such that you can easily see even if you delay initiation, even a couple of weeks, that is needless exposure to excess clinical risk.

Here in EMPEROR-Reduced, you have statistically significant benefit within 12 days of starting the drug. Again, something to keep in mind when you are thinking about, “Oh, maybe I will do it next visit.” Do you really have time to wait when we are talking about the risk inherent to the heart failure population?

Rapid Functional Status Improvement Within Weeks

When we talk about early benefits, not just the hard clinical outcomes, yes, that is very important. The patients also feel and function better with SGLT2 inhibitors, and they feel and function better quickly.

Here data from EMPEROR-Reduced again, showing the NYHA class, the clinician assessment of how the patient is functioning. Goes in completely different directions, whether the patient gets empagliflozin versus placebo. It goes in completely different directions at four weeks and stays in that direction thereafter.

Again, quick benefits on NYHA class.

Rapid and Sustained Improvement in Patient-Reported Symptoms Within Days

That is the clinician assessment, the NYHA class. What about the patients reporting outcomes themselves and how they are feeling?

Again, we see the same theme. These are data from the EMPULSE trial. This is in-hospital initiation of empagliflozin versus placebo. We see here the KCCQ, which is our standard patient reported quality of life measure in heart failure. Again, within 15 days, you see a large magnitude of difference in how patients have reporting their quality of life, again within 15 days early and sustained improvement in how patients feel.

SGLT2 Inhibitors Are Recommended in CKM Syndrome

When you talk about all these early benefits, you talk about the magnitude of benefit. We have talked about the heart failure data so far. Specifically, it is no surprise that you see SGLT2 inhibitors really front and center in our long list of heart failure guidelines, expert consensus documents.

SGLT2 Inhibitors Are Recommended in CKM Syndrome

The great thing about SGLT2 inhibitor, aside from just the efficacy, is also, I think of it as like almost the great unifier. We talk about all these different silos of specialists that we maybe 10 or 15 years ago were talking about, but now we are all under one tent. The diabetologist, the chronic kidney disease folks, the heart failure doctors, we are all talking together. Within all our guidelines, a unifying theme, SGLT2 inhibitors are more or less front and center.

Traditional Serial vs Selective Approach to GDMT

When we talk about SGLT2 inhibitors, a lot of times for HFrEF, this was the founding father of this pillar of therapy approach. Now we see pillars discussed in the other elements of CKM. Whenever you have multiple therapies to choose from, a common question is, well, which one goes first? Which one goes second? How do you sequence these therapies?

In HFrEF, we have had these four pillars now for a few years. A lot of us, historically have been thinking like this on this slide where you start, one, wait a few weeks, uptitrate the dose; you start the second one, wait a few weeks, make sure it is tolerated; start the third; start the fourth. SGLT2 inhibitors came out last, so a lot of times we go by the historical discovery of these different agents.

When you actually just simply do the math on this, it could take 28 to 56 weeks if you follow this approach before GDMT is fully implemented at the maximally tolerated or target dose. Then at multiple points in this long, circuitous pathway, you have multiple things that get in your way of success potentially.

You have like patient misses a clinic visit, it derails your whole titration plans. They get in the hospital and they stop medicines and whatnot. Or you are just in a rush in the clinic, you are behind, you are late. You are just like, “Okay, patient is feeling fine today. They are not complaining. Let us talk about the medicine change next visit.”

Needless to say, while we are doing this long, circuitous pathway with GDMT, the patient is needlessly exposed to excess risk of dying and going to the hospital the entire time.

4 Pillars of GDMT for HFrEF

To overcome what I would call an overwhelming culture of clinical inertia, myself and colleagues, back in 2021, we proposed the concept of simultaneous or rapid sequence initiation of quadruple medical therapy for HFrEF. The key concept would be to start all four mortality reducing drugs without delay on day one or in rapid sequence within a maximum of one week. The concept would be to prioritize the low doses, the sprinkle effect.

Then once you achieve a sprinkle, that is priority number one, then you focus on uptitration of the therapies over the coming days to weeks.

3 Pillars of GDMT for HFpEF and HFrEF

Now we are in the age of with HFpEF, we also now, I would argue, have pillars. We go from nothing now to multiple therapies definitively proven to either:

A. Improve heart outcomes; or
B. Improve quality of life.

Some therapies like SGLT2 inhibitors, I would argue, do both of those.

Needless to say, we cannot fall into the trap of repeating the mistakes we made in HFrEF, where we had multiple therapies. What did we do? We take our time slow and steady. Now in HFpEF, we have multiple therapies. Again, I will strongly advocate for rapid sequence or simultaneous initiation of these therapies without delay.

Addressing Hesitation: Starting Multiple Therapies at Once Increases Intolerance Risk, Right?

Then whenever I talk about, “Well, Steve, do you want us to start multiple medicines quickly in rapid sequence?” Like, how are people going to tolerate that? Would not it increase the risk of intolerance?

I will kindly push back and say, first, there is no objective evidence that starting more than one medication at the same time increases risk of intolerance. That is a theoretical thought. When you look at the evidence, there is no good evidence of that.

We do this all the time. When we talk about hypertension, we use combination medicines. Acute MI, we have a hospitalization where we will start dual antiplatelet therapy, cholesterol medicine, RAS inhibitors, beta blockers, all within a couple day hospitalization. Yet those patients, on average are even lower risk than our heart failure patients. If we are going to treat them with urgency, we certainly need to treat our patients with urgency.

A couple comments that I will say just for context, when we are thinking about starting more than one medicine at the same time or in rapid sequence.

I am not talking about starting high doses of these therapies all at once. I am talking about prioritizing low doses at the onset: carvedilol 3.125, spironolactone 12.5 for HFrEF, for example. I also think that we are talking about HFrEF when our four pillars, two of the four pillars, SGLT2 inhibitors and MRA rarely cause symptomatic side effects. Yes, there can be some lab issues that you see in everything, but from a blood pressure perspective, they do not really cause blood pressure lowering.

From a clinically significant side effect, the patients report they really do not cause much in the way of side effects at all.

The third thing is perhaps the most important. Disease progression in heart failure may be misinterpreted as a medication-related adverse event. That disease state worsening is much more likely if GDMT initiation is delayed. That sounded complicated. What on earth do I mean by that?

I already showed you the data on the right from EMPEROR-Reduced. These again shows that the NYHA class, how the patient looks and functions to the clinician's perspective. Completely different directions, whether they get empagliflozin versus placebo.

Putting this in a clinical context, let us pretend you have a patient with heart failure in your office today. They are feeling fine. They are not complaining of anything. You are in a rush.

You say, “You know what? I am not going to rock the boat. I do not have time to explain a new medicine change. Let us just essentially put them on placebo. I am not going to start an SGLT2 inhibitor.”

Well, by giving that patient placebo that day, essentially, you are indirectly increasing the chance that four weeks from now, you get a phone call about how the patient is not feeling as well. They are having dyspnea, more fatigue and whatnot. Then you are on the slippery slope of saying, “Well, maybe this shortness of breath and fatigue, maybe it is because of the beta blocker they are on. Let us cut the beta blocker, let us cut the ARNI.” You start withdrawing GDMT slippery slope, when in fact this is just heart failure progression, not really the medicine's fault they are on.

This entire situation could have been potentially prevented if you had a time machine go back to the clinic visit where they were feeling well, and you started a medicine proven to prevent you from getting in this situation to begin with. Again, just think about this like a risk of omission perspective.

STRONG-HF: High-Intensity vs Usual Care GDMT for Patients With Acute HF

The other thing people will say, “Well, Steve, you want us to start multiple medicines at the same time, but there is no clinical trial that ever starts multiple medicines at the same time. They are all starting one medicine on top of background therapy. Really, Steve, how do you know this is actually safe and effective?”

It used to be true until the STRONG-HF trial came out. This was a randomized trial of over 1,000 patients with heart failure, randomized to either rapid sequence, simultaneous initiation of GDMT, in-hospital initiation and post-discharge aggressive titration versus usual care, slow and steady, do what you normally would, right?

Overall efficacy you see here on the graph, dominant trial, stopped early by the DSMB. It was no longer deemed ethical to keep exposing patients to usual care. Imagine that statement. It is not ethical to keep doing the slow and steady usual care.

Aside from the efficacy, also take note at the safety, no significant difference in serious adverse events. Again, starting multiple medicines rapid sequence right away. No significant difference in adverse events.

Interprofessional Workflow Challenges

Obviously, overcoming clinical inertia. It is a tough thing to do in clinical practice, right? We need to try our best to battle it. Some of the questions relate to, well, who owns these drugs? Again, the good news is multiple people can be responsible for this drug. So multiple chances to prescribe it. Also we cannot be afraid of asking for permission and all this kind of stuff. We need to be aggressive err on the side of yes rather than the err on the side of no.

Other things people talk about, well, how are we going to overcome this? Again, you have different things about educational simulations. We talk about multidisciplinary care. We also talk about EHR prompts potentially as being helpful. Although I will admit, there is lukewarm data on this.

Also there is this movement on dedicated GDMT clinics or actually CKM clinics. We can talk more about whether hospitals have the resources for this consistently. Again, the bottom line is we have to do better. We need to scrap and claw and try to get these patients on these therapies.

Practical Strategies for Overcoming Clinical Inertia

In terms of some of the practical strategies, these are the things that I frequently hear when there is this therapeutic hesitancy for starting an SGLT2 inhibitor. One barrier people bring up all the time is, well, monitoring labs and specifically eGFR. People hear about this eGFR dip. Again, there is this fear of lowering the eGFR.

A couple key comments that I will say. Although we are trained in cardiology with a lot of our therapies like MRA and RAS inhibitors, we need to check an eGFR soon after we start these therapies. We are titrating diuretics. We want to check the potassium when we are titrating the furosemide, for example. If all you are doing is starting an SGLT2 inhibitor, there is no need to routinely monitor follow-up labs of kidney function. Just hear me out. In the clinical trials, there is no significant increased risk of acute kidney injury.

Now you talk about, what is about the eGFR dip and everything? Well, the eGFR dip is a clinical trial convention because as clinical trials do, they oftentimes check a lot of blood work, right? They are checking the labs for the trial. When you actually ask about acute kidney injury, when the clinicians are reporting adverse events, there is numerically fewer that are reported in the SGLT2 inhibitor group than the placebo. So do not conflate eGFR dip with what you in your practice would call an acute kidney injury. There is no increased risk of acute kidney injury in the clinical trials.

Every once in a while we do see these large declines in eGFR and whatnot. People are saying, well, it must be the SGLT2 inhibitor. My thing is take a step back and think about other causes. Again, SGLT2 inhibitors, we know from the kidney trial data, they are really the kidney's best friend. I am very hesitant to blame an SGLT2 inhibitor if someone's kidney function is falling off a cliff. Ask myself, “Hey, what are we doing with the diuretics? Did we start other therapies? Did we just give them an IV contrast load in the cath lab, for example?” Those are other much more likely evidence-based reasons to have the kidney function fall off the cliff.

The other thing I will say is, even if the kidney function does not get back to normal compared to where it was, what is the best medicine for chronic kidney disease? SGLT2 inhibitor. Again, really once these therapies are on board, no matter what the eGFR does, I am continuing these therapies almost always.

Practical Strategies for Overcoming Clinical Inertia (Cont’d)

We will think about some other concerns that come up. Hypotension and volume depletion. The risk is low in clinical trials. I do not think we need to always say, “Well, I am starting SGLT2 inhibitor, I need to back off on diuretics.”

In my own clinical practice, if someone is on a low-dose of a diuretic and like around 20 furosemide a day or 20 PRN, I will say, maybe try without it. This might be a nice substitute that also has organ protective benefits on top, rather than your furosemide.

Another barrier that comes up all the time is urinary tract infection. I got news to everybody is that older multi-morbid patients, they get urinary tract infections and they get urinary tract infections, whether or not you start them on an SGLT2 inhibitor. In the clinical trial data, there is no significant difference overall with rates of SGLT2 inhibitors versus placebo for UTI.

Now I differentiate that with genital mycotic infection where there is a small increased absolute risk. But for urinary tract infection, just because someone has had a urinary tract infection in the past does not mean we withhold a disease-modifying quality of life improving medicine. That is not a contraindication.

I tell my trainees, if someone has had two or three urinary tract infections in the past, well, they are going to get another one no matter what I do probably. So we might as well start by treating their end organs, treating their heart failure, and initiate an SGLT2 inhibitor.

Practical Strategies for Overcoming Clinical Inertia (Cont’d)

The last thing I will say is, again, we need to take ownership and have our default being yes rather than our default being no. Again, we

talk about the risks of omission. We talked about our patient case, where, again, they never really talked about it as an outpatient. Then the guy gets hospitalized and you are like, “Gosh, maybe this hospitalization would have been prevented if we had initiated a therapy proven to decrease the risk of heart failure hospitalization.”

Again, rather than asking for permission, I will ask for forgiveness is my general thought. Again, we all need to agree these therapies are an evidence-based therapy.

Pit Stop 2: Angela Would Like to Tell her Story!

Now we have our second patient case. I would like to introduce you to Angela, who is going to be telling her story.

Angela:
My name is Angela. I am 62 years old. For the last few years, I have been living with what I now know is cardio-renal-metabolic disease, and no one ever told me that until very recently.

I was diagnosed with type 2 diabetes in my late 40s. At first, my primary care doctor focused on my blood sugar. We talked a lot about my diet, A1C, and eventually insulin. I also have high blood pressure and high cholesterol, but those felt like background problems. A few years later, my labs showed worse kidney function. My doctor said it was something to watch, probably related to diabetes and blood pressure.

I was referred to a kidney specialist who adjusted my blood pressure medications and told me to avoid some medicines and drink plenty of water. Because my kidney numbers were not terrible yet, it did not feel urgent.

Then I started getting short of breath. I could not keep up on stairs and my ankle swelled by the end of the day. I went to a heart doctor. After some tests, I was told I had heart failure. I was started on a diuretic and we talked about salt restriction. The visits were short and focused on whether I was retaining fluid. I assumed that meant my treatment was complete.

About a year later, I was hospitalized for excess fluid. That was scary. During that time, different doctors came in and out. Medications were adjusted. When I was discharged, I left with a longer medication list, but it was mostly higher doses of things I was already taking. No one really explained what this meant, or whether my treatment plan needed to change in another way.

It was not until another visit this time with a different heart doctor, that someone sat down and explained how my heart failure, kidney disease and diabetes were all connected. She talked about guideline-recommended medications that protect multiple organs, not just treat symptoms. She mentioned things that could have been started years earlier when my diabetes was first diagnosed, when my kidney function started declining, when heart failure was diagnosed, and even at hospital discharge.

Hearing that was frustrating, honestly, not because anyone meant to withhold care, but because it made me realize how many chances there were to change the course of my disease. Each doctor was doing their part, but no one was looking at the whole picture.

If I have learned anything, it is that timing matters. Sometimes the best moment to start the right therapy is earlier than it feels.

Pit Stop 2: Angela Would Like to Tell Her Story!

Dr. Gluckman:
Awesome. We are going to go ahead and actually move into just individual table discussions. Steve, great presentation. I am going to ask Steve and Anne to move down in the audience and actually at your table, just discuss Angela, this case. It is an example of someone who was in the hospital, had had repeated opportunities. This is a common theme you are going to hear. Do you see patients like Angela? What can we learn about for missed opportunities and how do we improve the care?

We are a little bit behind in terms of schedule, so I am going to give you guys about 30 to 60 seconds to go through and just talk about some high level thoughts about that. Then we will reconvene together to talk about this and our last final section here as well.

Talk at your tables, if you could. We will ask Steve and Anne to circulate to talk further about this.

Again, for those of you that are online, really appreciate your patience in participating tonight. I think Angela's case is illustrative of what we unfortunately see quite often, individuals not necessarily rowing in the same direction. Everybody trying to do well by Angela's care. But at the end of the day, we have an individual who ends up in the hospital and even in their own self-reflection comes to realize that this is somebody who had an opportunity to do better in their care overall, and it is not until very late that we realize that there were missed opportunities in their care for an individual such as Angela. We will be back in just about a minute or 30 seconds to further discuss this as well.

I am going to give this about 15 seconds. Then we are going to ask Anne and Steve to report back.

Anne, I am going to start with you, if it is okay. Just a quick theme that you have heard from individuals that you are talked to.

Dr. Peters:
Our group is having lots of conversation here. There are two comments that are germane. One is about it depends on how you feel about starting a lot of drugs all at once, because I personally am somebody who does things a little bit more slowly, not because I am engaging in clinical inertia, but because I am trying to figure out how a patient tolerates these medicine.

Then there are times when, say, that blood pressure is really high, or there are other things going on when I want to start more than one agent. So we need to think about the clinical context for this, and then how we might want to start drugs in a way that works best for the patient.

I could not agree more with all of these things everyone has been saying about our overall approach to this and how not to be afraid of SGLT2 inhibitors. I do not know. I bet there is a trial or two where there was an increased risk for UTI, but overall there is not an increased risk for UTI with SGLT2 inhibitors.

Dr. Gluckman:
Steve, just your thoughts. I mean, you see this a lot when we think about the risks of actually commission associated with starting, but we do not necessarily think about it from a risk of omission standpoint.

Dr. Greene:
No, definitely not. A couple of key things from our conversation here is that people resonated with, yes, a person gets hospitalized and what is the big medication change? We are going to go home on a higher dose of furosemide. That is the big change, right? Because it is fluid, fluid, fluid, salt restriction. This gets all of our attention when we are not really treating the underlying issue.

I use a lot of analogies when I am talking to patients and I say diuretics are the band aid. They are like, if you break your arm, I can make your arm feel really well with pain medicine, but you still have a broken arm.

What I want to do is you want to use the medicine to fix your broken arm, fix your heart. Then you need less of the pain medicine, right? Just like less of diuretics.

Diuretics are important. I get it, but they do not want them to distract from the eye on the prize. The chemotherapy for our patients is the GDMT.

Navigating Curves: Patient Counseling and AE Management for SGLT2 Inhibitors

Dr. Gluckman:
Well said. I am going to welcome Steve and Anne back up to the stage. We are going to go through this last section. I am going to move a little more quickly to keep us back on time here. These are about the practical aspects of initiating this type of therapy. Because these are the questions that come up, how do you operationalize this overall.

Poll 5

Before we move forward with that, we are going to do a first polling question here, poll five. When a patient on an SGLT2 inhibitor expresses concern about potential or early side effects, how do you typically manage therapy?

A. Reassure the patient and continue therapy with education and monitoring;
B. Temporarily hold the medication and reassess after symptoms resolve;
C. Discontinue the medication and switch to an alternative therapy;
D. Individualize the approach based on severity and patient preference; or
E. Refer the decision to another specialist, an endocrinologist or nephrologist.

Please key in your answer.

Concerns in Patients With and Without T2D When Using SGLT2 Inhibitors

Okay. I am going to move through here and just highlight some of the topics that have already been brought up this evening. Thus, we can move through them a little more quickly. It is:

- Genitourinary infection;
- Hypoglycemic; and
- Euglycemic DKA, or diabetic ketoacidosis.

SGLT2 Inhibitors and GU Infections in Patients With HF

This was highlighted a little bit by both Anne and Steve. This is looking at the SGLT2 inhibitor data with regard to urinary tract infection, complicated urinary tract infection and genital mycotic infections. To Steve's point, while we have seen a small but increased risk of genital mycotic infection, really the effect size is rather small overall. It nonetheless reinforces the importance that those being initiated on SGLT2 inhibitor should be educated about how best to reduce the risk of genital mycotic infections and urinary tract infection.

When we see the actual prevalence rates by comparison to those receiving placebo, they are very small.

GMI and UTI Risk Factor Assessment Prior to Starting SGLT2 Inhibitors

This is a good flow diagram that I actually like a lot. If you are seeing a patient who is eligible for an SGLT2 inhibitor and they have an active genital mycotic infection, urinary tract infection, or they have had recurrent events or they have adult polycystic kidney disease, please do not initiate therapy overall. Wait until their genital mycotic infection or urinary tract infection has been effectively treated.

If they have had recurrent events, this is somebody that would benefit from a specialist like a urologist to help guide decision making. In contrast, if they do not have an active infection or their initial infection has been adequately treated and has resolved, you can then initiate an SGLT2 inhibitor. Your guiding decision-making, all the while assessing if those individuals may have a urinary tract infection or a genital mycotic infection. If it is uncomplicated, they are on an SGLT2 inhibitor and they have an uncomplicated infection, you can continue your treatment. In contrast, if they have a complicated infection, you should stop the therapy and reassess overall.

GU Infection Prevention With SGLT2 Inhibitor Use

In terms of preventive efforts overall, it is being proactive about raising awareness, letting patients know that this is a potential side effect so that you can intervene early and avoid conversion of an uncomplicated to a complicated infection, providing practical advice about hygiene and how efforts can be made to protect against this, including rinsing and drying the genital area after using the toilet and before going to sleep.

Topical treatments are usually very effective for this patient population, particularly for those that have mild to moderate infection.

Importantly for those with recurrent infection, despite appropriate guidance overall, they may need reassessment of whether or not this is a therapy for which the benefits overwhelm the risks, and that should usually be guided under the auspices of experts who deal with individuals who have recurrent infections.

Hypoglycemia Rates With SGLT2 Inhibitors in Those Without T2D

What about hypoglycemia? In short, we saw similar proportions of patients on SGLT2 inhibitors in the key trials and those receiving placebo in terms of rates of hypoglycemia without type 2 diabetes overall. In those individuals that had type 2 diabetes, rates of hypoglycemia were generally not increased with SGLT2 inhibitors in people with heart failure, acknowledging that concurrent use of sulfonylureas and/or insulin in patients with diabetes may increase the risk of hypoglycemia.

As a cardiologist, I am generally not initiating these glycemic medications. It is important again another reason to coordinate care.

Proposed Insulin and Other Diabetes Medication Adjustments When Initiating SGLT2 Inhibitors

SGLT2 inhibitors, as a takeaway, rarely cause hypoglycemia in the absence of concomitant insulin or secretagogue therapy. To prevent hypoglycemia, background therapies may need to be adjusted under the scenarios listed here:

- They have a history of hypoglycemia;
- They are on sulfonylureas, repaglinide or insulin;
- If their estimated GFR is less than 45, verify the possible hypoglycemia by self-monitoring to ensure that, in fact, symptoms that are brought out are in fact related to hypoglycemia; and
- If their hemoglobin A1C is less than 7.5%, you may reduce the dose of a hypoglycemic agent.

Ketoacidosis Concerns With SGLT2 Inhibitors

Anne had brought up ketoacidosis and concerns with it, and recognizing that these are not all people who have elevated blood sugars but have, in fact, including euglycemic ketoacidosis.

Symptoms that are listed here on the left-hand side, I would not read through all of them. But you should have your antenna up in terms of asking questions that for individuals that call in and recognizing they may not call you, but they may call a different clinician about the potential for ketoacidosis, as it is a rare but potentially life-threatening condition. It may be seen at a greater propensity, although still

uncommon, in those with restricted food intake, severe dehydration, acute intercurrent medical illness, surgery, or alcohol use.

Patients might present with normal or only moderately elevated blood glucose level, but serum ketones should be measured in these circumstances to identify someone with ketoacidosis. If you suspect, you are just thinking about but have not yet confirmed ketoacidosis, treatment with the SGLT2 inhibitor should be discontinued immediately, and they should seek medical attention for further evaluation and treatment.

Diuretic Considerations With SGLT2 Inhibitor Use

Steve brought this up already, so I am not going to repeat too much of this. Diuretic considerations with SGLT2 inhibitors. In meta-analyses that have been done looking at the SGLT2 inhibitor cardiovascular outcome trials, volume depletion was observed in low rates of individuals, mid-single digits in those receiving SGLT2 inhibitors, with a matching rate in those receiving placebo overall.

The party line for most individuals is it does not require an adjustment of diuretic therapy. However, in those receiving higher doses of, in this case, furosemide equivalent doses, those individuals may require a decrease in their loop diuretic while initiating an SGLT2 inhibitor overall. It is important that it does not stop there. Attention to volume status is going to be key for this patient population overall.

Surgery Considerations With SGLT2 Inhibitors

I will mention just briefly. We talked about the potential for ketoacidosis. What would be one of the reasons is they have poor oral intake. That may be because they are out in a warm temperature. They are not taking enough oral intake. It also could be related to the fact that individuals may be asked to not take food in because of a need for surgery.

In those individuals with restricted food intake or dehydration or who have a change in insulin requirements due to surgery and are at higher risk for ketoacidosis, you can see that the general standard approach is that for those undergoing surgery, where food needs to be interrupted for a longer period of time, and that includes fluid, treatment should be interrupted, and monitoring of blood ketones is recommended.

On the right-hand side, you should be able to restart your SGLT2 inhibitor once the patient's condition is stabilized, whether that is related to surgery and in the postoperative state, now resuming a more normal diet, or whether in someone who has intravascular volume depletion, dehydration that is been corrected overall.

In patients with diabetes, blood glucose may be higher than usual for approximately a day if you are interrupting their SGLT2 inhibitor, and that may require temporary attention.

When Should SGLT2 Inhibitor Therapy Be Paused?

When should SGLT2 inhibitor therapy be paused? This lists a number of the things that we have talked about in circumstances under which you are pausing, principally as it relates to a risk for ketoacidosis. Once that acute illness or acute situation is stabilized, an SGLT2 inhibitor should be able to be reinitiated again once those individuals have eaten normally for at least 24 hours.

General Patient Counseling Points for Possible Adverse Effects Related to SGLT2 Inhibitors

These are some themes and takeaways. I know we move through this quickly. There are a lot of themes here. Just as you are talking about counselling proactively your patients covering genital and perineal hygiene; highlighting susceptibility for orthostatic hypotension, if these individuals have poor oral intake or in particular are on higher doses of loop diuretics and you are initiating an SGLT2 inhibitor; being attentive to and highlighting the importance of having a high sensitivity for detection of DKA symptoms; avoidance of excess alcohol use, which can promote intravascular volume depletion, dehydration; and should be held prior to surgery.

Obviously, this always wants to be coordinated with relevant healthcare clinicians.

Emerging Therapies Targeting the CKM Axis

There are a number of emerging therapies targeting the CKM axis. The indented ones are not necessarily less important or more important than those that are not indented. Just highlighting that we have a number of therapies coming down the road, not that far away, or we have therapies that are already available, such as dual GLP-1/GIP receptor agonists already here today. It is just highlighting that this field is blowing up immensely. We are going to have a number of therapies to think about that are going to have hopefully favorable cardiovascular-kidney-metabolic effects in this patient population.

Strategies for Better GDMT Care

So summarizing things. We have multiple strategies for better GDMT care. We want to find ways to strategically overcome clinical inertia. We want to overcome peer resistance with guideline evidence. This is that concept of acts of commission. Steve has really

taught me a lot, not only tonight, but previously in a lot of his pioneering work and really reinforcing what are the consequences of me not initiating therapy.

I would be remiss, we could talk for hours about navigating insurance barriers and how to best interface with our payers. And practical adjustments for minimizing adverse effects.

Pit Stop 3: Listen to These Patients Describe Their Hesitation About Starting Therapy

We are going to just go through very quick snippets about four patients, two you have not actually met yet. Then we are going to ask you just to talk at your tables briefly.

Angela:
I have been reading about this medication, and I am honestly worried about the risk of infections. I have had issues like that before and I do not want to start something that might make it worse.

Joe:
My biggest worry is that it makes you pee more. I already feel like I get dehydrated easily. I am concerned about how this could affect my kidneys.

Patient:
I am already taking several medicines every day and I am not sure I want to add another one unless it is absolutely necessary. I worry about keeping track of everything.

Patient:
I am nervous about feeling dizzy or having low blood sugar. I live alone and I do not want to risk falling or passing out.

Pit Stop 3: Listen to These Patients Describe Their Hesitation About Starting Therapy

Dr. Gluckman:
I am going to ask Steve and Anne one more time to step down into the audience here. We are going to take one minute, a minute and a half maybe to just actually ask, do these resonate with you? How do we overcome or respond to these patients comments, which I suspect are ubiquitous in your practices?

I will just ask you for a moment. We will take a minute to just say which of these resonate more. Were there certain patients that stand out more to each of you? Talk amongst yourselves for a minute.

For those of you online, really appreciate your patience with all of this. For me personally, each of these resonate the challenges of polypharmacy. What about the last patient who lives alone is struggling with the issue of what would happen if, God forbid, they lost consciousness, passed out, or fell as a result of having too low of a blood pressure.

Respecting all of the concerns that patients have, we need to figure out ways in which we effectively address and respect the concerns, but also figure out ways to introduce therapies to best match their needs, while at the same time helping to effectively reduce the risk of complications related to their diabetes, their renal disease. In this case, much like we have discussed tonight, heart failure.

We are going to be coming back in about 15 to 20 seconds here to further discuss some of these issues overall.

I am going to give this about 15 to 20 seconds more. I am going to ask Steve to report out first and then Anne afterwards.

Steve, I hate to interrupt, I apologize. I know everybody is having great conversation. Any themes, thoughts from your perspective?

Dr. Greene:
Yes, people really resonated with people saying, “Oh, I am already on so many medicines. Do I really need this other one?” How do you pitch that question? For my own practice too, is that not every medicine on a medication list is created equal, right? Just because there is 10 medicines, they got there first. If you have the number 11, that is a really evidence-based medicine, that is disease-modifying, mortality reducing, quality of life improving, you got to make sure people really understand the risk of not starting it.

Then we also talked about deprescribing. We talk about it all the time. It is really hard to do in practice. I mean, it is a lot of work. If it is not your medicine, you do not want to offend your colleague that prescribed that medicine. In real life, not every medicine is created equal. The patients need to know why each medicine is prescribed and what the pros and cons of it are.

Dr. Gluckman:
Perfect. Anne, any additional thoughts?

Dr. Peters:
Yes, one really good thought was that it is often not the physician or the provider who does it, but the nurses and adjunctive helpers that really make the patient understand the need for some of this. I mean, my diabetes educators are everything. I mean, they are the ones who get these people to take the medicine, give their insulin, and do all of that. We really need to work out to the teams who help us.

Then another comment was how hard it is to get somebody back on one of these agents. They have already had a side effect. Particularly the GU side effects that you really need to talk to people about and stress the good points here, because if you once have a genital mycotic infection, you do not really want to get another one. But maybe we can help people not. But there got to be barriers in the way because of a history of a side effect.

Dr. Gluckman:
Great feedback. Great comments. We are in the tail stretch here. I am going to ask you all to focus. I am going to ask Steve and Anne to come back up. We are going to be going through just the same pre-activity questions now after tonight's presentation. Then there are a series of questions that you have all asked. As time allows, I am going to pepper our panel here with some questions quickly to be able to go through.

Postactivity Survey

Posttest 1

We are going to start with these are the cases you saw at the very beginning. A 67-year-old man with HFpEF type 2 diabetes and stage III chronic kidney disease. Started on GDMT after being hospitalized 18 months ago. Blood pressure and glycemic indices have remained near guideline-recommended targets, and he reports minimal symptoms. Guideline-directed therapies have not been increased during this period due to the patient's stability and concerns about polypharmacy.

Which of the following is most likely for this patient based on the current treatment approach? Again, which of the following is most likely for this patient?

A. Increased risk of symptomatic hypotension without meaningful improvement in long-term outcomes;
B. Favorable long-term outcomes, as long as blood pressure and glycemic measures remain near target ranges;
C. Higher likelihood of medication-related adverse effects if therapy is later intensified during clinical decompensation; and
D. Missed opportunity to reduce future heart failure hospitalizations and slow kidney disease progression.

Please key in your answer.

Awesome. The correct answer is D. Steve did a really nice job of talking again about those missed opportunities, as did Anne, to really intervene and make a difference in preventing an event that otherwise could have occurred, whether we are talking about heart failure, kidney disease and diabetes.

Posttest 1: Rationale

The rationale is listed up there for you.

Posttest 2

We will go to the next question. A 58-year-old woman is hospitalized with newly diagnosed HFrEF. After diuresis, she is hemodynamically stable with a blood pressure of 112 over 68, heart rate of 72 and estimated eGFR of 55. As she approaches the day of discharge, she is receiving a low dose of a beta blocker and a loop diuretic. Based on current evidence, which of the following is most appropriate to optimize her early outcome?

A. Begin low-dose initiation of the remaining foundational therapies prior to hospital discharge with rapid outpatient titration;
B. Gradually introduce one additional medication every four to six weeks to minimize adverse effects;
C. Initiate all remaining guideline-directed therapies at target doses before discharge; or
D. Defer initiation of additional therapies until a repeat echocardiogram is completed to confirm persistent LV dysfunction.

Please key in your answer.

Awesome job. Yes. This was reinforced a lot. Start low, but go fast I guess is the way to think about this in this racing theme tonight. The ability to be able to get people on foundational therapies that have been shown to improve the hardest outcomes overall.

Posttest 2: Rationale

The rationale is described here as well.

Posttest 3

we are going to go to our third post-test question. This is a 64-year-old man with HFpEF type 2 diabetes and stage III chronic kidney disease being considered for initiation of an SGLT2 inhibitor. Much like our fourth video patient, he lives alone, has limited health literacy, and reports of previous negative experience with a diabetes medication that caused bothersome side effects. He expresses concern about urinary symptoms, medication costs and taking something forever, but also states a strong desire to avoid future hospitalizations.

Which of the following counselling strategies is most likely to support successful guideline-based care in this patient's personalized care plan?

A. Prioritize reassurance that adverse effects are uncommon and focus on guideline endorsement to help him make a clear decision;
B. Support his perspective for not using an SGLT2 inhibitor, citing his advanced age and prior intolerance to glucose-lowering therapy and recommended lifestyle modifications;
C. Explain the medication's multi-organ benefits and discuss monitoring and how best to mitigate common side effects;
D. Initiate an SGLT2 inhibitor only after nephrology and endocrinology provide concordant recommendations to avoid conflicting messages.

Please key in your answer.

We just barely passed what you guys did beforehand. Yes, it is correct. Explaining the medication's multi-organ benefits and discussing monitoring how best to mitigate common side effects is the best of the options that are listed here in the presentation.

Posttest 3: Rationale

The rationale is listed down below for you.

Poll 6

Just a quick few polling questions. Then I am going to open up to Q&A to our panel. Do you plan to make any changes in your clinical practice based on what you learned in today's program?

A. Yes;
B. No;
C. Uncertain. I do not know.

Please key in your answer.

Poll 7

Please take a moment to enter one key change you plan to make in your clinical practice based on this education. I will ask you just to type that in while we are moving over to Q&A.

Q&A

Steve, I am going to start with you. We have got a few minutes just to do this. This is an unfair question. It is like choosing which is your favorite child. Some people have said, practically speaking, I may not be able to initiate all foundational therapies in someone who is treatment naive. Is there any guidance about if you can only start two classes of medication? And you are going to start the next two very quickly afterwards? Is there any data that would suggest two classes may be preferred over others as it relates to in-hospital initiation?

Dr. Greene:
Again, for all four therapies for HFrEF, let us say, it is like your children. You love all your children, but some of them are easier to parent than others, right? They do not get in trouble in school and all this stuff, or they do not get tantrums.

SGLT2 inhibitors are the most user friendly from a prescriber perspective. It is one dose once a day, no titration, no need for routine laboratory monitoring after you start it. They work quickly, improve quality of life. Again, you love all your children. They need all four therapies quickly. But if you had to choose one from user friendliness perspective, it is SGLT2 inhibitor.

The other one, everyone tolerates with HFrEF in my opinion, low dose spironolactone. It is a lab issue. It does not lower blood pressure.

It helps with decongestion. Those are two very easy therapies to start. Again, this is a cancer diagnosis. It is saying, you only get two of the chemotherapies when really it is R-CHOP. You are not just giving a couple of those. You need all of them right away.

The wrong answer is one today, the next one in like six weeks or six months. You cannot do that.

Dr. Gluckman:
Great answer. Anne, someone had asked the question about type 1 diabetes, SGLT2 inhibitors, but particularly should we be precluded from using in type 1 diabetes if they have heart failure or chronic kidney disease? Thoughts about it, without those conditions and then with those conditions.

Dr. Peters:
Let me just tell you what I think about it, unrelated to that exact specific question is that, in people with type 1 diabetes, since I have been the person who is trying to figure out how to make it work, I cannot 100% eliminate the increased risk for DKA. I just cannot, no matter what protocols. We have no tested protocols that show a reduction in DKA rates. You always are going to have a higher DKA rate.

The two subsets of people who tend to go into DKA more often are a lot of reasons for saying going on a low carb diet or reducing their total daily insulin dose. But are people on automated insulin delivery systems? Because those systems can stop delivering insulin and make people relatively insulinopenic increase their risk and females for whatever reason. If I have somebody on MDI who are on injections and I really want to put them on an SGLT2 inhibitor for heart failure or for CKD, I will make sure even if they are on automated insulin delivery system, that I have them on basal insulin, because I am just trying to give them something that stays in their system longer than rapid-acting insulin.

The real risk in a type 1 is not having enough insulin to inhibit ketosis. You cannot do it. You cannot eliminate the risk down to baseline. It just has never worked on any protocol. I cannot do it in my practice. All my patients have my cell phone. If I cannot do it, you cannot. But there are other drugs and we have talked about them. There are different approaches. These days I use a lot of incretin therapies in my type ones. I use semaglutide, I use tirzepatide, and that is helpful both in terms of renal effect as well as cardiac effects.

I think about the patient, but I cannot endorse routinely using it in people with type 1 diabetes unless you wish to accept that risk of DKA. It is just these older, fragile people. I just do not want to put them in DKA.

Dr. Gluckman:
Great answer. Steve, someone had asked the question, hemodynamically stable but receiving ongoing intravenous diuresis in the hospital. Any hesitation? Day one, day two of initiating these therapies? Or should we be waiting until the tail end when they are being transitioned to oral therapy?

Dr. Greene:
Again, for SGLT2 inhibitors specifically, no problem on day one, honestly. What are you trying to achieve on day one when they are in the emergency room coming to the floor? Diuresis, right? Guess what? These therapies add with decongestion.

Same thing with MRA too. Usually in diuresis, we are having the potassium go low. It would be nice to have something buffer it up.

Things like beta blocker. I do not escalate that until I get all the fluid off and everything. But the bottom line is when someone comes into the hospital, it is not just diuresis for three days and just focus on the GDMT for day four. Day one, think about length of stay. Median in the United States about four or five days, right?

Day one, what is our plan? For when they go home in five days, they are going home on optimal GDMT. We do not just fall asleep at the wheel for four days with diuresis, and then focus on day five for GDMT.

Dr. Gluckman:
Anne, someone had asked the question about, as we move in, do we consider both for diabetes? I will welcome Steve's input, that SGLT2 inhibitors are a class effect. We have seen some drugs with established clinical benefit and hard outcomes heart failure trials. Do you consider SGLT2 inhibitors as a whole as a class to be largely interchangeable from your perspective? Steve, welcome your thoughts as well.

Dr. Peters:
That is a slightly complicated question. I do think that they are generally interchangeable, but they may not always be. A lot of what I have to do is based on formulary. I mean, I may not have a choice because I all have patients who, at the county level, have to take what the county gives. We spend a lot of time planning this.

Can I just say one other thing, is that the one place you cannot treat too fast is if somebody comes to you who is very hypoglycemic and

has been that way for a while. If you bring down their glucose levels too quickly, you can precipitate a significant worsening in retinopathy.

Of all these things, because I am now going to be braver than ever about using SGLT2 inhibitor, thanks to Steve, I have really learned a lot here. I love this. That is why I come to these meetings.

In terms of diabetes, I actually go slow because if somebody has been high for a while, we know that worsens retinopathy, both type 1 and type 2. Just be careful. Start the treatment, but walk them down slowly. Not fast. Not the diabetes component of this.

Dr. Gluckman:
Steve, thoughts from you?

Dr. Greene:
Class effect. First thing I will say, practically speaking, people are better off on some SGLT2 inhibitor than no SGLT2 inhibitor. The ones that are most evidence-based are empagliflozin, dapagliflozin, and sotagliflozin. Those are FDA-approved for heart failure patients.

Again, I try to use the evidence-based, the ones we have the big trials for showing heart failure benefit. Again, I do believe that some SGLT2 inhibitor is better than no SGLT2 inhibitor.

Dr. Gluckman:
Last question Steve, I am going to leave with you. Someone had asked the question, are we going to see polypills with combination therapies in the future, especially as we have availability of generic options? Do you see that coming?

Dr. Greene:
There is a small pilot study at the AHA last year that showed that it did seem to have benefit in terms of adherence and even hard outcomes, that kind of exploratory stuff. The bottom line is I certainly hope so. Again, part of the reason why I hope so is, yes, it will help with adherence. Polypills seem to consistently help with adherence for whether it is post-MI, hypertension, etc.. That is important.

Also hopefully it will help with prescriber inertia too. I mean, I joke tongue-in-cheek that if sacubitril/valsartan was two medicines rather than one medicine. We prescribe even less of it. Because first do no harm, right? It goes slow and one at a time.

When medicines are a combination pill, we just relax about it for whatever reason, right? It is all psychology. Again, maybe if we just knew it was one heart failure pill, low doses, and we just had one medicine, we would forget that there are actually four components in there, and we blissfully prescribe all four right away and everything.

We need to think about the risks of oermission with these medicines. Again, when people have side effects, we feel bad, but when people die or get hospitalized without the medicines, we should also feel bad. Again, I just want to be open and honest about that there is a lot of preventable deaths and hospitalizations out there that, again, if we prescribe the medicines proven to prevent those events, we would have fewer.

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