Transcript: MTT - Assessing the effects of ARBs and beta-blockers in Marfan Syndrome

**Dr. Shaine Morris:** My name is Dr. Shaine Morris, and I'm a pediatric cardiologist at Texas Children's Hospital in Houston, Texas. And I serve as the medical director of cardiovascular genetics. I'm really excited to be interviewing Dr. Alex Pitcher. Dr. Pitcher is a consultant cardiologist at Oxford University Hospitals, and he is the lead investigator on a recent trial of results that he just presented.

This is the Marfan Treatment Trialists' Collaboration, and they were investigating the persistent question for many of us that take care of patients with Marfan syndrome on the efficacy of treatment of angiotensin receptor blockers, and beta blockers, and possibly the combination, in slowing aortic root growth and possibly delaying surgery. I'm really excited to hear the results of your study, Dr. Pitcher, can you tell us a little bit about the study and what your results showed?

**Dr. Alex Pitcher:** Thanks very much for inviting me to speak, it's great to be here. I mean, as you say, we were very motivated to work on this area. I care for patients with Marfan syndrome in my clinic in Oxford. And as you know, the main problem that patients with Marfan syndrome face is progressive enlargement of the aortic root. And if that is not dealt with, it can lead to large aneurysms which have to be dealt with by surgery, which is obviously a major deal for young patients to undergo, typically in their 20s or 30s. And, you know, that's very disruptive of their lives, sometimes of their studies, or family planning and things. And so, we would really like to find a treatment that can defer surgery.

And for many years, there's been uncertainty about the optimal treatment strategy for those patients. Over the last few years, as you and your viewers will know, there have been a number of trials of angiotensin receptor blockers in Marfan syndrome, which has been an exciting phase for the condition. And we performed an overview, or a meta-analysis, of all of the trials that we were able to access and that had been published, to look at some of the remaining outstanding questions to try to resolve these issues.

And we were able to compile data from over 1400 patients into what is called an individual patient data meta-analysis, which we think is one of the most powerful ways of addressing additional outstanding questions. And essentially, we had a number of key findings.

First of all, we were able to conclude, using direct meta-analytic techniques, that angiotensin receptor blockers, compared to placebo or control, are... We found compelling evidence to suggest that this treatment is effective in slowing the rate of aortic growth. If you look, for example, at the rate of change of aortic root Z-score, which is a commonly-used measure, as you know, of the rate of aortic expansion, that was halved on an annual basis, for patients with Marfan syndrome in those who are taking the treatment compared to those who were on control treatment. So we think that's an important finding.

The second finding is that we were able to exploit some of the differences between the trials to use indirect methods to look at angiotensin receptor... Not so much angiotensin receptor blockers, but also beta blockers, which is a treatment that's been used for many years, but perhaps without as much evidence as we would really like to be able to guide patients really confidently. And we were also able to show that we think the beta blockers are effective as well. And we found additional supportive evidence to the evidence that already exists. That helps us to, I think, really guide patients in that way as well. And the magnitude of that effect was pretty similar to angiotensin receptor blockers. So I think, really, what we can say is that we think we've got two effective treatments for patients with Marfan syndrome, which gives patients choice if they want to say just one treatment, but maybe for patients who want to be on the best treatment to slow down aortic root growth, that maybe their best option might be to take both treatments if they can tolerate both.

**Dr. Shaine Morris:** This, you know, I think, confirms what a lot of us who take care of these patients have suspected, but it's really wonderful to have rigorous data behind this. I would say, you know, I think sometimes people think or recommend dual treatment in patients who have larger or more dilated aortas. And when you did your subgroup analysis, did you find that the treatments had different effects depending on the size of the aorta?

**Dr. Alex Pitcher:** One of the strengths of doing what's called individual patient data meta-analysis, as you know, is that it's more difficult, because one has to compile data from all of the original trial data. And we were very fortunate in having collaborations from many of the trialists who conducted the original trials, who very generously shared data with us.

And we conducted the meta-analysis in conjunction with them. That allowed us to look at specific subgroups of patients. And in relation to what you asked about, we found that there was no evidence for differences in treatment effects, depending on the baseline aortic size of patients.

I should say that patients without baseline aortic enlargement were generally not included in any of the trials, and so, they were perhaps underrepresented. And patients with only slight enlargement of the aorta were probably underrepresented. So I can't be really definitive about that, but certainly over the range of the aortas that were included in the trial, we found no evidence for that.

I should say, generally, that we found very little variability in the magnitude of the treatment effect depending on all kinds of subgroups. So we found no variability with age, we found no variability with sex, we found no variability with a whole bunch of baseline characteristics. And that's generally what we find with effective treatments. If treatments vary or appear to vary a lot, just with certain subgroups and not with others, it tends to cast a little doubt on the treatment. And so, we were somewhat reassured that the treatments were very consistent.

There was one subgroup that did seem to have a particularly important effect, and that was the baseline mutation. So as you know, but maybe the cardiology audience is perhaps not not quite so familiar with, Marfan syndrome is usually caused by mutations in the fibrillin-1 gene. Not always, but maybe, I don't know, 80 to 90%. Do you think that's about right?

**Dr. Shaine Morris:**  That's right.

**Dr. Alex Pitcher:** And we looked at whether that was important. And when we looked at patients who had FBN1, or fibrillin-1 mutations, we found that the treatment effect was particularly great in those patients. Now, that's not to say there's no treatment effect in people who don't have that mutation, but the effect wasn't as great in those patients.

And so, having a fibrillin-1 mutation was a particularly strong factor in terms of determining the magnitude of the treatment effect. And we think that's important. Not so much in terms of deciding who should get the treatments and who shouldn't, but we think it is very reassuring that the treatment effect that we are seeing is real. Because that is exactly what you would see, if a treatment really worked, in people with Marfan syndrome.

Because to some extent, having an FBN1 mutation is a marker of security of diagnosis. And so, you would really expect that the people with FBN1 mutations would have a really big treatment effect, and that's exactly what we saw. So it reassures us that our overall finding in respect of angiotensin receptor blockers is correct.

**Dr. Shaine Morris:**  So has this changed your practice as a clinical cardiologist? If you have a young adult or an older person come in who has a reasonable degree of aortic dilation, what approach would you take, and has this altered your therapy?

**Dr. Alex Pitcher:** For me as a doctor, it has altered the conversations that I have with people. You know, I want to share this data with patients, and I want to talk to them and explain it to them, and I feel as I've got a duty to do that. I think that one of the big advantages that we have in dealing with patients with genetic diseases is that we often know that they have the problem from very early in their lives, sometimes before they're even born. And that gives us a potentially huge amount of time over which we can impact on their condition. You're a pediatric cardiologist, and so you can... I'm an adult cardiologist, and you can start treating them at a very early age.

And so, if pediatric and adult cardiologists work together, we can potentially impact on their aortas over decades. And so, if we can see treatment effects just over the three or four years of a clinical trial, just imagine what we can do over 30 years of treatment. And so, sometimes people look at the results of trials and meta-analyses and say, "Well, okay, but we're just talking millimeters, here."

But if you add that up over many years, and in fact, what you should do is compound it, then we could see really big treatment effects. And then, if you add together the effects of two treatments and compound those, then it would make a lot of sense if that would then result in substantial delays to surgery for patients. And that might mean that instead of having surgery in their 20s or 30s, it could be pushing that off for quite some time. So that's where we think it gets exciting for patients.

**Dr. Shaine Morris:** Well, it's very exciting to me. This is what I tell my patients all the time. You know, multiple of these trials have shown that the earlier you start treatment the better, including in very young children. So I 1000% hear you, and I'm glad that you have done this so rigorously to help us have evidence for our patients. So thank you so much for taking the time to speak today, and congrats on the paper.

**Dr. Alex Pitcher:** Well, thank you for your kind comments, and thank you very much for having me. Thanks a lot.