radcliffe cardiology

Title: ACC 24 Late-Breaker Discussion: The ARISE-HF Trial
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Dr Harriette Van Spall and Prof James Januzzi

" **Dr. Harriette Van Spall:** I'm Harriette Van Spall, Associate Professor of Medicine at McMaster University, and I'm so honored and delighted to have with me Professor Jim Januzzi, Professor of Medicine at Harvard Medical School. He is Principal Investigator of the ARISE HF study and here at ACC 2024 to discuss this trial in the Late Breaking Clinical Trial session. Welcome, Professor Januzzi.

Prof. James Januzzi: Thanks very much, Dr. Van Spall, great to be here, thanks for having me.

Dr. Harriette Van Spall: We are going to discuss this very interesting trial and a very novel therapy, maybe not so novel, but in the context of your hypothesis, certainly new. Tell us about your intervention and the hypothesis that you sought to test.

Prof. James Januzzi: Sure. Thanks very much for the opportunity to talk about this heart failure prevention. When we think about how we want to reduce the issues associated with heart failure, prevention would be the goal. Rather than treating overt disease, there's been a lot of focus on identifying patients that are at high risk for proceeding on to overt heart failure. And persons with diabetes represent a really clear opportunity, because people with diabetes have a more than doubling in their risk for development of heart failure. Furthermore, we have tools to identify certain individuals that are likely to proceed on to heart failure. And in the population of persons with diabetes, so-called diabetic cardiomyopathy, which exists in about one in four people with diabetes and it's related to chronicity and severity of hyperglycemia, is a clear risk factor for progression to overt symptoms. So what we sought to do in this study was to evaluate the effects of an aldose reductase inhibitor—and I'll explain why in a moment—to prevent progression to overt symptomatic heart failure among individuals with type two diabetes and diabetic cardiomyopathy. The reason is because the polyol pathway, which is activated by hyperglycemia, is an intracellular pathway whose rate-limiting step

is catalyzed by aldose reductase. And indeed, although you point out correctly that aldose reductase inhibitors are not new therapies—they've been around for 20 or more years—the problem is that aldose reductase inhibitors previously developed had a lot of off-target side effects and were relatively non-potent. That said, in studies of aldose reductase inhibition, there was a sense there was evidence in retrospective analyses that it might improve exercise capacity among people with diabetic cardiomyopathy. We were fortunate in the development of a newer aldose reductase inhibitor called AT001, which is highly potent, very specific for aldose reductase, and very well tolerated, which allowed us to study the impact of this drug in people with diabetic cardiomyopathy.

Dr. Harriette Van Spall: Sure. Would you go over your inclusion and key exclusion criteria so we know who this trial involved?

Prof. James Januzzi: Sure. Yeah, absolutely. So, very briefly, we had sort of complex inclusion and exclusion, but it can be simplified down to people with type two diabetes and stage B heart failure. So they needed to have either structural heart disease or elevated cardiac biomarkers, as defined by the universal definition of heart failure, together with exclusions of established ASCVD, valvular heart disease, or established arrhythmia. So, in essence, we're looking for people who actually have stage B heart failure without other causes, I guess, is the way you would put it. In addition, by regulatory requirement, the FDA and other regulatory agencies required that these patients have well-controlled blood pressure and well-controlled blood glucose at the time of inclusion in the study. So, essentially, taking a population with heart muscle disease without other known causes and then randomizing them to receive placebo or ascending doses of AT001.

Dr. Harriette Van Spall: Sure. And the prevalence of ischemic heart disease is so high in patients with diabetes, and I probably would guess that many people would ask, why exclude people with ischemic heart disease? Was there any concern about safety or efficacy in this population? Or was it merely to tease out those who had diabetes as the sole cause of...

Prof. James Januzzi: It's the latter, actually, Harriette. Yeah. So, really, you know, one could argue, for example, if diabetic cardiomyopathy is related to presence and severity of hyperglycemia, why restrict to patients with well-controlled blood glucose? Right. Hemoglobin A1C less than 8.5 was an inclusion criterion. So, I mean, it's exactly as you say. The idea is to try to focus down on a population of patients who have the diagnosis of diabetic cardiomyopathy. But to be clear, in studies of DBCM, it certainly can coexist with individuals with coronary disease or valve disease. The problem is, when we're trying to get down to mechanistically, what's driving the impaired exercise capacity in these patients, which was also an inclusion criterion. They had to have impaired peak VO2 in order to participate. We didn't want to be enrolling patients with active ischemic heart disease, where the treatment would be a very different intervention.

Dr. Harriette Van Spall: Tell us about the study design, then.

Prof. James Januzzi: Yeah. So patients had a cardiopulmonary exercise test at baseline to evaluate their eligibility. If they had a peak VO2 less than 75% of age and sex match controls, they were then randomized to receive placebo or ascending doses of AT001. We looked at a lower dose at 1000 milligrams twice daily, and a higher dose at 1500 milligrams twice daily. Now, the higher dose was the dose that we were intent on studying based on the phase two studies of the drug. The lower dose was included as part of a regulatory request, but the primary endpoint was a comparison between placebo and high dose AT001. After a 15-month treatment duration, patients had a second cardiopulmonary exercise test, and the goal was to look at the effects of AT001 to stabilize exercise capacity. So we looked at the difference in peak VO2 between placebo and high dose AT001 at the 15-month time point. In addition, when randomized, we stratified patients on the basis of their region of enrollment, their baseline cardiopulmonary exercise test performance, as well as use of SGLT2 inhibitors or GLP1 receptor agonists at baseline.

Dr. Harriette Van Spall: Sure. Had there been a preceding dose finding or phase two trial to guide the dosing? What was the regulatory request about?

Prof. James Januzzi: Yeah, great questions. So there was. And the phase two experience suggested that 1500 milligrams twice daily was both well-tolerated and effective in lowering circulating sorbitol concentrations. Through the activity of aldose reductase, sorbitol is generated, which is part of what leads to tissue injury as a cause of the polyol pathway's damage. But the previous experience with aldose reductase inhibitors, which included off-target effects such as liver function abnormalities, kidney dysfunction, and other nasty side effects from less specific and lower potency ARIs, has led to regulatory agencies asking us to look at lower doses. But the intention right from the start was to look at 1500 milligrams as the goal dose.

Dr. Harriette Van Spall: And what guided your selection of the primary endpoint?

Prof. James Januzzi: Yeah, so, really wonderful question. When we look at individuals with stage B heart failure, it's very clear. And you see this, I'm sure, clinically as well. But although by definition, stage B is neither past nor present symptoms of heart failure, it's pretty obvious that many patients with stage B heart failure who have never been given an overt diagnosis of heart failure actually have functional limitation. And indeed, when you look at individuals most likely to transition in relatively short order to symptomatic heart failure, one can identify folks that have reduced exercise capacity, really a phenotype in transition from asymptomatic cardiac dysfunction or pre-heart failure on their way to developing symptomatic failure. So we looked at this population as being a target because they are the most likely to develop overt symptoms within a relatively short period of time.

Dr. Harriette Van Spall: Sure. So your primary endpoint was the between-group difference in the change in peak VO2 from baseline to 15 months. What were your secondary endpoints?

Prof. James Januzzi: Yeah, great question. So you articulated the primary endpoint and that was particularly between placebo and high dose AT001. The key secondary endpoints were the percentage of study participants that had a meaningful decrease in their peak VO2. In the CPET literature, that's a greater than or equal to 6% decrease. We looked at change in N-terminal proBNP concentration, as well as changes in feel

and function endpoints such as the KCCQ score, the physical activity scale for the elderly, which is essentially a questionnaire that assesses activity levels. And then lastly, we also looked at progression to symptomatic heart failure events as a secondary endpoint as well.

Dr. Harriette Van Spall: Sure. What was your sample size and baseline characteristics in each group?

Prof. James Januzzi: Sure thing. Yeah. So our power estimates were that we needed approximately 180 study participants per treatment group. In the end, we randomized 691 total, just around between 185 and 190 or so per group, placebo, low dose, and high dose, to receive the various study drug concentrations. And then when you look at the balance of how these patients randomized, this was an international study and so we have a very interesting and unique patient group. Actually, the average age was around 68 years. It was slightly female predominant with about 52% women. Patients were relatively diverse. About 40% were Black or African American, another 40% were White, and then the remainder were of mixed racial heritage. And overall, this population, in addition to being older, more female predominant, also had relatively well-controlled blood pressure and relatively well-controlled blood glucose. The median hemoglobin A1c was around 7.2, systolic blood pressure around 128. So, overall, a well-controlled but high-risk group of patients.

Dr. Harriette Van Spall: Sure. And what were your findings?

Prof. James Januzzi: Yeah. So, it's interesting. The trial was a bit of a mixed result. When we look at the primary endpoint of the effect of AT001 high dose versus placebo on change in peak VO2, the trial was positive. There was a statistically significant and clinically meaningful difference in peak VO2 change between placebo and high dose AT001. Patients that received high dose AT001 had a stabilization of their peak VO2 at the 15-month time point compared to the placebo group, which had a decrease. The between-group difference was about 3%. So, this was actually a clinically meaningful and statistically significant result, which was positive and really the main goal of the trial. When you looked at the key secondary endpoints, however, there were no differences.

In other words, there was no difference in the percentage of patients that had a decrease in their peak VO2. There was no difference in feel and function endpoints like KCCQ score or the PASE scale. And there was no difference in change in N-terminal proBNP concentrations. Likewise, there was no difference in progression to symptomatic heart failure events. So, overall, the trial was positive, met its primary endpoint, and it met its goal of suggesting that stabilization of exercise capacity might be possible by targeting diabetic cardiomyopathy using this drug. But the secondary endpoints suggest there are a lot of other things we need to consider in terms of how this drug impacts patients with diabetes.

Dr. Harriette Van Spall: Sure. And were there any safety signals with AT001?

Prof. James Januzzi: Yeah. So, surprisingly well-tolerated drug, actually. So, there were, at most, no statistical or clinical differences between placebo and high dose AT001 for any adverse events, serious adverse events. Overall, a well-tolerated drug, which was really positive in terms of its potential future development.

Dr. Harriette Van Spall: And what's next for AT001?

Prof. James Januzzi: Yeah. So, that's the million-dollar question, Harriette. I think that, you know, when we look at these data, we see a drug that appears to be doing something for stabilization of exercise capacity. You know, obviously, other aspects of heart failure prevention need to be evaluated in this population. But the phase three program for this drug in diabetic cardiomyopathy, in addition to our trial, is intended to be launched later this year.

Dr. Harriette Van Spall: Sure. We look forward to seeing how that phase three program evolves. Professor Januzzi, thank you very much for joining us and congratulations to you and your collaborators on the results of your trial.

Prof. James Januzzi: Thank you so much. I really appreciate it. Thanks for having me."