

Transcript Details

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Cardiometabolic Insights in HCM: The Emerging Role of SGLT Inhibition

Announcer:

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Dr. Day:

Hello, I'm Dr. Sharlene Day, and today I'm going to be reviewing the emerging role of SGLT inhibition in the management of hypertrophic cardiomyopathy, or abbreviated HCM.

So sodium-glucose transporter inhibitors were originally developed to treat people with diabetes. They bind to a channel in the kidney that blocks reabsorption in sodium and glucose. But they were found serendipitously in later studies to be enormously beneficial for treating heart failure, including reducing hospitalizations for heart failure and lengthening life in people that suffer with heart failure with and without diabetes. So even people without diabetes and heart failure have benefited from these drugs.

SGLT inhibitors are the first drug to work not only for heart failure with reduced ejection fraction, but also heart failure with preserved ejection fraction. So these drugs are really now widely approved for treating heart failure of both types with the highest level of recommendation in national guidelines for benefit.

Importantly, patients with HCM were excluded for participation in these trials because HCM is really a special condition. It's not heart failure with either reduced or preserved ejection fraction. But there are some similarities, and I would say most of the similarities are with heart failure with preserved ejection fraction. In particular, they're both characterized by increased ventricular stiffness and impairments in diastolic function. So although patients with HCM were excluded from these trials, there's reason to believe that these benefits might extend to people with HCM.

So backing up a little bit to talk about the different types of SGLT inhibitors, some are more selective and block only the SGLT2 isoform. These would be empagliflozin, dapagliflozin, as examples. And some also have dual action to block both SGLT1 and SGLT2, and an example of this would be sotagliflozin. Now, SGLT2 is not expressed in the heart at all, but there are other potential targets in the heart that have been identified to which SGLT2 inhibitors might bind and exert their action that way.

For the dual inhibitors, SGLT1 is expressed in the heart, and it's possible that dual inhibition could be acting favorably through its action on the SGLT1 receptor. But we don't really know that yet for sure and that's something that's under exploration.

Some of the beneficial effects that we and others have observed in the heart through use of either dual or SGLT2 inhibitors include improving the way the heart uses fuel, and so the way that the heart uptakes different forms of fuel to make ATP or energy. And we've also observed a slight dampening of contractility in human heart tissue slices when exposed to SGLT inhibitors. This benefit was a little bit more potent in the dual SGLT inhibitor sotagliflozin compared to the selective SGLT2 inhibitor empagliflozin. There are numerous ways in which these drugs may be beneficial directly in the heart and many of them are still being explored in experimental studies.

Extrapolating from the clinical trial data from heart failure with preserved and reduced ejection fraction, as well as these experimental studies that have identified potentially beneficial targets in the heart, there is a phase 3 clinical trial now underway called SONATA-

HCM, and I'll just walk you through a little bit of the study design and endpoints for that trial.

The duration of the trial is 26 weeks. It is a placebo-controlled trial, and it's being conducted at 135 sites in 20 countries with the goal to enroll 500 participants. There are 30 sites in the United States in total.

The trial is enrolling adults with hypertrophic cardiomyopathy, and importantly, we're enrolling patients with both obstructive and non-obstructive HCM. And the reason for this is because the mechanism of action is not thought to target obstructive physiology itself and could be beneficial across the spectrum of patients with HCM. The eligibility criteria, that the patients need to have some level of symptomatic limitations, so that's NYHA Class II or III, and based on their response to the clinical summary score of the KCCQ, or Kansas City Living with Heart Failure questionnaire, their score needs to be under 85 so that they have, again, demonstrating some symptomatic limitation in their daily life.

The ejection fraction needs to be at least 50%. And if they're on a cardiac myosin inhibitor, then the ejection fraction needs to be at least 55%.

So the randomization is 1:1, sotagliflozin at 400 mg versus placebo, with 250 patients expected to enroll in each arm. There's a 5-week screening period followed by a 26-week double-blind treatment period and a 4-week follow-up period. The primary endpoint of the study is change from baseline in Kansas City Living with Heart Failure clinical summary score. And there are a number of secondary endpoints that include proportion of patients with at least class 1 improvement in NYHA classification, change in baseline in KCCQ total symptom score, and a number of other endpoints based on cardiac imaging by echocardiography.

So to summarize a few key points, SGLT inhibitors have become standard of care for heart failure with both reduced and preserved ejection fraction.

They appear to be acting directly in the heart to improve the way the heart uses fuel, as well as to improve cardiac performance. The dual inhibitors may be acting favorably in part due to their inhibition of the SGLT1 isoform, which is expressed in the heart. The beneficial effects of SGLT inhibitors may extend to patients with HCM, and I say this based on the similarities to heart failure with preserved ejection fraction in terms of diastolic function as well as metabolic abnormalities. And we're very excited to see the results of the SONATA trial, which are expected to be available in the first quarter of 2027.

Thank you so much for watching.

Announcer:

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