- I'm Harriette Van Spall, associate professor of medicine, cardiologist and researcher at McMaster University in Canada and it is my absolute delight to invite my friend, Justin Ezekowitz, professor of medicine in the division of cardiology at University of Alberta, who is here at ACC 2022 to present his late breaking clinical trial the SODIUM-HF trial. Welcome Justin.

- Thank you, Harriette and great to be here.

- I'm so delighted to talk to you about this trial because it is rich with clinical implications that will inform the care of our patients. You and I both take care of patients with heart failure and sodium restriction has become the default order on many of our in-patient order sets. It is something we also advise patients to do to self manage their heart failure care and so your trial is particularly important. Tell us why you conducted it and what the research question was that you aimed to answer.

- So thanks Harriette and so one of the things that as you as a practitioner, you know, heart failure clinic and and myself as well is you realise you make recommendations, a lot of things around medications and devices and self-care every day and one of the things that I was struck by was that we make this recommendation, you know eat less salt and it comes out in a variety of different ways, but that's generally what it means and, you know, I started looking at why do we make this recommendation? And we're using high dose diuretics, We're doing all these other fancy things but we just don't have a good scientific rationale to do so. So I started to look at this area with my colleagues and we said, well why don't we actually look at the scientific, the clinical trials, a higher quality evidence and realised that there's really a lack of good high quality evidence from which we could support our recommendation which of course led to the design of a small protocol which led to a larger clinical trial design And we of course then set out, you know what are our real objectives? And so we decided we wanted to really tackle this area and say, does reducing the dietary sodium improve or reduce the number of clinical events? So really is it, can we link the diet to the clinical event? And that was a really fundamental difference from just saying, hey, can we measure sodium in the diet? That was a big difference from the prior clinical trials where that was really the fundamental thing they were doing.

- Right, And so yours was a multicenter clinical trial in ambulatory patients with chronic heart failure and your primary composite endpoint encompassed clinically relevant outcomes of all cause mortality, cardiovascular hospitalizations and emergency department visits. Tell us a little bit about the trial design and how you facilitated appearance to your intervention which is a tough intervention for many.

- Absolutely, and the intervention itself which, so patients were randomised one-to-one to the intervention or usual care. Now, usual care, first of all is really just following any general recommendations given by any clinician around any dietary modification of sodium which for most patients meant that they have a dietary sodium content of around anywhere from 2,500 milligrammes per day or or sometimes greater, sometimes lower. We did exclude people who are already eating an exceedingly low dietary sodium of less than 1,500 milligrammes a day. Once patients were randomised, the intervention was really centred around a behavioural intervention which is what nutrition is. We all eat food and we all have to think about how we shop for and eat our food. We looked at different designs. We thought about the Dash Diet which was, you know meals that are fed to people made by a metabolic kitchen. We knew that that was not either pragmatic or or even feasible in a larger scale. So we took upon a menu based system where patients were given menus based on their caloric intake, their requirements, and just, we substituted out at higher sodium things for lower sodium things and so they could select off the menu whatever they wanted and it turns out there's a lot of good variety in there. We further adapted this to really the six countries that were involved, Canada, Chile, Columbia, Mexico, Australian, New Zealand. We adapted those menus because we all eat locally and just then tracked it by food records to see what their dietary sodium intake was. The three day food records are quite valuable because then a dietician could both counsel, like could assess and counsel based on that information.

- Right, so was this diet directed by a nutritional scientist? How did you devise these menus?

- Yeah, so we had a really smart set of dieticians that form the dieticians working group and they were from around the world that were part of the clinical trial and they helped to shape the the menus and how they were designed. So they were, you know, balanced and appropriate and all those usual things that we get from our dietary colleagues. Now, once we designed the menus, I'm not a dietician. So, you know, I don't have the expertise from which to design that, we had to think about how they would be deployed and from a very pragmatic approach, we looked at the clinical trial sites, you know the 26 clinical trial sites from around the world and for sites that had a dietician, it was pretty straightforward, for sites, we had some nurses, nurse practitioners even some physicians giving this advice after they went through appropriate training to make sure they were skilled to do so and really we found that the menus were widely accepted by patients as a generally easy to do type of activity. It was much easier than following a Dash Diet type of approach where they got their meals which would not be very feasible if they're going out or eating with family or friends. So they, you know, they were making a dietary modification but also a behavioural intervention at the same time.

- Right, certainly in observational data sets there are concerns that diets low in sodium may also be low in some of the micronutrients. Did you sort of design the the diets around micronutrients as well or was it strict sodium restriction? And the second part is how did you determine what that sodium level was going to be?

- Yeah, so two really good questions. The first is, we chose to only modify the dietary sodium. So the diets were balanced and we didn't want to modify anything else because we really wanted to solely test dietary sodium without changing micronutrients. Now, of course, anytime you change a diet, you naturally are changing those things. So we'll have plenty of data from the three day food records which are followed serially every three months, so for which we can digest those micronutrient changes that may have occurred. So we will have to do then second explorations of our data. We just haven't yet got to that. We did also track things like fluid intake which I think people would naturally think might be a link and really there's no difference in fluid intake for each group. In terms of how we track it, we chose not to track urinary sodiums which is one method that's being used in other projects. There's two really good rationales of why not to do that. Most of our patients were on a diuretic, and urinary sodiums have been tested by our colleagues of Toronto, looking at patients with heart failure. They actually don't track what they eat very well or dietary sodium. So it wouldn't it been a great marker. The second is it becomes very impractical because urinary sodiums, tracking urinary sodiums requires spot urinary sodiums reflected to a 24-hour urinary sodium. It's just not very feasible in a large clinical trial setting. So we chose the food records and after all, that is what patients were recording their eating, so that is a thing we're trying to change and better to measure.

- Okay, so you randomised patients to 1,500 milligrammes of a sodium restricted diet versus a usual diet and tell us how long you followed up the patients for and what you found.

- Yeah, so the primary endpoint was 12 months. We have an ongoing longer term follow up going but the primary endpoint is at 12 months, overall, we looked at our primary endpoint and found a couple of key things. First of all, did we lower sodium enough? We lowered sodium by about 415 milligrammes per day by 12 months. So it was met by about six months and 12 months was about the same. So we were able to get close to what we wanted which was around 500 milligrammes of sodium lowering or difference between the groups. We didn't have any weight changes, blood pressure changes or energy intake, you know, caloric intake changes. So we were very well balanced in terms of just lowering sodium as much as we can assess it, in terms of the primary outcome, we did not see a statistically significant difference in the primary outcome. Hazard ratio was 0.89. This was not statistically significant between the two groups. There is a hint or an indication that the lower sodium group may have had a slightly better outcome where we looked at our individual outcomes such as cardiovascular related hospitalizations but there was no statistically difference, significant difference across any of the three components that made our primary outcome. So we have to conclude based on the purist view of that there was no significant difference on the primary outcome by lowering dietary sodium.

- So very important findings. How do you think that these are going to translate to clinical care? How do you perceive the guidelines are going to adopt the findings of your trial and recommendations that they make?

- Yeah, so this is a really key question that's been on my mind as a former guidelines chair is how would I integrate this into the overall recommendations. Now there's a couple of other tidbits that may influence that, the first is we tracked two other or three other things that I think may influence the guideline or a clinician or a patient to decide what they might want to do. The first is we had a small indication that there was an improvement in a six minute walk test and that may indicate that there's a functional gain by a lower sodium diet, but it was not significant. However, the quality of life scores were actually clinically and clinically meaningfully different on a lower sodium diet, as in they got a better quality of life being on a lower sodium diet over the six and 12 months. Similarly, the NYHA classes were also better on a lower sodium diet compared to the usual care. So when you ask, you know, how do we integrate this? We have, you know, no difference on the clinical endpoints but we do have an important one on the quality of life as well as NYHA classes. So as a clinician, I might say this may be part of a strategy to improve overall care of a patient. From a patient perspective, it might be seen as something as they can drive as their own self care and from a guidelines committee, you know this is going to be a tricky wicket, is if we are only focusing on the overall clinical outcomes which is what we generally focus in on versus secondary outcomes, which may indicate that it's generally better to be on a lower sodium diet and I think that's where people will have to have a lot of discussion and debate as to what the relative value is of our trial compared to the prior literature.

- Right, and were your secondary endpoints adjusted for multiplicity?

- Yeah, so we've done a number of secondary looks at this at how we do this. We've done multiplicity, we've done some co-variant adjustment and in fact, we've done a number of different factors, which really, I think we will find are, they're robust, the secondary outcomes, but I do think that's where people have to kind ultimately read the manuscript, digest the information and then as we work through secondary analysis of our dataset, I think that's where a lot of the information that might further influence what we decide to do a year or two years from now as we kind of go through that longer process of trying to figure out more of the information from our data.

- Yeah, and I agree, health status, health related quality of life are such important endpoints that we underemphasize in so many of our regulatory approvals processes. Although it's starting to change at FDA. I wonder if you would tell us a little bit more about how you measured health related quality of life and whether the differences were beyond the minimally clinically important difference thresholds.

- Yes, so we measured, we used KCCQ and we chose chose this because it's well validated and it's been kind of our general go-to for a quality of life, disease specific quality of life assessment. We measured it at baseline six and 12 months and so we have, once we adjust for the baseline differences, we have an adjusted mean difference in the overall summary score of 3.66, sorry, 3.38 and that is very similar to our large clinical trials. In fact, it may even be greater in the difference between the two groups once you account for the baseline variation. So, very similar to that of our larger scale trials. When we looked at the physical limitation score, also an interesting one for me 'cause of the six minute walk differences, we had a difference about 3.77. So you put that together as to what the differences between the groups are. That's quite important because overall our differences in the quality of life from baseline are about five or six points. So that's like very similar to the overall difference and then the difference between the groups is in the three to four range and those generally are meant to be clinically important differences. We're always striving for the five, but very rarely seen in even our larger clinical trials.

- Right, and another question that comes up is whether the patients knew, were they unblinded to the intervention? So did the patients know that they were on sodium restricted diet or not?

- Yeah, absolutely. This was an unblinded to patients 'cause we looked at many different ways to try to blind this and there just weren't any feasible ones from the patient level. So that influences any of the things such as a quality of life assessment, six minute walk test, you can imagine even the NYHA class, even though we blinded the outcome assessors, is when they were gathering the KCCQ data or assessing the NYHA class or doing the six minute walk test, the patient did know what diet they were eating. There's just no way to really blind that effectively. They could have known that very easily even if we had not informed them. They would've kind of realised when we took out capers and all the salty good stuff, they would've realised very quickly which one they're on.

- Right, well, I think your trial is super exciting and really transforms the way we counsel patients about sodium restriction. It's almost become a mantra that previously was informed a very modest quality evidence and you've really shown us not only the lack of clinical benefit in sodium restriction but the possibility of improving patient reported measures and so balancing the findings from your primary analysis with your secondary endpoints but also how a well executed trial can answer a question in a manner that changes the way we deliver care even when it is something that's dietary based which often takes a back seat to some of the drug and device interventions that we tend to focus on and celebrate. I celebrate your findings. I'm so proud of you as a colleague, congratulations on being here at ACC and on yet another important trial that you've led. Thank you for spending your time with us, Justin.

- Oh, thank you, Harriette and thanks for the interest in the trial and also being such a good colleague. So my appreciation to you.

- My pleasure.