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What the SODIUM-HF Trial Means for Heart Failure Patients

Dr. Butler:
The SODIUM-HF trial assessing sodium intake in heart failure patients was designed to assess the effects of a low-sodium diet on adverse cardiovascular events in these patients. And now that the study results are in, we're taking a look at the findings and what they might mean for our patients.

You're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler. And joining me today to discuss the SODIUM-HF trial is Dr. Justin Ezekowitz, who's the Co-Director of the Canadian VIGOUR Centre at the University of Alberta and Professor of Medicine in the Division of Cardiology. Dr. Ezekowitz is also the lead author of this study and presented its findings at the 2022 American College of Cardiology annual scientific meeting.

Dr. Ezekowitz, welcome to the program.

Dr. Ezekowitz:
Thanks so much, Javed. Pleasure to be here.

Dr. Butler:
So to start us off, can you give us a little bit of a sense of what did we know prior to the randomized controlled trials, just some observational data, the general sense of sodium intake in patients with heart failure? What were the guidelines saying originally?

Dr. Ezekowitz:
Sure. So, Javed, we've been looking at sodium for over a hundred years. Now clearly, I'm not a hundred years old, so lots of the data I had to review before we even started the trial. We realized that we've been looking at this question as a medical community for a long time for any situation of volume overload. There's been large surveys of patients in the general population with cardiovascular disease and even with heart failure to look at their sodium intake, and when we start to look at it across both regions and within countries, it's quite variable; but in general, the epidemiology shows that patients with heart failure, first of all, are consuming about anywhere around 2,800 to 3,000 milligrams or 3 grams per day of sodium depending on the region of the world. This differs a bit from the cardiovascular non-heart failure community and also from the general population. There are very 3 distinct sodium intake populations.

We also were realizing that there's been a few very small trials early in the study of heart failure, and they have been meta-analyzed with no consistent outcome. Guidelines started to recognize this and really backed away from very hard and fast rules around the recommendation because the scientific background is weaker than anticipated, and people moved away from that overall.

Dr. Butler:
So that makes a lot of sense that the physiology of heart failure may be different than a general healthy population where low-sodium diet is recommended. Were there any clinical trial data prior to your study that suggested that there is a potential for harm? And why did you choose to pursue your study?

Dr. Ezekowitz:
Sure. So there's 9 or 10 small studies, most of them have been very inconclusive just based on their size or their intervention. There has been a nice study from Mexico which showed some potential benefit for patients as outpatients with heart failure with a lower-sodium diet less than 2,400 mg a day, but conversely, there have been a series of larger trials that have been associated with a potential harm, and this was in conjunction with strict fluid restriction less than a liter a day, very high doses of diuretics, and so it was very hard to tease out is it the low-sodium diet that's causing the negative effects or is it something else, such as a strict fluid restriction or the very high dose of diuretics. So when you put them all together, really no consistent message across the ambulatory care, inpatient environment, HFpEF, HFrEF, short-term, long-term duration. So we had a number of studies but really very inconclusive overall.

Dr. Butler:
So there is a pretty global consensus that reducing salt intake as a primary prevention measure at population level is associated with lower blood pressure, lower risk of stroke, and improved outcomes. Can you just tell us a little bit about the pathophysiologic underpinnings in heart failure patients and where there might be some concern?

Dr. Ezekowitz:
Sure. So this is a very complex area, and I just would suggest people read a terrific article by Gupta, et al. in circulation in 2012 which really lays out the pros and cons of a lower dietary sodium diet. Now on the pro side, there is potential to reduce the total volume of the body—that's a potential—reduce the diuretic dose, reduce the wedge pressure, and potentially keep people in a little more compensated state overall. Now on the con side, that any time we are reading a lower-sodium diet, there's a chance for intravascular volume contraction, lower cardiac output, lower sodium delivery to the nephrons, and decreased renal perfusion, and these all activate the renin angiotensin system, and so you can understand that if those are the case, that those are deleterious effects even for people on appropriate medical therapy. So the balance of those 2 means that we have to be a bit more thoughtful that it's not just as simple as reduce this one thing and you'll get the one outcome that's only green. We ought to look on the red side too to make sure that we understand both parts of that equation.

Dr. Butler:
So with that background, can you tell us a little bit about your study design and what were the aims?

Dr. Ezekowitz:
Sure. So we designed the SODIUM-HF trial to be a very pragmatic multicenter, multinational trial testing whether or not reducing dietary sodium in ambulatory patients with heart failure to below the currently recommended target would improve their overall quality of life, NYHA class, and reduce the number of clinical events, so it was a M and M trial. We looked carefully at whether or not we could reduce dietary sodium below a level that currently is recommended, and generally speaking, most patients in a heart failure clinic are recommended to eat less than about 23-- or 2,400 mg a day, and they have had that advice over time, so they kind of changed their diets a bit. We wanted to test it lowering it even further to less than 1,500 mg a day using a very pragmatic approach of menu-based system rather than a feeding trial where you get all your prepared meals. And we wanted to do this over a longer period of time, so we did it over about a year, so the patients were individually followed up for over a year—and we have a 2- to 5- year outcomes also being tracked. We did this trial in 6 countries and 26 sites, about just over 800 patients enrolled, and what we tried to identify was, number 1, do we reduce the chance of all-cause mortality, cardiovascular hospitalization, or cardiovascular ER visits? That's number one. And then secondary, do we improve quality of life, NYHA class, and 6-minute walk test?

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. Justin Ezekowitz about the SODIUM-HF trial and its findings.

I have to say, even before you tell us the results, a huge congratulations and kudos. I mean, feeding trials are difficult to do, so absolutely fantastic how you were able to conduct this trial. So can you walk us through some of the results?

Dr. Ezekowitz:
Sure. So first of all, the trial was stopped early and I think people should be aware that we stopped early due to operational considerations as well as the COVID pandemic, but also because the DMC had met after the first 500 patients that had completed their 12-month follow-up to make sure that there was no other efficacy or futility concerns, and they also recommended stopping based on a number of factors. So we overall did enroll 806 patients who were randomized 1:1. For the primary endpoint, it was not statistically different between the 2 arms, and I would highlight that the lower-sodium arm had numerically fewer clinical events overall than the usual care arm. That's important to recognize. But the hazard radio was 0.89, so not statistically significant. We then also wanted to ensure that we had to reach our sodium reduction. And in fact, between the 2 groups, we had reached a 450 mg delta or difference between the 2 arms of the trial, and that was appearing very early on, as early as 6 months and continued on to 12 months, so the dietary sodium reduction was sustained, but the clinical events linked to that did not change the overall outcome.

Now when we broke it down, we didn't see any of the individual endpoints that were statistically significant, so we then looked at our secondary endpoints to understand if there's other things we should understand about the data. When we looked at the quality of life, we used the KCCQ score to really look at this, and we used both the overall summary score, the clinical summary score, and the physical limitation score to really understand it. And when we looked at this, we saw that the low-sodium arm had a greater improvement in quality of life by all 3 different measures by about 3 to 3.5 points, so that's both statistically significant and clinically meaningful in terms of the quality of life improvement for patients in the lower-sodium arm compared to usual care. We then looked at the NYHA class. Patients in the lower-sodium arm of the trial had a greater likelihood of improving at least 1 NYHA class compared to their usual care compatriots, and so the NYHA class matched the quality of life improvement we had seen, so a clinician and a patient would be at different viewpoints. Then we looked at the 6-minute walk test and identified that although there is numerically a greater distance walk by people with lower-sodium diets, this was not statistically significant. And I just caution that we had very few people who were able to complete that at the 12-month mark, so that really did reduce our power to demonstrate a difference at the end of the trial.

Dr. Butler:
So, what were the actual sodium levels in the 2 arms? And what I want to highlight here is to just make sure I get your opinion that if the primary endpoint of the difference was not met, does that mean that patients can eat as much salt as they want?

Dr. Ezekowitz:
Wow, that's a loaded question, and it's loaded with salt. Javed, that's great. Let's first start with what was the baseline sodium intake for our patients, and they started off at around 2,200 mg per day. Now we didn't do 3-day food records. We didn't do urinary sodiums, recognizing that on diuretics their urinary sodiums aren't as translatable to a food consumption. So people were starting off at about 2,200 mg a day. We had people, of course, with a much greater intake than that, and so they will be diving that into secondary analyses. By the end of the trial, the usual care group was eating around 2,073 mg a day, which is about a 3 or 4% reduction over time, so really not different over time statistically, but the intervention arm was eating about 28% less sodium, so we actually had a decline by about a quarter in those individual patients, so that is clinically meaningful. For any of us to reduce our sodium intake by a quarter is quite difficult. So they're starting off at about 2,200 mg a day. They are reducing it further. And when we look at our diets, such as, Javed, if you and I went for dinner and we went out to a restaurant, we're going to probably have 2,200 mg of sodium in that restaurant meal alone, so these people were making a change throughout their entire day and their lifestyle to reduce their dietary sodium. We need to recognize that we had to balance the fluid intake, calories, and all the other nutrients. We actually only had the menu system change dietary sodium rather than all the other factors that can come along with that.

Now in terms of what should we be recommending, I think that's really where it gets tricky. Based on the clinical trial, you could say, "Well, there's no change in clinical events by the statistical analysis, so maybe we should just stop recommending it." I would say that that's probably not what we should pursue. I think there is still an 11% reduction based on the hazard ratio that's underpowered in the overall trial, so we have to recognize the kind of flaws in any clinical trial. We did see a quality of life improvement for patients in the lower-sodium arm and conjointly an improvement in NYHA class, so if those 2 things are very important as our goals for an individual patient, and that as you talk to patients, I think those are still very important to realize that those are potential benefits of a lower-sodium diet. Now does it reduce clinical events? I need to then be a bit more mindful when I'm seeing a patient in clinic. If they ask me, "Will this reduce my chances of being in the hospital or ER or dying?" I have to be a bit more thoughtful in how I answer that in saying, "We don't actually know the answer to that question." The largest trial doesn't demonstrate that. Therefore, if your goals are quality of life and improving your overall functional status, yes, this will work, but let's be a little bit more cautious in our approach to it.

Dr. Butler:
Well, great. I very much appreciate your insights both as a clinician and as a clinical trialist. So thank you very much once again, Justin. It was absolutely a pleasure speaking with you today.

Dr. Ezekowitz:
Thanks so much, Javed. Great to talk to you.

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.