**Title: ACC 23 Late-breaker Discussion: The REVIVED-BCIS2 Viability Study**

**Participants: Dr Harriette Van Spall, Dr Divaka Perera, Dr Peter O’Kane**

**Date: 1 March 2023**

**Dr Van Spall**

Hello, I'm Harriette Van Spall, Associate Professor of Medicine and cardiologist from McMaster University in Canada and I’m absolutely delighted to be here at ACC.2023. And welcome doctors Divaka Perera and Peter O'Kane to discuss the results of their revived BCIS Two substudy on myocardial viability and revascularization. Dr. Perera is a professor of cardiology at King's College London and the PI of the revived BCIS II trial. And Dr. O'Kane is a consultant interventional cardiologist at the Royal Bournemouth and Christchurch Hospitals and Editor in Chief of the ICR3 Journal. An investigator in the revived BCIS III trial. Welcome doctors Perera and O’Kane.

**Dr O’Kane**

Thank you.

**Dr Perera**

Hello, Harriette. Thanks for setting up this interview.

**Dr Van Spall**

It’s my pleasure. We are so excited to learn the results of your sub-study and I wonder if Dr. O'Kane might start by telling us what the primary results of the BCIS-II REVIVED or the revived BCIS II trial revealed in the context of prior literature.

**Dr O’Kane**

Thank you, Harriette. Well, it was a great pleasure and honour to be part of this very important study. And we in the UK recruited 700 patients into this trial. With the, it is a long study, it took quite some time to complete and the primary endpoint for us was a bit of a, perhaps, surprise as an interventional community because for years we've always felt that treating patients and revascularizing them would benefit them, improving their prognosis and reduce the incidence of heart failure admission inpatients who have ischemic cardiomyopathy. In fact, when Divaka presented the results in Barcelona at ESC in August last year, there was a gasp in the room when he showed the Kaplan-Mayer curve. First of all, obviously, the endpoint was quite high of 38% in patients with medical therapy. But sadly for us, perhaps, PCI did not have any effect on this and did not improve that endpoint. So it didn't change the rate of death or it didn’t change the rate of cost of admission, which is clearly a very important finding and the practice-changing in how we now treat these patients and view them in the future. And until this time, there really wasn’t a trial of PCI in a setting. We obviously had STICH and STICHES in terms of revascularization with bypass surgery, but a very different thing looking at surgery, of course, from PCI and it just showed you can't extrapolate the concept of revascularization just because it is revascularization as minor other factors involved.

**Dr Van Spall**

Right, Divaka, tell us about your patient population.

**Dr Perera**

Right, so we selected patients who had ischemic cardiomyopathy, so very severe left ventricular systolic dysfunction and extensive coronary artery disease, but also those who had a minimum threshold of viability. Now, that was defined as having at least four segments that were dysfunctional at rest but was seen to be viable on any of the modalities that could be used in the trial. So, cardiac, MRI, dobutamine stress echo, SPECT or PET for such segments that could be revascularized by PCI. So it was a minimum threshold for entry. But of course, we were aware that once you met that minimum threshold, there would be a wide spectrum of viability and scar in the patients who were enrolled. And tell us about this substudy. What were you hoping to answer with it? Well, we were trying to understand the impact of viability status at baseline on the treatment effect primarily, which shown in the trial, as Peter said in the overall trial, that PCI didn't reduce the incidence of major events. But what if we characterize patients by viability? And so this is a prespecified substudy.

**Dr Van Spall**

And what was your hypothesis?

**Dr Perera**

So actually, we had several interlinked hypotheses. The first hypothesis was that viability characterization at baseline would predict the rate of death and heart failure hospitalization, and it would predict the rate, the recovery of LV function. Those two were the primary and major secondary outcomes of the REVIVED trial as a whole, as you remember. And then that if they did predict those outcomes, they would also be beneficial in choosing patients who might benefit from PCI compared to medical therapy. Would there be an interaction between the treatment effect and viability status at baseline? And what did you find? So, firstly, I'll tell you a little bit about how we characterize viability in the trial. To go into the trial centres, adjudicated their own viability using the modality. But in this substance, we collated all of those data, CMR in the main, but stress echo as well, and analysed them in blinded core labs, core labs that were blinded to the treatment assignment. That’s an important sort of quality-controlled step, if you like. And we had 610 core lab adjudicated cardiac MRs or stress echoes. We didn't include any of the radioisotope scans in this particular analysis. Before I go on to the first finding, let me tell you two ways in which we characterize viability. The first was a quantification of recoverable myocardium. And that's what we have in our heads when we think about hibernation. If it's dysfunctional at baseline, what’s likely to recover with medical therapy or revascularization, so, dysfunctional but viable. And the second was quantifying scar, which is something we can do in patients who have CMR as a standalone entity. And we looked at both of those aspects. Now, coming to the findings, what we were surprised to find was that recoverable myocardium, so dysfunctional but viable at rest, didn't seem to have any association with the primary outcome of death or heart failure hospitalization or, interestingly, the likelihood of left ventricular recovery. Now, conversely, scar, or the burden of scar as a proportion of myocardium was highly predictive of both death or heart failure hospitalization and the likelihood of LV recovery. So the more scar you had, the more likely you were to have a primary outcome event. Now, interestingly, that stood up even when you corrected for baseline left ventricular ejection fraction. But the reverse wasn't true. Left ventricular ejection fraction, which is what we all use routinely a sour crude but widely available stratifier. LVEF at baseline was no longer predictive of those outcomes when it was corrected for scar. So scar emerged as a really powerful risk stratifier and a predictor of early recovery. But going back to the main question, which is how does it affect your randomized treatment? There was no interaction. So PCI doesn't seem to improve outcomes compared to medical therapy, even when characterized by Viability status at baseline. And the final observation was that if you do have left ventricular recovery at six months, then your outcomes are vastly better than if you don't have early recovery. And this is reassuring because it kind of affirms the biology that we think we understand and actually perhaps clarifies that question that was raised by stitch when they didn't find a relationship between recovery of early function and outcomes. So I think it's given us a lot of information and it will change practice.

**Dr Van Spall**

How did you define LV recovery?

**Dr Perera**

So that was based on echocardiography and we did it in a binary way as well as in a continuous sense. The results I've just presented have been on binary LV recovery based on recovery above the median. So the median change in LV ejection fraction was 4.7%, let's say approximately 5%.So those who had more than a 5% LVEF gain at six months were said to have recovered and those who had less than that or in fact had a deterioration in LV function were the non-recovery group. And if you like, we have yet another layer on the forest plot to say, however, you stratify this by age, diabetes, based on LVEF extent of coronary disease and now viability status, the result is still the same that PCI doesn't seem to improve outcomes. Right, and it might also speak to the efficacy of guideline-directed medical therapy, which has come a long way since the previous era of ischemic heart disease care and heart failure with reduced ejection fraction. And so you've demonstrated nicely that PCI does not improve Prognosis or LV recovery in these patients compared to guideline-directed medical therapy. And tell us what the uptake of guideline medical directed therapy was in this group of patients. It was really good throughout the trial and I suppose that's what comes from being under the spotlight of an RCT. These are patients who are said to be stable on good medical therapy, but I think there was even further titration of drug doses and so on, which is why even the stable patients all had an improvement in LVEF with a median of 5%.So I think medical therapy and medical and device therapy, I should say ICD and CRT included, was really excellent. The rates of beta-blockade, ace inhibition or use of ARNIs combined with about 90% for each of those, MRAs were used in at least 50% of patients. By the end of the trial, more than half of the cohort had received ICDs. So this is pretty good medical therapy. I think we've compared BCI against the best that medical therapy currently can offer.

**Dr Van Spall**

Dr.O'Kane, this substudy nicely demonstrates that scar burden can guide prognostication. But would you use viability testing in your decision-making around care provided to patients with ischemic cardiomyopathy?

**Dr O’Kane**

Well, it's a great question now, I think certainly before these results were announced, I think we've all been using viability as a tool to help guide who we should select. And I guess we've always felt that if we pick patients with viable myocardium in a ventricle that's got scar or may have a lot of scar, may not have much scar, but we've always felt that that would benefit in the patients by treating them. And also, even if you don't treat with PCI, treating with medical therapy, often if things were viable and left scar, you probably had a better feel for the patient in terms of their prognosis. And that does seem to be true. So high volume scar is bad and I think that’s an important learning point and it does make us focus more on this medical therapy and be more aggressive with our drugs, be more aggressive with selecting patients for device therapy. And I know that the guidelines currently don’t use scar and they fix very much on ejection fraction as being the marker, particularly, for instance in primary prevention after acute myocardial infection. I’ve always had many debates with my GP colleagues about the patient who's gone the foot borderline of35-36% that has a big anterior wall scar. I think this helps to focus our minds that actually they are at risk and that patient probably should be considered particularly in the grey zone and I hope it will lead to some guideline changes later.

**Dr Van Spall**

Right, and so, partly related to your VT substudy you previously presented, I'm just going to give the final word to Dr. Perera. What does this substudy and your trial in general add to what was previously known? You alluded to the STICH and STICHES trial. What does this add that we didn't know before?

**Dr Perera**

I’d probably summarize by saying we shouldn't throw viability testing out as was the interpretation of STICHES by some people, but we need to use it differently to how we have been using it before. We shouldn't use it to select patients who have had PCI in addition to medical therapy because we've shown that that doesn't work. We should, however, look at how much irreversible injury or scar there is because that's a really powerful predictor of outcomes and of the likelihood of LV recovery and perhaps begin to use that earlier in our stratification of who should get ICDS and more advanced therapies. But I think the whole paradigm of reversible LV dysfunction and hibernation needs to be rethought because what we've found doesn't support that theory. It may well be that repetitive ischemia is what causes LV dysfunction in the first place, but perhaps it's naïve to think that relief of that ischemic substrate is automatically going to lead to a reversal of all the cellular processes that led to that in the first place. And so the major output of viability testing as itis used at the moment, which is to characterize the amount or quantify the amount of myocardium that's dysfunctional, but looks like it has potential for recovery, that metric doesn't seem to be very useful. So perhaps findings that highlight that we're in the golden era of medical optimization for ischemic cardiomyopathy and heart failure with reduced ejection fraction.

**Dr Van Spall**

And perhaps I'll end by asking you, who does this trial not apply to? Are there any patients that you would not apply these findings to?

**Dr Perera**

Yes, we excluded patients who come in with an acute Myocardial infection, and I don't think we can extrapolate. So we exclude the patients who are within a month of an acute MI. We can't extrapolate these findings to that group at all. And also, we have to be a little bit cautious about extrapolating the viability and scar findings to a population who have sort of lesser degrees of LV systolic dysfunction. Because the entry point into our trial was an ejection fraction less than 35%, we don't know what the same messages and the same lessons would apply to a population who have an EF between 35 and 50. It may be that even in that population, if they have a certain burden of scar, we should be thinking about secondary prevention. But that is a whole other trial that needs to be done. We can't infer that from the REVIVED results alone.

**Dr Van Spall**

Well, let me thank the two of you for spending your time with us. Congratulations on your presentation at ACC 2023.

**Dr Perera**

Thank you.

**Dr O’Kane**

Thank you.