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Reviewing the Role of SGLT2 Inhibitors in Heart Failure

Dr. Butler:
With the prevalence of heart failure continuing to rise worldwide, recent trials have shown that sodium glucose co-transporter 2, or SGLT2, inhibitors may improve impairments and decrease the risk of hospitalizations. So based on these recent findings, what exactly is their role in the management of patients with heart failure?

You're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler. And joining me today to discuss SGLT2 inhibitors is Dr. Mikhail Kosiborod, Professor of Medicine at the University of Missouri-Kansas City and Vice President of Research at Saint Luke's Health System.

Dr. Kosiborod, welcome to the program.

Dr. Kosiborod:
Thanks very much, Javed. It's great to be with you as always.

Dr. Butler:
Great. So let's just dive right in. Can you tell our listeners the mechanism of action of SGLT2 inhibitors in relationship to their potential benefit in heart failure?

Dr. Kosiborod:
Well, it's a great question. The answer is relatively complex because we're still trying to understand all of the different mechanisms through which SGLT2 inhibitors may provide benefit in heart failure, both heart failure prevention and heart failure treatment. First is just to acknowledge that there does appear to be some decongestion effect. You can call it diuretic effect. It's likely relatively modest and it's unclear whether it just happens early in the course of treatment or persists longer term. It does appear certainly in acute setting, that there is a greater diuretic or decongestion effect just in terms of fluid dynamics. There is at least a transient increase in fractional excretion of sodium, but again, that's relatively modest. We do have trials showing that pulmonary artery pressures go down with SGLT2 inhibitor therapy within about a week, so there certainly is some diuretic/decongestion effect even though I wouldn't necessarily put an equal sign between those things because decongestion does not just happen because of the diuretic effect. If you make heart failure better through other mechanisms, you certainly may have affected decongestion from that as well.

There also is a remodeling effect on the left ventricle. Certainly, we see that in heart failure with reduced ejection fraction, but there are some data that even in patients without heart failure who have structural heart abnormalities what we would call ACC/AHA class B heart failure, there are some structural improvements and resolution—or improvement in the structural abnormality that we see, such as left ventricular hypertrophy, left ventricular mass, and so on.

Perhaps the last one that I will mention is the metabolic effects, and it's undeniable that those occur. The actual mechanism of action of an SGLT2 inhibitor, which is why they were developed for treatment of type 2 diabetes to begin with, is a blocking of sodium glucose co-transporter 2 in a proximal tubule in a kidney, and so as a result there is increase in glucose excretion because of glucosuria. And while that by itself may not necessarily have a significant impact on heart failure outcomes, it sets off a number of metabolic changes and pathways that may well play a role in heart failure benefits. One is myocardial energetics and switching between different types of

fuel and mitochondrial effects that actually occur.

Dr. Butler:
As clinicians, we sometimes have this desire to have just 1 mechanism of action to explain everything, but what I'm hearing you say is that there are effects on the kidneys, the heart, the vasculature, metabolism, energetics, etc. Do these drugs have a potential role in acute heart failure?

Dr. Kosiborod:
I think the simple answer to that question, Javed, is yes, they absolutely do. We now have at least 2 reasonable-sized clinical trials that, in fact, indicate that. A trial called SOLOIST worsening heart failure trial that was done with sotagliflozin—that's a mixed SGLT1/2 inhibitor—where over a thousand patients were randomized to sotagliflozin or placebo, and those patients were either in a hospital with worsening heart failure or just within a few days of discharge. And what we saw in that study is over follow-up of about a year, patients treated with sotagliflozin had a significant clinically meaningful reduction in rates of important events, such as composite of cardiovascular death and repeat heart failure hospitalizations and urgent heart failure visits. There was also an improvement in the Kansas City Cardiomyopathy Questionnaire, which is a measure of health status, which is symptoms, physical limitations, and quality of life. So the triple goal of care in patients with heart failure was in acute or chronic setting is to make patients live longer, keep them out of the hospital, and hopefully be able to make them feel better and do more. And the SOLOIST trial, all of those were accomplished successfully when they examined those outcomes.

The second trial that was presented at the American Heart Association in 2021 and recently published in *Nature Medicine* is called EMPULSE, and that was a trial of patients hospitalized with acute decompensated heart failure that were assigned either to empagliflozin or to placebo, and these patients included those with either worsening chronic heart failure or de novo heart failure, those patients with new onset heart failure that weren't previously included in other trials. They also included patients with or without diabetes and regardless of ejection fraction. And what we saw in that study is that empagliflozin significantly improved the likelihood of total clinical benefit, which again included things like a death, repeat hospitalizations, or urgent heart failure visits, and improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score, which is a measure of symptom burden due to heart failure. There was a significant improvement with empagliflozin versus placebo, and again, that occurred quite early. The follow-up for the study was just 90 days.

So the bottom line is clearly these medications effectively prevent heart failure, and we know that in patients who don't yet have it. They effectively treat heart failure in those with chronic heart failure, regardless of ejection fraction. And I'd say also are quite effective in improving outcomes in patients acutely hospitalized with heart failure. So it's really across the entire continuum from prevention to therapy.

Dr. Butler:
Can you just quickly comment on a couple of things. Renal function is really important in management of heart failure patients. Do these drugs have improvement in renal function in patients with heart failure? And what sort of time frame do we have to start these therapies?

Dr. Kosiborod:
Of course preservation of kidney function and prevention of worsening kidney function is also an important treatment goal in patients with heart failure. Why is that? Well, first of all as the kidney function worsens, patient outcomes worsen as well, so there is a much higher risk of repeat heart failure hospitalizations and death in patients that experience worsening kidney function even if they have heart failure regardless of ejection fraction. Also just from a practical standpoint, certainly, as the kidney function declines, management of heart failure becomes a lot more complex, and therefore, I think all cardiologists will agree that if you can prevent the progression of kidney function, that's really, really important.

Now the good news is that SGLT2 inhibitors, in fact, do that. What we see very clearly is whether you look at trials of SGLT2 inhibitors in patients with diabetes who don't have heart failure but at high risk of atherosclerotic, atherothrombotic events or whether you look at patients with established heart failure, such as those with established heart failure and reduced ejection fraction combining data from the DAPA-HF and EMPEROR-Reduced with dapagliflozin and empagliflozin respectively, or whether you look at dedicated trials in

patients with chronic kidney disease, what we see consistently is a significant reduction in the risk of progression of kidney disease. And we're not just talking about surrogate outcomes, such as albuminuria. They do do that—they reduce albuminuria—but we're talking about heart-kidney outcomes, things like doubling of creatinine or significant reduction of eGFR progression to dialysis or a kidney-related death, so they're not just effective cardioprotective therapies. They're very effective nephroprotective therapies as well.

The onset of benefit happens within a few weeks after randomization and that really applies to both heart failure hospitalization benefits as well as quality of life benefits, so you don't have to wait very long. And another key point here also is that the SGLT2 inhibition can be added to whatever background therapy patients are on for heart failure. The effects are very similar regardless what other guideline-directed medical therapy patients are receiving.

Dr. Butler:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Dr. Mikhail Kosiborod about the role of SGLT2 inhibitors in heart failure management.

So that's great information. Now all of this is on one side of the ledger, all the benefit, but all drugs have side effects and limitations. So can you give us some idea what the clinicians should be on the lookout for when they give SGLT2 inhibitors?

Dr. Kosiborod:
In terms of tolerability and safety factors, I think it's fair to say that overall SGLT2 inhibitors are well-tolerated. They're easy to use because certainly in heart failure, it's just typically 1 dose. Regardless which SGLT2 inhibitor you go with it's 1 pill a day, and there are very few drug-drug interactions to worry about. There is little that needs to be monitored in terms of laboratory parameters, and the effects on blood pressure, especially in patients with heart failure and reduced ejection fractions that have low blood pressure at baseline, are very, very modest.

So one of the things that we do need to monitor and tell patients about is genital mycotic infections. So as I mentioned before, SGLT2 inhibitors do increase excretion of glucose in the urine, and as a result, there is an increase in a risk of]vaginitis in women and balanitis in men. And they usually can be treated in a relatively straightforward way either with topical or, if necessary, systemic antifungal therapy.

There are some other much more rare potential tolerability or safety issues, and one is euglycemic diabetic ketoacidosis. First of all, that is pertinent really just to patients that have diabetes. SGLT2 inhibitors have been studied in patients with type 1 diabetes, and there the risk of DKA is higher and is currently not indicated for use in patients with type 1 diabetes primarily for that reason. In patients with type 2 diabetes, that risk is exceedingly low, roughly about 1 in a thousand or potentially even less than that. The one thing to be predominantly aware of is that it may occur without necessarily very high blood glucose levels, so patients should be informed that if they have kind of systemic symptoms, such as nausea, abdominal discomfort, or if they have an acute illness for another reason. And if they potentially have a concern due to kind of the systemic symptoms, it's not a bad idea to check ketones and make sure that there isn't an issue with elevated ketone levels. You know, if that were to occur, obviously temporary discontinuation and restart is not unreasonable. But again the most important thing to keep in mind about euglycemic DKA is a very rare event in people with type 2 diabetes and has not been noted at all in patients who don't have diabetes.

Dr. Butler:
Well, that is simply a fantastic amount of information. I very much appreciate all your insights regarding the role of SGLT2 inhibitors in the management of patients with heart failure. Unfortunately, that's about all the time that we have. So I really want to thank you, Dr. Kosiborod, for joining me today. It was really great speaking with you.

Dr. Kosiborod:
It's my pleasure. Thanks for having me.

Dr. Butler:
For ReachMD, I am Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD.com/HeartMatters, where you can Be Part of the Knowledge. Thanks for listening.