Transcript: REVIVED - Percutaneous Revascularisation for Ischaemic Ventricular Dysfunction

**Dr. Tamis-Holland:** Hey, I'm Jacqueline Tamis-Holland. And I am here today with Dr. Divaka Perera from St. Thomas hospital and Kings College in London, UK. He's here to talk to us about the REVIVED trial. Dr. Perera congratulations. This is an outstanding trial. I personally found it very interesting because from a guideline perspective, if you look at the US guidelines, there really is no recommendation for PCI in patients with LV dysfunction.

Of course, it's a Class I recommendation for CABG in patients with an ischemic cardiomyopathy and multi vessel disease, but not for PCI. And I think it's because we really had a lack of data to support a recommendation in any way.

So this is a really provocative and informative study and I congratulate you on your work. Let's start by telling me, you know, what led you to decide to go ahead and design this trial?

**Dr. Perera:** Jacqueline firstly, thanks very much for taking the time to talk to me. You've really touched on two of the strands that led to the design of this trial.

Firstly, that we didn't really, across the globe have any clear guidelines on whether PCI had a role for treatment of patients with severe airway dysfunction and coronary disease. In Europe the ESC guidelines gave it a Class IIa recommendation but acknowledged the lack of evidence behind it, the level of evidence was “C,” so just consensus opinion.

And the AHA/ACC were a little bit more cautious and actually declined to offer any recommendation for good reason. And even coronary bypass surgery, the guidelines are a little bit reserved because the results of the STICH trial seemed a little bit difficult to interpret. If you recall, when STICH first came out and it was published five years after the trial started, there seemed to be no benefit.

But it's when you looked more closely that you realized that there was an excess of mortality in the coronary artery bypass surgery arm at 30 days. But if you waited long enough, the benefits of revasc seemed to declare itself. And in fact, it wasn't until they went up to 10 years, that they saw that benefit.

And that really was our hypothesis that we could give patients the benefit of revascularization, but without the hit from the initial procedure itself, because we know that across most clinical scenarios PCI offers a lower procedure or risk than than coronary bypass surgery. So that's what led to us designing the trial.

**Dr. Tamis-Holland:** Yeah, I mean, that's a great introduction. I mean, as an interventional cardiologist instinctively, just like the ESC guidelines pointed out, instinctively you want to say that there would be some benefit in terms of improving outcomes in many different ways, by doing PCI as opposed to just continuing medical therapy. So why don't you go ahead and tell us some more about the trial, how you designed it and what the results are.

**Dr. Perera:** Sure. So firstly, the population, we wanted a group of patients who had quite severe left ventricular dysfunction. So an entry criterion was an ejection fraction, a left ventricular ejection fraction, less than 35% but also lots of coronary artery disease cause we didn't want to include any incidental coronary disease in on the background of a cardiomyopathy.

So, you needed to have at least two or three vessel coronary artery disease, which we quantified by using the British Cardiovascular Intervention Society Jeopardy score, a maximum score of 12 could be scored and you needed at least six to get in.

So proximal LAD, multivessel disease and we allowed left main coronary disease which was a first really for RCTs where one arm is medical therapy.

And the third criterion distinguished us from STICH, which is that you needed to have demonstrable viability in at least four segments that were dysfunctional at rest, shown to be viable on cardiac MRI, dobutamine stress echo, et. cetera and could be treated by revascularization with PCI.

So, it was only once you met all of those criteria that we put patients into the trial. And the aim was to randomize 700 patients, which we achieved, in a one-to-one basis to optimal medical therapy alone. And optimal medical therapy was the best pharmacological and device therapy. And it was a guideline that updated along the course of the trial because there had been so many developments in pharmacotherapy.

And that was given to patients in both arms. So, one arm had PCI and optimal medical therapy and the other arm had optimal medical therapy alone. The mandated minimum follow up was two years.

And the primary outcome was all-cause death or hospitalization for heart failure. And that was pretty tightly defined as to what we meant by that as well. And there were a whole host of secondary outcomes, but the two major secondary outcomes were left ventricular function because we often believe that if we do give patients a benefit, we'll see evidence of that benefit by improvement in left ventricular function.

And of course, a more patient-centric outcome which was quality of life. And we used various tools like the Kansas City Cardiomyopathy Questionnaire EQ-5D-5L and the good old fashioned simple but perhaps less granular NYHA Classification. And we completed follow up in March 2020, sorry, completed recruitment in March 2020 and then completed follow-up two years later.

So, it's pretty hot off the press and we've been working hard to get the data ready for now. And should we go on to talk about the results?

**Dr. Tamis-Holland:** Yeah. So we're opening up the envelope and the winner is? Let's hear it.

**Dr. Perera:** Absolutely. One of the first thing to note was what the outcome rate was in the medical therapy group. So 38% of patients either had died or had at least one heart failure hospitalization during follow up. Now that's a pretty high rate for what we believe to be you know, contemporary medical and device therapy.

So, the first point to answer was this is not a problem that's been resolved and we really do need to try and move the dial and lower the event rate.

But the next part of the outcome is that the event rates were identical in both arms throughout the trial. The Kaplan-Meier curves are virtually superimposed throughout all of follow-up. We didn't see the early spike in debts and events that were seen in the STICH trial. So that's reassuring.

We don't cause any excess harm, but actually they didn't deviate at all either. There was a hazard ratio of 0.99 with an narrow confidence interval and a P value of 0.96. So statistically, I think there was very little doubt that this was a definitive result. And we looked of course at the components of that primary outcome. And the interesting thing is that the main driver of that composite was death more than heart failure.

**Dr. Tamis-Holland:**  And what was the mortality in both arms? Obviously they were similar, but what was the...

**Dr. Perera:** Yeah, so the mortality rate was approximately 32% in each arm. And the total composite event rate was about 38%.

**Dr. Tamis-Holland:** Which is similar to what you have, somewhat similar to what you had in STICH, which was about 40%, I think at five years. And if you think about it, it was 10 years ago the therapies that you had back then.

**Dr. Perera:** Yeah, absolutely. So, I mean that's a really interesting point you picked up on. So if you look at STICH and REVIVED as the only two RCTs that involve revascularization, but put alongside that, all of the pharmacotherapy trials all the way through to the gliflozin trials from when ARNIs came on board and you adjust it for the length of follow up, it's really striking that the annualized mortality rates haven't really moved in 10 years.

And that's despite major advances in medical therapy. Now, admittedly, I think we have enrolled a much higher risk population than perhaps went into some of those earlier trials. So corrected for baseline risk, it's quite remarkable what we seem to be managing but still you know, and more than a third of your patients either dying or going to hospital is not really acceptable.

**Dr. Tamis-Holland:** Yeah, and the group you selected, what I like about the trial is that again, as interventional cardiologists, you tend to think, Oh the ones with the viability or the ones with the real disease that you can, you know, target that's the groups that you would think would benefit. You know, if you say all comers, you looked at an observational data. Well, maybe it's kind of including people who had really bad diffuse disease or not disease that was viable but yet you really selected the group of patients that one would think would benefit the most from revascularization with PCI.

**Dr. Perera:** Very much so. We tried to design the selection criteria to mirror what you and I would do in clinical practice. Which patient would we want to do PCI on. And embedded in that decision is the belief that we can A, achieve a good result and B, the myocardium will benefit from the result we achieve. So it was really enriched for a population who should benefit in terms of survival and heart failure hospitalization.

But what we haven't spoken about is the secondary outcome, which is that ventricular function. Now we've so far only got global left ventricular function as assessed by echocardiography. I don't yet have any segmental data, but while there was an improvement in left ventricular function ejection fraction at six months and one year compared to baseline, that improvement was seen in both groups. So, I think that was probably medical therapy because there was no difference again, between the two arms. Now this really turns on its head, everything we know about hibernation or have believed to know, because if that were the case, once you select a population with this much viability, we should see some reverse remodeling, which we didn't see.

**Dr. Tamis-Holland:** Yeah. They're excellent points. I have another question for you about your secondary outcomes particularly related to the quality-of-life data. So, you know, it's interesting cause you definitely see early on: that six months or so, a separation in the curves and a significant difference between the two groups but then that sort of peters out.

And the question is, does it peter out because you think that that's more of a placebo effect or do you think that there really was a difference and that perhaps it peters out because there's crossover to revascularization and medical therapy arm?

**Dr. Perera:** Yeah, so really interesting. And you've sort of touched on all of the possibilities we've been looking at over the last few months. So just to summarize, there was a clear difference in the improvement between the two arms in favor of PCI, in quality of life whether you looked at it with Kansas City Cardiopathy Questionnaire or the EQ-5D-5L. At six months and at 12 months.

And it's not that that effect waned over time, it's that there was a slower gradual catch up in the medical therapy arm. Such that there still was a difference at two years at 24 months, but it was no longer significant. So it is possible that it was a placebo effect that caused the initial improvement because this was an open label trial and they were sort of self-declared answers to the KCCQ questionnaire. So we can't rule it out.

But it's interesting that it's not that there was an improvement for six months and then patients dropped their scores. They stayed up but there was a catch up with medical therapy. Then we looked at the rate of revascularization, and one outcome measure that was clearly in favor of PCI was unplanned revascularization. There was a big difference and bear in mind that this didn't include staged PCI we very carefully captured planned stage PCI since it was complex intervention that couldn't be done in one sitting. And also acute myocardial infarction but we don't believe that that accounts for the difference that we saw in quality of life.

**Dr. Tamis-Holland:** Okay. Very, very interesting, really amazing data. I have one last question for you and this is going to be a tricky one for you to answer. Where do you see PCI for LV dysfunction going forward? Is this the end of the road for PCI, or do you think that there's a role for additional evaluations?

**Dr. Perera:** Well, I think we need to separate out the clinical scenarios in order to answer that question fully. If we look at the Revived patient, so stable, on good medical therapy, we didn't talk about it but 90% were on ACEI/ARB or ARNI, 90% are on a beta block or 50% on a mineralocorticoid antagonist. So really good medical therapy. But for those patients -- established heart failure, good medical therapy, minimal symptoms.

We didn't talk about angina either, but two-thirds of our cohort had no angina at all. And the remainder had a class of Angina so low that it didn't impact on the quality of life. In those patients, I don't think we can offer them PCI on prognostic grounds alone, but patients of angina are a different cohort and we can perhaps extrapolate from other normal LV data sets to know that that's a good treatment.

And specifically we excluded patients who were within a month of an acute coronary syndrome. So these data can't be extended to ACSS. So I think those are areas where we will continue to do PCI to treat coronary artery disease. But I think we have to be cautious about telling our patients we can give them prognostic benefit if they are the REVIVE-type patient. I think the results are definitive and the guidelines will now be clarified across the pond.

**Dr. Tamis-Holland:** Yeah, incredibly interesting. And I want to thank you again so much. Congratulations on the work you've all done. And thank you again for this incredibly informative interview.

**Dr. Perera:** Jacqueline thank you. It's been great talking to you.