NAVEEN PEREIRA: Hi. My name's Naveen Pereira. I'm a consultant in cardiovascular diseases at the Mayo Clinic in Rochester. I have the privilege of moderating a roundtable review on a very exciting trial, the RELAX trial, which was presented recently at the American College of Cardiology annual meetings. And I have the privilege of having with me today Maggie Redfield, who is the Director of Circulatory Failure at Mayo Clinic Rochester, and was the principal investigator of the RELAX trial. And Barry Borlaug, who's a consultant, Cardiovascular Diseases, at Mayo Clinic Rochester, and was a co-investigator on the trial.

So, Maggie, let me start off with you. We all know that there's not a lot of headway, as far as heart failure with reduced ejection fraction is concerned. We stopped kind of at neural-hormonal antagonism. So why move on and study heart failure with preserved ejection fraction, as you did in the RELAX trial?

MAGGIE REDFIELD: Thanks, Naveen. Well, we know that we're in the middle of a heart failure epidemic. And at the community level, over half of people who have heart failure have preserved ejection fraction. So, obviously, it's a huge problem. And, importantly, it is the predominant form of heart failure in women, which is very important, an underserved, understudied population.

In this group of patients, they have the same morbidity and mortality, pretty much, that patients with heart failure and reduced ejection fraction, or systolic heart failure, have. There have been a few studies HFpEF. They've looked at RAS antagonists, ACE inhibitors, and ARBs, and really, no significant benefit. They've looked, not very much, at beta blockers. We still don't really know the role of beta blockers in treating HFpEF.

However, for both these standard heart failure therapies, it's a bit of a moot point. Because when patients present with HFpEF, 70% to 90% of them are already on a RAS antagonist or a beta blocker for their other conditions. Their hypertension, coronary artery disease, afib.

And the negative trials thus far in HFpEF have really spoken for the need to step outside the box, and look at something really novel that would target the pathophysiology. So this is what this trial did. It looked at PDE5 inhibitors, which, as you know, are used for erectile dysfunction and primary pulmonary hypertension, or Group 1 pulmonary arterial hypertension.

This trial came from Mayo, but it was further designed and executed in the Heart Failure Network. And it was a very complex trial. And so the Network was the perfect venue to perform this trial.

NAVEEN PEREIRA: Excellent. Barry, let me move on to you and ask, as to why choose PDE5 inhibition for heart failure with reduced ejection fraction. We know PDE3 inhibition, such as using milrinone, is useful in heart failure with reduced ejection fraction and low cardiac output states. Can you explain the basis of using PDE5 inhibition with sildenafil in heart failure with preserved dejection fraction?

BARRY BORLAUG: That's a great question, Naveen. Well, just in the way of review, PDE3 inhibitors increase cyclic adenosine monophosphates, cyclic AMP levels. And that's an inotrope and also a vasodilator.

In contrast, PDE5 breaks down cyclic GMP, cyclic guanosine monophosphate, which is more of a vasodilator and enhances diastolic function in the ventricle. We've traditionally thought about HFpEF as really just a disease of diastole. But recent work from our group and others has shown that it's much more complex. There is subtle abnormalities in systolic function. The changes in ventricular remodeling that we see play an important role. There's vascular dysfunction. There's endothelial dysfunction.

So it's really the complex interaction of all of these abnormalities, including autonomic abnormalities, that sort of leads to the symptoms. As it turns out, PDE5 inhibitors can affect many of these different pathways. In animal models of pressure overload heart failure, they can abrogate, or even reverse, the deleterious changes in ventricular remodeling. This can also be associated with preservation or reversal of systolic dysfunction and diastolic dysfunction, and improvements in systolic and diastolic reserve capacity. So there was great deal of hope there. If you increase cyclic GMP activity, it can have diastolic favorable effects, improving diastolic capacitance in the ventricle.

We know from patients with heart failure and reduced ejection fraction, who frequently have endothelial dysfunction, just as patients with HFpEF do, that use of PDE5 inhibitors improves endothelial function. So we believe that this would also affect nitric oxide bioavailability elsewhere, perhaps in the skeletal muscle. There is evidence that it could improve sympathetic stimulation of the heart, which we also think is abnormal and contributes to pathologic remodeling.

So there's lots of reasons why PDE5 inhibitors should really work. There's even evidence of improvements in gas exchange in the lungs. And it can reduce the excessive hyperventilatory responses to exercise, again taking the example of patients with heart failure and reduced ejection fraction. So we really thought that we were setting it up with lots of opportunities to succeed, because of the pleiotropic and complex nature of the disease.

NAVEEN PEREIRA: Thanks, Barry, for explaining the pathophysiological basis of using sildenafil. Maggie, there was a lot of excitement at the American College of Cardiology meetings. Many people were looking forward to listening to the results of the RELAX heart failure trial. But before we go on the results, can you explain to us a little bit about the basic design of the trial?

MAGGIE REDFIELD: Pretty simple design. But I think it's worth pointing out that we had very careful entry criteria. Patients had to have Class II to IV heart failure symptoms. They had to have an EF greater than 50%. And they had to have objective evidence of heart failure, which could either be a heart failure hospitalization, or if they had had a right heart cath for the evaluation of dyspnea and were shown to have consistent hemodynamics. Or, if they had echo evidence of diastolic dysfunction, and we chose left atrial enlargement as that marker of chronic elevated filling pressures in the setting of chronic diuretic therapy for heart failure.

Now those are somewhat standard entry criteria for a HFpEF trial. But then we went one step further. They had to have a screening cardiopulmonary exercise test, and have a peak VO2 that was less than 60% of what their age and sex normal predicted value would be. And they had to have an elevated NT-proBNP. All

There's a lot of controversy over do patients really have heart failure, or is their dyspnea due to something else? We were really very careful to select patients who truly had heart failure. Once they satisfied those criteria, they had their baseline studies, which included the cardiopulmonary exercise test, six-minute walk distance, Minnesota Living with Heart Failure Questionnaire, a comprehensive echo Doppler. If they were in sinus, they had a cardiac MRI, and they had blood for biomarkers. Then they were randomized to either placebo or sildenafil at 20 milligrams, three times a day.

And if you remember, that's the dose that was shown in patients with Group 1 pulmonary arterial hypertension to improve exercise capacity within four weeks. And so they were on this first dose for 12 weeks. They came back, had a repeat visit. And at that time, the dose was increased to 60 milligrams tid for the final 12 weeks of the study. And then at 24 weeks, they had baseline studies repeated.

NAVEEN PEREIRA: Wonderful. Barry, heart failure with preserved ejection fraction is a very heterogeneous disease. You described different pathophysiological mechanisms. Do you think we chose the right population?

BARRY BORLAUG: Yeah. I think that's a very important question. And there's really sort of two questions. One, did they really have heart failure? And that's not trivial. So dyspnea is a very common symptom, as is fatigue.

And if you have a low-ejection fraction, people usually feel pretty confident in saying it's systolic heart failure. But if you have a normal ejection fraction, it's often difficult. And indeed, one of the criticisms of a lot of the previously published trials is, well how do we know all these patients really had HFpEF? Maybe that's why the results were neutral in many cases.

So it's an important question to ask. When you look at the baseline characteristics in RELAX, it's really unequivocal in my mind. We see significant evidence of diastolic dysfunction. So the echo Doppler estimated left heart filling pressures were very high. The E/E prime ratio average was 17. The left atrial volume was markedly enlarged. It was over 40. So that's sort of what we say the hemoglobin A1c of chronic diastolic filling pressure. So this suggests not only ambient elevation and filling pressures, but chronic elevation as well.

There was elevated pulmonary artery pressures, which we see very commonly in patients with heart failure with preserved EF. That's actually one of the really common diagnostic markers that we look for. They had marked exercise intolerance and symptomatic limitation. Their peak oxygen consumption was 11.7, which is only 40% predicted for this age group.

So they were really profoundly limited, with a true cardiac limitation. Six-minute walk distance, again, very depressed. And their B-type natriuretic peptide levels, or NT-proBNP levels, were also very elevated. They were 700, and in other studies from the PEP-CHF trial and others have shown that this is a very important marker of worse outcomes. So we feel very confident. These patients clearly had significant exercise intolerance, and really was ascribable to a cardiac etiology.

The other concern, then, is, is this the type of HFpEF that we all see in the community? And in the only other trial of PDE5 inhibitors and HFpEF, the group they studied clearly had heart failure. But it was a bit atypical. There was a lot of right ventricular enlargement, profound RV dysfunction, more severe pulmonary hypertension.

This is not what we usually see in everyday practice. The patients that we saw in RELAX, that we enrolled and participated in RELAX, really are this more garden-variety type of heart failure. These older women, atrial fibrillation. Men, hypertension. Typical co-morbidities. This is really exactly what we see. So we felt confident we were starting the right patients that we want to know about.

MAGGIE REDFIELD: And, you know, one of the real strengths of the Network is often industry sponsors a trial. And there's a very small amount of phenotypic characterization. In this trial, we had the MRI, the echo Doppler, and neurohumoral measurements. And these patients had the high BNP level. But they also had high aldosterone levels, high endothelin levels, high troponins, high CRP. So they really were well-characterized, and clearly had heart failure.

NAVEEN PEREIRA: It's a very important group, well phenotyped, and I feel I'm at the Oscars. So, Maggie, do you want to disclose the results to our audience?

MAGGIE REDFIELD: Sure. And, of course, the paper was published simultaneously in JAMA. So hopefully, some of our listeners have read it. I think two points. Sometimes you do a trial, and you kind of get mixed messages. We didn't get mixed messages in this trial.

And, you know, the reason we did this trial-- it was a small trial, sort of surrogate endpoints-- but we were looking for a signal of benefit. Is there anything that suggests this drug is going to help these patients? And the answer was consistently and resoundingly no evidence of benefit.

So our primary endpoint was change in peak VO2 between the two groups. No significant difference. No trend towards a significant difference. And so then we moved on, and looked at sub-maximal exercise, change in six-minute walk distance. Absolutely no trend to benefit.

We did this clinical rank score, which was a composite score. Time to death. Time to hospitalization. And if you were alive without a hospitalization. Change in your Minnesota Living with Heart Failure Questionnaire. And absolutely no trend to benefit there. No trend towards benefit in change in Minnesota Living with Heart Failure Questionnaire.

So then we went on. And we looked cardiovascular structure function, based on all the animal studies that Barry talked about. And so, because of variability, we had designated that we would use the MRI, changes in LV mass, because it's very reproducible. And you can detect very small changes in LV mass.

Patients didn't have severe hypertrophy, but they had hypertrophy on average. And there was no difference in the change in LV mass. We looked at diastolic function. The change in the E/E prime ratio, which is this fairly good surrogate for filling pressures. No difference there. And, surprisingly, given that this drug can target the pulmonary vasculature, we might have expected a change in pulmonary artery pressures. No change. No difference in the change in pulmonary artery pressures. So, really, a very consistent message.

We also looked at change in BNP. And, actually, there was a difference there. But it was in the wrong direction. The BNP went up a little bit more in the sildenafil-treated patients. And, surprisingly, because every animal study that's had a model of renal dysfunction and looked at sildenafil, it's improved renal dysfunction. But in the RELAX trial, the patients treated with sildenafil had a modest, but statistically significant worsening of the renal function. And that was associated with this increase in BNP, an increase in endothelin, and increase in uric acid. So, modest, but obviously physiologically real. Because there were these other changes.

NAVEEN PEREIRA: A quick question, Maggie, that comes up in randomized clinical trials. Were we adequately powered?

MAGGIE REDFIELD: We were very well-powered for our primary endpoint of change in peak VO2. If we would have just had 76 patients in each group, we would have had 85% power to detect a between-group difference in the change in peak VO2 of 1.2 mils per kilo per minute, which is sort of the minimal clinically significant difference.

So we actually ended up with 94 patients in one group, 91 in the other. So we were well-powered for that. We were well-powered for the LV mass, as well.

NAVEEN PEREIRA: Barry, when we look back at clinical trials and results, we always try and identify subgroups that could potentially benefit from this therapy. Can we tease out any subgroups, do you think, in heart failure with preserved ejection fraction who would benefit from sildenafil?

BARRY BORLAUG: Right. Yeah, we always do that. And when the primary is not met, we always worry about doing that, of course. But we don't even have to worry in this case, because very consistently, in all pre-specified subgroups, we didn't see any signal of benefit. We looked at patients with or without elevated pulmonary artery pressures. We looked at patients with or without elevated BNP levels. Patients with or without left ventricular hypertrophy. Men versus women. ACE inhibitor, ARB, yes no. Beta blocker, yes no.

Consistently, we saw an absence of benefit in each of these different subgroups. We really saw no signal of benefit whatsoever.

NAVEEN PEREIRA: OK. Maggie, these are one of the few prospective randomized trials looking at the use of sildenafil in cardiovascular disease. We use it in primary pulmonary hypertension. We use it sometimes in secondary pulmonary hypertension, as an off-label use. Were there any adverse effects that you all noted in this trial that we should be worried or cautious of?

MAGGIE REDFIELD: Right. I think, obviously, it was a small trial, not powered to really look at a lot of clinical outcomes. I talked about the little bit worsening of renal function. There was no significant difference in adverse events or serious adverse events. There were numerically more patients who had an adverse event or a serious adverse event, but it didn't approach statistical significance.

And I think it's really, really important to emphasize that these results should not influence the decision to use this drug for erectile dysfunction or pulmonary hypertension. There's a tremendous amount of post-marketing surveillance that's done in this drug. And no signal of harm, other than the rare side effects in erectile dysfunction. And we know how sick patients with pulmonary arterial hypertension are. And this drug is of great benefit.

So, really, things might be different in HFpEF, but nothing to indicate that we shouldn't continue to use this drug in erectile dysfunction and pulmonary arterial hypertension.

NAVEEN PEREIRA: Thank you, Maggie. So here we are. We have targeted a pathway to try and help patients with heart failure with preserved ejection fraction, PDE5 inhibition with the use of sildenafil. The results were negative, but they were very important results. There were a lot of important reasons why we had to study this drug in this disease process. So my question to both of you is, did we target the wrong pathway? What are the reasons, perhaps, that we didn't see positive results? And where do we go from here in this very complex, but important disorder?

MAGGIE REDFIELD: Well, I think one of the things that's important to point out is we actually measured cyclic GMP levels and sildenafil levels in the trial. And so the patients who were treated with sildenafil, as you would expect, had dose-dependent increases in their sildenafil levels. Interestingly, very minor increases in cyclic GMP. Not what you would expect. It inhibits the breakdown of cyclic GMP. You would expect increases in the circulating levels of cyclic GMP.

Some people think that NO-derived cyclic GMP doesn't elevate your plasma levels. But certainly other studies that have given the drug to humans have shown pretty dramatic increases in cyclic GMP, circulating cyclic GMP. And so the change in cyclic GMP was not even statistically significant difference between the two groups, despite good sildenafil levels.

So that might be telling us that, yes, cyclic GMP we know can be of benefit. But the problem is not enhanced degradation. Maybe the major problem is the endothelial dysfunction. They don't have functional NO, so they're not making cyclic GMP. And we know that natriuretic peptide levels, while elevated, are much lower than in systolic heart failure, in HFpEF. So maybe it's not enough NO, not enough natriuretic peptides, or downregulation of the natriuretic peptide receptor activity. So I don't think we need to give up on the cyclic GMP pathway. But I think we have to use a different strategy.

BARRY BORLAUG: Yeah. Yeah. I agree completely. It may just be that, for whatever reason, phosphodiesterase 5 is not really upregulated in this disease, the way that it is in animal models of pressure overload hypertrophy and that we believe it's upregulated in people with pulmonary arterial hypertension, or heart failure with reduced EF.

So far, the patients that seem to do better are the patients that have more hypertrophy, more right ventricular dysfunction and enlargement, more pulmonary vascular disease. So that might be more the right sort of substrate or patient to benefit from a PDE5 inhibitor. But we're still very hopeful that the cyclic G maybe increased activation, rather than trying to prevent degradation, will be very effective.

MAGGIE REDFIELD: And, you know, the NIH is also right in the middle, or just starting a large trial, an outcomes trial, of PDE5 inhibition in HFrEF. And I think absolutely that trial should go on. Unfortunately, we have kind of a long track record of things working in HFrEF that didn't work in HFpEF. So I don't think that we should translate the findings of RELAX to HFrEF. I think we've learned that lesson, and that we should do that trial.

NAVEEN PEREIRA: Thank you, Maggie and Barry, for shedding light on the RELAX heart failure trial. That was a very interesting and stimulating discussion. We look forward to more trials from the Heart Failure Research Network, led by both of you. And I would like to thank the audience on behalf of the Mayo Clinic, on heart.org. And we hope to see you again soon.