New Standard Therapy for Heart Failure with Reduced Ejection Fraction - When and How to Introduce SGLT2 Inhibitors

Announcer: Welcome to the Mayo Clinic cardiovascular continuing medical education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Bell: Welcome, everyone, to today's session of Interview with the Experts. I'm delighted to have my friend and colleague, Dr. Maggie Redfield. She's a heart failure specialist in our Department of Cardiovascular Medicine. She's also a Professor of Medicine and the former Chair of our Division for Circuitry Failure. So welcome, Maggie.

Dr. Redfield: Nice to be here, Malcolm.

Dr. Bell: Yeah, so today, we're gonna be talking about an incredibly important group of drugs, the SGLT2 inhibitors, but particularly with the respect to the treatment of patients with heart failure with reduced ejection fraction. We are aware that there are some other indications for these drugs, but the patients with HFrEF, the topic for today. So maybe I'll just have you start and tell us what is the evidence that we should be using these drugs in this group of patients?

Dr. Redfield: Well, I think that's a great question and the evidence is really overwhelming. I can't think of a medication that so quickly amassed such a body of evidence for its use. So when we're talking about its use in heart failure with reduced EF, we're talking about 40% or below. And first and foremost, we know that this class of drugs prevent heart failure, with empagliflozin, canagliflozin, dapagliflozin, in diabetics, three huge trials in diabetics, most without heart failure, 90% didn't have heart failure, just high-risk diabetics. Use of these drugs produced a consistent, I mean it was almost identical in each of those three trials, reduction in incidence of heart failure. Over 35,000 patients in these three trials and it was highly significant reduction in new heart failure. And we got a lot of information about safety of these drugs and tolerance of those drugs from those prevention trials. Then, of course, now we have three trials presented within a year, essentially, three trials in heart failure and reduced ejection fraction. And these three trials, two of them enrolled both diabetics and non-diabetics. That's the DAPA-HF trial with dapagliflozin and the EMPEROR-Reduced trial with empagliflozin. And then there was the SOLOIST-Worsening Heart Failure, which was with sotagliflozin, which is actually an SGLT1 and 2 inhibitor. And that one was in hospitalized heart failure patients with diabetes, so three trials and a big meta-analysis of all three of these trials published in the European Journal of Heart Failure. And what those three trials showed was, again, incredibly consistent findings of reduction in the primary endpoints of heart failure hospitalizations or cardiovascular death. It was a very dramatic reduction and also analyzed each component of the primary endpoint and showed that it reduced hospitalizations, reduced cardiovascular death, and very, very importantly, reduced all-cause mortality with these agents. Now in these trials, you had to have systolic heart failure. As I said, could be diabetic or nondiabetic. Had to have an EF less than or equal to 40%, had to have a GFR of above 30, and all three trials had an NT-proBNP entry criteria, that they had to be above about 600 in sinus rhythm, above about 900 in AFib, and you had to have a blood pressure around 95 to 100 to get in. And again, very consistent findings. So now ESC guidelines recommend their use in HFrEF. The ACC guidelines are being redone, but an ACC expert

consensus document recommends their use. And of course, empagliflozin and dapagliflozin are both labeled for HFrEF, so really a compelling story of benefit.

Dr. Bell: Yeah, thank you for that summary, and just going back to your earlier comment about, you know, the just amount of data we have supporting this, and if I remember correctly, I mean, these started off really as diabetic drugs and the cardiovascular benefits were almost sort of serendipitous in terms of just proving safety, but they've sort of had an explosion of their own indications since then and-

Dr. Redfield: Yeah, if you go back and read the protocols for those three big prevention trials, they don't even mention heart failure. They all collected data, but it was all focused on ischemic events, so I guess it shows that even today accidents still happen.

Dr. Bell: Yeah, and as you said, you know, you couldn't remember a time that, or maybe another drug or intervention that's had, you know, so much, you know, published on, and maybe a future impact and, you know, would we be going too far to say that this is, you know, maybe just reminiscent of the effect that statins had. You know, over the last 20 years have just changed the landscape of atherosclerotic disease and outcome. And it's like a no brainer that you're gonna be on a statin and it really has just really had a major, I guess, effect and revolution on just how we treat patients with cardiovascular disease. Do you see this class of drugs maybe having similar impact?

Dr. Redfield: Yes, not so much on atherosclerotic disease, but on heart failure and on renal failure, which, as you well know, goes hand-in-hand with heart failure. And so the fact that these drugs have also been shown to improve renal function and decrease adverse renal outcomes, really it is sort of like a new and different statin. I agree.

Dr. Bell: Okay, well, yeah, I mean I think our listeners are gonna be very interested in your how do you start this, you know, medication, but before we do that, maybe just very briefly, I mean who are the patients that we would not consider this? And hopefully this is a relatively small group, but maybe just dispense with that very quickly.

Dr. Redfield: One thing, what we're always afraid of in heart failure is are we gonna drop the blood pressure? And these medications have very little impact on blood pressure, so you don't have to worry so much about that, although the trials had entry criteria of 95 to 100. Most people would probably maybe go down to 90. They obviously cause loss of glucose, which produces an osmotic diuresis and sodium in the urine. And most of the patients in the trials were fairly well-compensated, so patients can get dehydrated on these. So you gotta make sure they have adequate fluid intake, and then we check a set of electrolytes within two weeks of initiating them. Not for use in Type Ones, Not for use in Type Twos with the history of DKA. You have to have the GFR above 30. And the two things that come up are UTIs, because you're losing sugar in your urine so it makes it a better culture media. So, you know, elderly women with a lot of urinary tract infections, you gotta be very careful with them and stay on top of it. And then there's this really rare necrotizing perineal fasciitis that can happen, but it's super rare, less than 1%, and it wasn't significantly different in these cardiovascular trials in placebo versus SGLT2 inhibitor-treated patients. So that's the main thing, not Type One, adequate renal function, and

talk about the perineal fasciitis and the urinary tract infections. Make sure your patients are looking out for that.

Dr. Bell: No, I may be mistaken here, but I thought that these drugs had been used in patients who have type one diabetes who are, not the heart failure patients, but in the diabetic heart failure, they're not using that?

Dr. Redfield: No, not so much because, you know, if you have an insulin deficiency and you're losing, you know, sugar via a different way, they can cause a propensity to DKA. So no, not for Type Ones.

Dr. Bell: But could be Type Two who's on insulin, of course?

Dr. Redfield: Yeah, insulin doesn't matter, yeah.

Dr. Bell: Perfect. Okay. So now, let's say you're seeing a patient in the outpatient clinic today, and let's say it has established heart failure- Systolic heart failure, and is on the beta blockers, the ACE inhibitors, et cetera, is this a patient that you're now interested in starting one of these agents? And if so, how would you do it? Or, and then maybe just address the question of is there any titration required? What sort of things are you looking for in these patients?

Dr. Redfield: Well, where are you gonna see heart failure patients? So first one is the scenario you presented, outpatient, on your best... First of all, guideline-directed medical therapy, beta blockers, some sort of RAS antagonist, hopefully Entresto if they can afford it. And then Aldactone antagonist if they can afford that. Then if you're seeing a patient like that, remember 75% of the patients in the trials were class II, so doing pretty well, class I or II. So just because they're doing well, that's exactly the patients you should start. So yeah, it's everybody in that scenario who meet the guidelines should be started. In non-diabetics, you just start it, 10 milligrams of dapa, 10 milligrams empa. You review the side effects. We check an electrolyte panel in two weeks. You're good to go. Now what's the other scenario? You might be in the outpatient setting seeing a patient with systolic heart failure who you're still uptitrating. There's a cogent argument to just going ahead and starting it anyway. You know, more emphasis is now being placed on, rather than waiting till you get the RAS antagonist, the beta blocker, and the aldosterone, and then add dapagliflozin, some people are really arguing, or empagliflozin, some people are really arguing that you should do it right away. So that's, we'll wait and see what the guidelines say, but there are several position papers that are advancing that, that even if you're not finished uptitrating, go ahead and add it in. And then the third and the most important, I think, scenario is you're in the hospital and you're-

Dr. Bell: Before we get to the hospital, Maggie, let's just... Because I think that you're really important practical advice you're giving here. So again, in that patient that you're actually initiating treatment with ACE inhibitors, diuretics, you know, and the other drugs that you mentioned there, what you're saying here, I mean, particularly is it's not really gonna affect their blood pressure, which most of those other drugs do, maybe you do start it there. You don't have to wait and bring them back a few months later and tolerate-

Dr. Redfield: Right, and one of the things that goes to that argument is, well in the trials, everybody was on excellent guideline-directed medical therapy, so you should always do that. But the question is, do you have to wait until you're done? And that's an area that the guidelines will have to address. But you could consider adding it in early.

Dr. Bell: But this was in the non-diabetic patient. Now what about if the patient has diabetes, is on metformin, or insulin, looked after by a diabetic specialist, is this a drug that you're gonna feel comfortable starting yourself, or are you gonna wait for the diabetic specialist to do it? Or is there some other way we could make sure that this patient's not gonna miss out on the benefits of this drug?

Dr. Redfield: That's a great, great point. And I think it's important to communicate with whoever is managing the patient's diabetes. And if the patient is well-controlled, if they're on metformin and another oral agent, a different type of oral agent, you can stop the other oral agent and add it to the metformin. That's a pretty clear, but you really gotta communicate to it with whoever is managing the diabetes.

Dr. Bell: So let's move to the inpatient practice then. That's obviously where, you know, we see a lot of these patients, and very often with acute or chronic decompensation of their heart failure or a new diagnosis of acute heart failure.

Dr. Redfield: Well, if the patient's in with decompensation or new onset, we didn't get to delve into the specific trials, but that SOLOIST trial, which was hospitalized diabetic with heart failure, starting it there, regardless of EF in that trial, but it was mostly HFrEF, and regardless of background therapy, resulted in a number needed to treat of only four. And analysis of all these trials, the SOLOIST and the other trials, you start to see the statistically significant impact on the primary outcome within a month.

Dr. Bell: And the primary outcome, just to remind everyone?

Dr. Redfield: Most cases, it was cardiovascular death, or heart failure, hospitalization, or cardiovascular death, and heart failure, rehospitalization. So, you know, therapeutic inertia is something really to avoid here because the effects come on fast and a very small number needed to treat, and it's the people who are in the hospital who are obviously at the highest risk of rehospitalization. So, you know, we're really working hard, and it is difficult because you don't know if the patient's insurance will pay for it, so you gotta write a prescription for them, have them, you know, contact the pharmacist at their fulfilling pharmacy and see what their copay is and see if they can afford to be on it, because that's really a window of opportunity to have the biggest impact.

Dr. Bell: Do you see your continued hesitation then among cardiologists in prescribing these drugs, and what can we do to overcome that therapeutic inertia, as you put it?

Dr. Redfield: Yes, well, there always is therapeutic inertia and we just need to do better with these class of drugs. And the big thing is the cost for the patients. If the therapeutic inertia for the physicians, I think, is maybe some hesitancy about a diabetic drug or saying, "Well, they're doing

pretty well," you know, but that's what we have to emphasize is that, yeah, those are the patients who are in the trials who obtained so much benefit. The number needed to treat for not the hospitalized patients, but the patients enrolled as outpatients was only 15 to 20. So that's pretty low for an NNT. The cost of these is kind of about like Entresto, not everybody's insurance will pay for it, but I think the roll in is going much more smoothly than it did for Entresto. We're getting fewer turndowns as the experience with it grows.

Dr. Bell: So as I attempt to summarize this then, so we've got this new class of agents, have very powerful, you know, effects, particularly on cardiovascular outcomes in terms of hospitalization for heart failure, mortality. I mean, these are, you know, really strong endpoints, and then that hospital population, number needed to treat of only four is, that's something that should always get our attention. That's something that's incredibly important to understand. For the non-diabetic patients, whether they're in the hospital or the outpatients, this should be pretty easy for us to prescribe. And we should start doing that. The ones who are diabetic, and again, just to clarify, these are Type Two diabetics, whether or not they're on insulin, and these benefits apply to those who are diabetic and non-diabetic, but the diabetic patients, we probably have to have close communication with the diabetic specialist. I'm not sure if they're suffering from any therapeutic inertia in these patients. You may want to make a comment there, but regardless I think communication is gonna be very, very important. Anything you wanna add maybe before we wrap up here?

Dr. Redfield: That's a great summary. I think the only other thing I would emphasize is that this is an easy one. No uptitration. Very good safety profile. Maybe just a set of electrolytes two weeks after starting. Compared to what we go through with beta blockers, and RAS antagonists, and aldosterone, this should be easy. And then the diabetics, there is already the ESC recommend SGLT2 as first-line agent. We don't know yet what this side of the Atlantic will recommend as far as unselected patients with diabetes, but our diabetic specialists have been good to work with, and, you know, most of the primary care providers are managing the diabetes and they're very open to this. Just takes a phone call.

Dr. Bell: Yeah, and one final practical question, in the patient who ends up getting admitted to the cardiac intensive care unit, pulmonary edema, you know, whether or not they've had a history of heart failure in the past, but has DKA, and maybe this is the first time they presented with DKA, is this a patient that you would hold off starting this?

Dr. Redfield: Absolutely, yeah. It's group ones and group twos who are prone to DKA. You would definitely want a diabetologist involved if you were even gonna consider it.

Dr. Bell: Thank you so much. Maggie, it's always a pleasure talking with you. You're such an expert in the field of heart failure and we are very, very fortunate to have you discuss this topic with us today, and I think our listeners and viewers will really appreciate the information that you've shared with us today. So thank you so much for your time.

Dr. Redfield: All right. Have a great day, Malcolm.

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