MATT: We're very lucky today to have Dr. Sean Pinney with us for his Grand Rounds on "Innovations in Heart Failure." Dr. Pinney completed his medical school at Georgetown University School of Medicine. He then went on to complete his internal medicine residency training at Beth Israel Deaconess up in Boston. He finished his cardiology fellowship, as well as heart failure fellowships, at Columbia, before joining us here at Mount Sinai.

Dr. Pinney is an active clinical researcher who has led both NIH and industry-sponsored trials in heart failure, cardiac transplant, and mechanical circulatory support. He serves on the American College of Cardiology Heart Failure and Transplant Committee, the International Society for Heart and Lung Transplantation's I2C2 Committee, and the Medical Advisory Board for the New York Organ Donor Network. Dr. Pinney is currently a Professor of Medicine here at Mount Sinai, and is the director of the Advanced Heart Failure and Cardiac Transplant program.

Please join me in giving a warm welcome to Dr. Sean Pinney.

[APPLAUSE]

DR. SEAN PINNEY: Thank you very much, Matt, for a very kind introduction. And my thanks to you, the other chief residents, to Dr. Murphy, and to the leadership of the Department of Medicine for inviting me to be with you today. It's always a terrific pleasure for me to come in and speak at Medical Grand Rounds. It's always an inducement also to come and attend Medical Grand Rounds a little bit more frequently, because it's really a fantastic learning opportunity.

So these are my disclosures. I will also be talking about some off-label investigational devices, and I'll point those out. So this is a very--

AUDIENCE: We can't hear--

DR. SEAN PINNEY: Cannot hear? Is this microphone on?

AUDIENCE: I'm on it.

DR. SEAN PINNEY: You're on it? So one of my many gifts is to be a very quiet talker. Oh there we go. Thank you for that.

So this is a very exciting time to be practicing in heart failure. There are a number of innovations that are percolating throughout the field, specifically pharmacology, areas of cardiorenal syndrome, specific device therapies, a resurgence of interest in transplantation, clearly advancement in the mechanical circulatory support in LVADs, and also the new technologies in mobile health technologies, which are transforming the way that we deliver care.

I highlighted these on this slide, because all of these things that I put up here are projects that we are currently developing, or participating in clinical trials, or that are currently in clinical use. And as much as I would like to talk about all of them, clearly an hour or 45 minutes is not enough time. So I'm going to talk about four specific areas.

But it all starts here with the foundational understanding of what we mean by heart failure, and it begins with the neurohormonal hypothesis. And this neurohormonal hypothesis holds that there's some injury to the myocardium, and in response to that injury, there is a drop in performance. And in response to that drop in performance, the body activates specific neurohormonal systems, in particular the renin-angiotensin-aldosterone system, the sympathetic nervous system, the endothelin system, and others.

And in response to that, we see salt and water retention, which drives the symptoms of congestion and exercise limitation. But there are also specific hemodynamic alterations that lead to an inability to exercise, because of a reduction in cardiac output. But more importantly, there is a progressive effect on the left ventricle and the right ventricle themselves, leading to progressive left ventricular remodeling, which then accelerates the cycle of worsening performance, more neurohormonal activation and worsening symptoms, and ultimately drives the outcomes of heart failure.

Now, this all leads to the concept of left ventricle remodeling. And we can think about this in the global sense, where you see a change in the overall shape of the left ventricle. It goes from being a [INAUDIBLE] ellipsoid to being more spherical. If you want to translate this into a sports analogy, it goes from being a football to a basketball. But in addition to that, not only do you see a drop in ejection fraction, but you also see changes in the mitral valve apparatus. There is an increased distance between the papillary muscles. There's increased tethering of the mitral valve leaflets, and this leads to an increase in mitral regurgitation.

But the remodeling process also happens at a microscopic level. In the middle of the slide is what a normal cardiomyocyte looks like, and on the right, and with electron microscopy, you can see what the extracellular matrix looks like with myocytes and collagen. Now, in diastolic heart-- excuse me, in dilated cardiomyopathies, or in volume-overloaded states, you see an increase in muscle fiber, and that's because you see the addition of sarcomeres in series, and so the myocyte itself becomes elongated. But there's also remodeling of the extracellular matrix, where there's thinning and loss of collagen fibers in the myocardium.

Now, contrast this to a pressure-overloaded state. This could be due to hypertensive heart disease, aortic stenosis, or some other form of pressure overload. And what you see is that the sarcomeres are added in parallel, and that leads to overall hypertrophy. But you also see an increase in collagen fibers, and significant change in the extracellular matrix. So two different forms of LV remodeling, and we're going to be focusing on the top one.

Now, from that neurohormonal hypothesis came the way that we treat systolic heart failure, which is to use medications like ACE inhibitors, angiotensin receptor blockers, beta blockers, ARNIs, and MRAs, all of which try to block that neurohormonal response. And one of the observations are that those medicines that improve survival, and improve symptoms in heart failure, also abrogate the remodeling process, such that you do not see further increases in LV volumes. And in some cases, you can actually see reverse remodeling or reductions in left ventricular volumes. And this just happens to be an example with an ACE inhibitor, but we can show similar data for beta blockers and MRAs.

Now, what's coming to the fore now is the idea that it is the remodeled ventricle itself which is a target for therapy. And there have been a number of devices which have been developed over the years to try to address the remodeled ventricle itself. So the first was the Acorn CorCap. This was a mesh device that was sewn around the heart to try to passively restrain the left ventricle and the right ventricle from remodeling.

The second idea was the Myosplint. So these are a series of three buttons which has a tensile cord between them. And the attempt there was to take this global, spherical left ventricle, and reduce it to a bi-lobe where you have two separate spheres with smaller radii. And as a result of that, you can decrease wall stress.

And the last idea was something called the Parachute device. This is a device that sits within the left ventricle itself, percutaneously deployed to try to isolate the non-contracting apical aneurysm, in an attempt to exclude that volume, and to facilitate reverse remodeling.

Now, all of these devices work to a certain extent to achieve their primary hypothesis. However, none of them have been approved by the FDA, either because of difficulty in deploying them, or because of an adverse safety profile. However, this theory of targeting a remodeled ventricle as a site for therapeutic intervention continues to persist.

So this is an investigational device called the AccuCinch. It consists of a series of anchors which are implanted into the myocardium, and through which is threaded a cable that can then be tightened up. There are a number of spacers between the anchors that make sure that the force is evenly distributed as you tense up on this cable. And what it does is it pulls in the left ventricle to facilitate remodeling of the left ventricle. And when properly applied, it will not only pull the ventricle in, but may also pull the mitral valve annulus together. So as opposed to some devices which are specifically targeting the mitral valve annulus, this device is deployed a few centimeters below the mitral valve annulus, and it is threaded behind the papillary muscles to pull in the lateral wall of the left ventricle.

And this is data that was presented just this past fall at TCT, showing the effect of this device on left ventricular remodeling. And you can see, although the slide didn't translate too well from my Mac to PC, you can still see graphically that there have been early and sustained reductions in systolic volumes. And this is paired data between samples, granted, small numbers of patients.

But one of the things that's very interesting is that the degree of remodeling, it seems to be greater than just the mechanical constraint that's placed upon the ventricle, suggesting that there are ongoing changes in the neurohormonal milieu that facilitate ongoing reverse remodeling of the left ventricle. This is just one patient from that example showing that when the AccuCinch is applied and then tightened up, you can see that it pulls in the ventricle with a reduction in left ventricular diameters. And over time, however, you can see that the left ventricular volumes begin to fall even more than they do immediately after the application of the device.

And this is probably better illustrated here in these 3D reconstructions from the CT angiogram, showing in magenta what the initial implant state looks like, and in blue, the further reduction in left ventricular volumes that occurs over three months.

Now, we're about to enroll in a phase III trial this device here at Mount Sinai. We'll be one of the participating sites to see whether these changes in left ventricular volumes translate into meaningful clinical benefits, including not only improvements in functional capacity, but also survival.

Now this leads to a second hypothesis, which is, can we identify patients who have secondary or functional mitral regurgitation who might benefit from a mitral valve repair in order to favorably reverse remodel of the left ventricle and forestall heart failure progression?

So just for a point of review, this is what the normal mitral valve looks like. You have the anterior and the posterior leaflets, the subvalvular apparatus, which consists of the cords which are tethered into the papillary muscle, and during systole, hold the mitral valve closed so that you do not develop regurgitation, and all of the stroke volume goes out the aortic valve. Now, in cardiomyopathies, particularly in dilated cardiomyopathies, again, you have lateral displacement of the papillary muscles so that the distance between those two papillary muscles increases. There's also greater downward force on the mitral valve leaflets from the tethered cords that leads to functional mitral regurgitation.

Now, the degree of mitral regurgitation is controlled by two opposing forces. On the one hand, you have the tethering force. These are the forces that hold the mitral valve closed during systole. And you can see that as the ventricle remodels, and the papillary muscle is pulled away from the annulus, you get further tethering of the mitral valve leaflets. And the other opposing force is the closing force. So this is the force that is generated by the left ventricle. So as it contracts, it pushes upward on the mitral valve leaflets to close the leaflets shut. Now, in the case of a cardiomyopathic patient, your LV dP/dT, or force of contractility, slows, such that you have a reduction in your closing force and an increase in your tethering force. Those two things together lead to significant mitral regurgitation.

And we recognize that the secondary form of mitral regurgitation is very important in the clinical syndrome of heart failure. It occurs in about 30% of patients following myocardial infarction, and about 35% to 50% of patients who have heart failure with a reduced ejection fraction. There is a significant increase in mortality that's associated with the presence of significant mitral regurgitation, and as a result of that, we know that it's associated with worse outcomes. But is it also a target of therapy, such that if you abrogate the mitral regurgitation, can you improve clinical outcomes?

So this, again, making the case that the presence of mitral regurgitation is associated with poor outcomes. This is data from Dr. Agricola who works in Dr. Alfieri's hospital in Italy. And Dr. Alfieri, who you may or may not know, is the surgeon who developed the Alfieri stitch. This is basically a cross stitch that goes and links the two mitral valve leaflets together to try to reduce mitral regurgitation, known as the first form of mitral valve repair.

But here you can see that over a period of five years, those persons who had moderate or severe mitral regurgitation had significantly impaired heart free survival. Here in the United States, this was looked at, at the Mayo Clinic, 1,200 patients with mild, moderate, or severe functional or secondary mitral regurgitation. And you can see that over a five to seven year period, those persons who had severe functional mitral regurgitation had a poor freedom from heart failure hospitalization or from mortality. Now this was true whether or not patients had ischemic cardiomyopathy, or if they had non-ischemic cardiomyopathy. We saw very similar results.

So how do we treat it? Well, one of the best ways is with cardiac resynchronization therapy. And so we know from heart failure trials that cardiac resynchronization therapy reduces left ventricular volumes, it increases left ventricular ejection fraction, and it also reduces the amount of mitral regurgitation. Now, how does it do this? Well, if you look at what cardiac resynchronization does is that it increases stroke volume.

So these are pressure volume loops that Dr. Kass at Johns Hopkins compiled from patients a few years ago. And I'll just draw your attention to the lower left hand quadrant, which is pacing from the left ventricular free wall. So he took a patient who had a dilated cardiomyopathy paced from the right ventricle, which is in red, and then paced from the left ventricular free wall. And what you can see in this pressure volume loop is an increase in stroke volume, which is essentially the difference between these two points, your end-diastolic and your end-systolic volumes.

Now, that's great that you can increase your stroke volume, but how does that decrease mitral regurgitation? Well, it goes back to what I said about dP/dT. So as you provide cardiac resynchronization, you increase dP/dT.

So shown here is with cardiac resynchronization off, and you can see that there is a slow rise in left ventricular pressure. And when cardiac synchronization is turned on, you have a more rapid rise in left ventricular pressure, showing that higher dP/dT, or increase in contractility. What that effectively does is it increases those closing forces on the mitral valve leaflets. It gets the mitral valve to slam shut sooner. And it decreases your EROA, effective regurgitation orifice area, such that it is below 50% of its peak value for the majority of time during systole.

But nonetheless, we're left with this hypothesis. Can we treat a ventricular disease, namely a dilated cardiomyopathy or ischemic cardiomyopathy, at the level of the annulus, simply by reducing the degree of mitral regurgitation?

Well, probably the best study that exists to try to answer this was performed at the University of Michigan, now over 14 years ago. They did a propensity-based analysis looking at individuals who underwent mitral valve repair versus those who did not undergo mitral valve repair, tried to control for as many clinical factors as they could in their analysis, and showed that over a period of four years, there was no difference in survival for those individuals who had surgery versus those who did not. There was a 5% 30-day mortality, perioperative mortality, which, overall, is relatively low, at least in an era from about 12 to 15 years ago, clearly better nowadays. But nonetheless, it did not provide any long term benefit in survival.

Now, as a result of that, and some other evaluations, the ACC and the American Heart Association updated their valve guidelines in 2017. And just to draw your attention to secondary mitral regurgitation or functional mitral regurgitation, the recommendations from the professional societies in the setting of having functional mitral regurgitation is to first treat coronary disease, then to aggressively treat heart failure, to consider CRT for those individuals who are appropriate, specifically, those with a left bundle branch block.

And then for those who have either progressive mitral regurgitation, or if they are asymptomatic, the recommendation right now is leave them alone. Treat them medically, but don't do anything more than that.

However, if you remain symptomatic, and severely so, with significant deterioration in your functional capacity and quality of life, in selected persons, it might be appropriate, particularly for the relief of symptoms, to offer mitral valve surgery. And if you were going to offer mitral valve surgery in the setting of secondary mitral regurgitation, it's recommended that you perform mitral valve repair rather than mitral valve replacement.

But what about percutaneous approaches to mitral valve repair? So this is the MitraClip. The MitraClip is a percutaneous device that's inserted up the inferior vena cava. It's passed across the interatrial septum down across the mitral valve, at which point this clip grabs the anterior and the posterior leaflet and brings them together, such that you reduce the amount of regurgitation by reducing the effective regurgitant orifice area.

It sounds really easy. I made it sound really easy. These cases take about three to four hours or so in the cath lab. But nonetheless, that's the concept, which is to percutaneously reproduce what was known before as the Alfieri stitch.

Now, for those of you who love hemodynamics like I do, I'd be willing to spend the next 45 minutes describing exactly what you see here, because to me this is fascinating. Instead, I'll just take a step back, and broadly say a few things.

So these are pressure volume loops that were acquired from a group of individuals who had a secondary mitral regurgitation, or functional MR, or degenerative mitral regurgitation, or primary MR, showing changes in left ventricular performance before and after application of the MitraClip. Now, as you can kind of see, just without knowing anything about pressure volume loops, that each one of these patients, the loops look a little bit different, which speaks to the pleiotrophic nature of functional mitral regurgitation, and primary mitral regurgitation. So it's not all one process. But there are some commonalities, and I've highlighted them here.

So the first thing that we see when you apply the MitraClip is that you increase afterload. That makes sense, because you're taking the pop-off valve, which is the mitral valve, and you're closing it, which means that you are increasing the afterload, because the left ventricle now has to generate more pressure to get all the blood going forward out the aortic valve, which is a higher pressure system.

But it also decreases preload, because it takes out regurgitant volume off of the left ventricle. It decreases your ejection fraction. Well, that's true, because a lot of the ejection fraction was being driven by backward stroke volume. In other words, a lot of blood was going back into the left atrium. It wasn't forward stroke volume. So once you close off that pop-off valve, your ejection fraction drops.

However, importantly, there was no change in your end systolic pressure volume relationship. Translated another way, there was no drop in contractility. End systolic pressure volume relationship is probably the best way that we can measure intrinsic contractility of the heart. And we can show that by doing this, you do not weaken the heart even though there's a drop in ejection fraction. And there was no change in the total mechanical energy that's expended by the heart in a cardiac cycle. And as a result of that, myocardial oxygen demand should not increase. So if you put that all together, what we're saying is that we make the heart pump more efficiently, and we may allow for reverse remodeling.

So how does the MitraClip perform in actual clinical use? So this is a large registry report from Germany, because the device is approved for use in Europe for secondary mitral regurgitation. 1,000 patients at 20 German centers, the majority of whom were very, very sick and had NYHA Class III, Class IV symptoms, secondary or functional mitral regurgitation was present in about 70% of them, high STS score, very good procedural success of 95%. Then you can see at three months, there is a 12% mortality rate and a 12% hospitalization rate. However, 2/3 of them-- I'm sorry, in a good note, 2/3 of them actually improved and became New York Heart Association Class I or Class II.

Now, there are a number of ongoing trials of the MitraClip. And there have recently been reported two of the larger trials. The first one was MITRA-FR. So this was a study that was conducted in France. They screened and enrolled 452 patients. They had a number of patients who were excluded, about 300 were randomized. And ultimately, in the two comparative groups, there was 109 who were included in the per protocol analysis, and about 137 got the device. To be enrolled, you had to have severe secondary mitral regurgitation with an effective regurgitant orifice area of greater than 20 millimeters squared, or a regurgitant volume of 30 ccs per beat.

Now, this becomes important because there's a difference between the United States and Europe. In Europe, if you have an EROA of greater than 20, you have severe mitral regurgitation. However, in the United States, it has to be greater than 40 in order for it to be considered severe. So what we call severe differs depending on what side of the Atlantic you're on.

They all had low ejection fractions. They were symptomatic. The primary outcome measure that they looked at was death from any cause, or unplanned heart failure hospitalization at one year.

And here is the primary outcome analysis. And you can appreciate that there was no difference between the group that received the MitraClip and those that continued on medical therapy. Now, there are a couple of things to point out. The average age in these patients was 70, so it was an older population. 92% of patients had a reduction in their mitral valve regurgitation severity of greater than or equal to two. But look at this. A quarter of the patients were dead within a year, and 50% were hospitalized within a year, and that's regardless of treatment. So it speaks to how sick heart failure patients are once they become Class III and Class IV.

Now, there were a number of pre-specified subgroup analyses. I'll just draw your attention to the one at the bottom which looks at that effective regurgitant orifice area. And you'll see that the point estimate favors percutaneous repair in those individuals who had very large ventricles greater than 40 millimeters squared, not so much if you had-- I'm sorry-- if you had more mitral regurgitation, so if you had an EROA of greater than 40, and not so much if you had lesser degrees of mitral regurgitation.

So this degree of mitral regurgitation becomes important when we consider the next major trial, and this is the COAPT trial. This was presented at TCT back in the fall, back in September. And this was looking at a parallel controlled open label multi-center trial of about 600 patients with three plus or four plus secondary mitral regurgitation who remain symptomatic despite maximally tolerated medical therapy. They were randomized in a one to one fashion to either receive the MitraClip plus ongoing guideline-directed medical therapy versus guideline-directed medical therapy alone.

This is the [INAUDIBLE] diagram showing that about 900 patients were initially screened, felt to be ineligible. There were 665 who were ultimately eligible for enrollment. There were a number of roll-in cases. Ultimately, you had a group of 614 patients who were randomized at 78 sites with about 300 in each arm.

And one of the nice things about living in the modern age is I could not attend TCT, but I had, let's say, money on this about what the outcomes of this trial was going to be. And I will tell you right now that I said it's going to be negative. I knew MITRA-FR. I knew the German data. I knew some other data. I'm like, it's going to be a negative trial. So I'm literally having lunch with my son when a buddy of mine from Chicago sends me this while he's in the audience.

And this was the primary outcome, which is the cumulative admission rate for heart failure or hospitalization over 24 months. And there was a significant reduction in the number of heart failure or hospitalization in those patients were treated with the MitraClip. And as impressive as that was, the one that got me to fall out of my chair was this, which was that there was also a significant reduction in all-cause mortality. Now for all the trials previous to this, the MitraClip had shown improvement in functional capacity, but no other significant change in clinical endpoints. It didn't reduce hospitalization.

I didn't do it. I swear. Sign of the apocalypse.

It didn't reduce hospitalizations, and it didn't impact mortality. But none of them were powered for this. However, this was a secondary endpoint, but all-cause mortality was significantly reduced by the application of the MitraClip. And the thing that drew my eye was the separation of the Kaplan-Meier curves. You see the separation begin somewhere between 9 and 12 months. And I'll come back to that in a minute.

So why was there such a difference between MITRA-FR and COAPT? And both of these papers were published within a couple of months of each other in the *New England Journal.* So they were well vetted out. Nonetheless, you have two strikingly different outcomes. So why is that?

Well, one of the thoughts has to go back to the severity of mitral regurgitation and the size of the ventricles. So in MITRA-FR, there was less mitral regurgitation. And in fact, in the subgroup analysis, you saw that the benefit was realized in those patients who had more severe mitral regurgitation with an EROA greater than 40. Couple that with the size of the ventricle. So in COAPT, the ventricles were relatively smaller. So 90 is the upper limit of normal, so these were enlarged ventricles, but not 135 like we saw in France.

And so, if you put these two things together, what might explain this is that the cohort of patients in France had more advanced cardiomyopathy with greater degrees of remodeling, probably sicker patients, but less mitral regurgitation. This is a cardiomyopathic patient. On the other hand, in COAPT, what you have are patients with smaller ventricles, but way more MR, which means that the MR is probably more active, and there may be a little bit more contractile reserve in these folks. Hypothetical, but nonetheless, an observation which holds.

The second thing is the way that guideline-directed medical therapy was applied in the two trials. In MITRA-FR, the guideline-directed medical therapy was not established, meaning that it was the practitioners who could adjust the doses and the choice of medications over time. However, in COAPT, there was a clinical event committee that made sure that before patients were enrolled, they were on maximally tolerated doses of guideline-directed medical therapy, and the patients who were candidates for CRT had received a CRT before they could be enrolled. So there might be a little bit more confidence that the patients who were in COAPT were more aggressively medically treated than the ones in MITRA-FR.

And then the last is some technical stuff. In France, this was really early use of the MitraClip. The technical success was a little bit less than what we saw in COAPT. There was the need for more devices in France than in the COAPT centers. And there was also more persistent mitral regurgitation at the end of the cases in MITRA-FR than there was in COAPT. So this is the working hypothesis that explains the difference between the two trials. However, at this point, it's still a hypothesis.

Now, nonetheless, this idea of trying to get rid of mitral regurgitation is a very robust area for investigation. We are now looking at a number of percutaneous mitral devices to try to replace the mitral valve with a either percutaneous or transapical device. And there are a number that are currently in clinical trials.

And they have different approaches and different mechanisms to anchor the mitral valve in the mitral valve annulus. Some of them act like a champagne cork, so that when you have pressure that's applied from below, the device actually bulges out and holds onto the annulus. There are others that use these winged winglets that kind of anchor itself into the annulus itself and into the septum. One has a tether that actually tethers the valve in place with a wire, so it doesn't displace.

Now, this is the TIARA valve. This was the first in man that was published in *JACC* a few years ago now. This uses an anterior anchor that actually goes underneath the mitral valve leaflet to hold it into place. And this is just proof of concept that one could put in a transapical mitral valve. Now, by transapical, I mean that you're literally going through the apex of the left ventricle. So this is not like the percutaneous device like the MitraClip. This is really a lesser invasive surgical procedure, but is still, nonetheless, a surgical procedure.

This is the Intrepid transapical mitral valve. Now, this uses that champagne cork technology to kind of anchor itself in the mitral valve annulus. This is made out of nitinol, which is self-expanding. So you have an outer ring that holds it into the mitral valve annulus, and then you have an inner ring upon which the mitral valve itself is suspended.

And this is being tested here at Mount Sinai, as well as a number of other sites across the United States. And I'll just point out that our surgical colleague and chief of cardiothoracic surgery, Dr. David Adams is the national principal investigator along with Marty Leon and Dr. Michael Mack. So we have enrolled a number of patients here already in this trial.

And after the publication of the COAPT trial, there was a lot of discussion amongst the investigators as to whether or not one should continue with this transapical approach to placing a mitral valve. And the decision was to move forward with this. Although, I think that there's general understanding that if this is going to be a technology that excels in the future, you really need to have a percutaneous approach so that you can deliver it across the interatrial septum.

OK. So let me pivot and talk about a few other things that we're doing here, and talk about a few other technologies that are improving our ability to take care of heart failure patients. So many of you are familiar with this. This is called the ReDS technology. ReDS stands for remote dielectric sensing. I have no idea what that means. It sounds really good. In reality, it is a medical application of a military technology that uses a radar technology to look through walls, that they now use to look through the walls, through the chest wall, in order to measure the amount of water that is in the lung.

Now what exactly does it measure? Here you have a transmitter. Here you have a receiver. It's applied externally, and it samples an area in the right middle lobe. And it measures lung fluid content, what's the percentage of fluid that's in the lung.

And it was tested and validated by looking at CT scans and measuring the Hounsfield units. CT scan was felt to be the most precise way of measuring lung water. And you can see that there is a very, very tight correlation between the percent lung fluid measured by CT, and that measured by the vest itself.

Now we've talked about deploying this vest in a number of different areas. This is the cycle of being at home, being in the hospital, coming back into the hospital after going home, going to your follow-up clinic, et cetera, et cetera. So the first application of the use this device was here in the outpatient clinic. This is our so-called rapid follow-up clinic. This is a nurse practitioner-led clinic, led by our own Jennifer Ullman, that has the goal of seeing every patient discharged from Mount Sinai Hospital with the primary diagnosis of heart failure.

So, our approach to these patients was to perform a history and a physical, to review all their medications to see how they're doing, and then to apply the vest, and based upon the readings that we get from the vest, to adjust our diuretics. So, we have this nice little speedometer here that kind of graphically displays what we're doing over here, which is that if you're in the normal zone, which is a lung fluid content between 25% and 35%, the goal of therapy at that point would be to advance your guideline-directed medical therapy like an ARNI, or an ACE inhibitor, or a beta blocker. If you're in the yellow zone, where you're retaining some fluid, you should increase the diuretics, and come back to the clinic in another couple of weeks to have a reassessment. And if you're in the red zone, either be treated with a dose of IV diuretic in the outpatient area, or to go to the emergency room for either treatment or admission.

So, we looked at a year's worth of data, looking at our experience of deploying this in the rapid follow-up clinic. We had 314 patients who were assigned a follow-up appointment. And these were from all of the units in the hospital. It was not just from cardiology, but cardiology and medicine. We had 94 patients who did not show up for their appointment, and for us a no-show is defined as anyone who was seen after 10 days of their discharge, who canceled, or who rescheduled, or simply did not show up. We had 94 of those. And we had 220 who kept their appointment, which I have to say is really a testament to Jennifer and our heart failure nurses, that they stayed in contact with patients early after their discharge to make sure that they would come to this appointment.

Once they came to the appointment, there were 139 patients who did not have the vest applied. And there were various reasons, if they were very obese, if they had a defibrillator on that side, if they had a life vest that they didn't want to take off, or if they had a central catheter, we did not perform ReDS. And there were about 80 patients who did have ReDS performed.

And here are our results. So we looked at all-cause rehospitalizations, stratified by whether or not patients kept their appointment. So for those patients who no-showed, we had a hospital 30-day all-cause readmission rate of 23%. And if they came and had a visit, we had an 11% readmission rate. So let me underscore how impressive that is. So a nurse practitioner visit alone was able to reduce the readmission rate from 23% to about 11%. So by point of comparison, our publicly reported 30-day readmission rate is 22.7%, and we can lower this to 11% just by having our patients see a skilled nurse practitioner.

Now what about the group that had the ReDS vest applied? We saw further reduction in 30-day readmission. So for those patients who had the nursing visit alone, it was 14% readmission, 6.5% readmission if you had that plus the ReDS vest to guide therapy. So we've gone from double digit, 22%, down to single digit, 6% to 7% readmission rate with the combination of a skilled nurse practitioner and new technology.

Quite honestly, my other hat is that I oversee the heart failure for the Mount Sinai Health System, and I am banging the drum as loud as I can that every one of our hospitals needs a heart failure physician, a skilled heart failure nurse practitioner, and one of these new technologies, including the ReDS vest, and then we can solve the readmission problem. We can improve the care of patients by tailoring our therapy to either reduce congestion or advance guideline-directed medical therapy, but quite honestly, the results speak for themselves.

OK, and this is just showing graphically RFU versus no RFU, and ReDS vest versus no ReDS vest, significant reductions in heart failure readmission.

Now, there are other technologies that we use for remotely monitoring our patients, and one of them is the CardioMEMS device. This is an implantable pulmonary artery pressure sensor that really consists of just a loop of wire that acts as an induction coil. When you lie down on a pillow that has an antenna, it couples with this radio frequency antenna, emits radio frequency waves that vary depending upon the pressure that's placed on the sensor.

So from that, we can get high fidelity, remotely transmitted pulmonary arterial wave forms. This is literally what the data looks like. We can also track and trend that data over time, and we get the PA systolic pressure, the PA diastolic, and the PA mean pressure. We can then adjust our diuretics based upon the PA diastolic pressure as a surrogate for the pulmonary capillary wedge pressure, to make sure that patients remain appropriately decongested.

Using this in a large, multi-center, national trial, you can see that those patients who had the device and had their heart failure management guided by the device, had lower rates of hospitalization at six months. This exists not only for a trial population, but also exists in a Medicare population, so data that I'm not going to show.

So let me wrap up with talking about advanced heart failure. And there have been a number of innovations in both the fields of left ventricular assist device and also heart transplantation. We've moved from these large pulsatile pumps to smaller continuous flow pumps.

The one that was first approved as a continuous flow pump is the HeartMate II. This is an axial flow pump that acts like an Archimedes screw. It spins at around 9,000 revolutions per minute, basically bores into the volume that's coming down from the left ventricle, and can generate blood flow of anywhere between 3 and 10 liters per minute.

This is the heartware HVAD. This is the same concept, but a little bit of a different mechanism. This is a continuous flow pump that uses centrifugal flow, basically a rotating disk that is hydrodynamically and electromagnetically elevated, such that you have a completely frictionless surface. This spins at around 2,500 revolutions per minute. It is contained entirely within the pericardial sac and can generate blood flow, just like the HeartMate II, of around 3 to 10 liters per minute.

Now where the rubber hits the road, these two devices are exactly the same in terms of survival rates and also bridge-to-transplantation rate. However, they do have some differences in terms of their adverse event profile. And three of the things that we worry about the most are bleeding, particularly gastrointestinal or mucosal bleeding due to a combination of Heyde's syndrome and also degradation of large molecular weight von Willebrand factors; stroke, both hemorrhagic and ischemic; and then pump thrombosis.

So this is the new generation device. This is the HeartMate 3, now approved by the FDA for both short-term and long-term support. And this was a device that we participated in the clinical trial.

It has three engineering principles that were designed in order to make this device more biocompatible. The first thing is that there are wide gaps between the rotor and the housing, such that there's less trauma to the blood as it goes through the pump. The second is that the device is completely frictionless. It's fully magnetically elevated, and does not touch any of the walls. And then lastly, it has an intrinsic pulse where the pump slows down for a fraction of a second and then accelerates up for a fraction a second before returning to baseline. And that's done to wash the internal components of the pump to prevent areas of stasis from developing, and to prevent thrombosis.

So the main technological advance is that there's less shear stress by the centrifugal flow compared to the high shear stress that one sees as the blood passes through the impeller of the HeartMate II.

Now, this was tested in the MOMENTUM3 study. This was a large prospective randomized trial that enrolled 366 patients. And by long term, we mean a plan for two years of follow-up. They were randomized to receive either the HeartMate 3 pump, which is the centrifugal flow pump, versus the axial flow HeartMate II. And we compared about 189 to 172 people in those two groups.

The primary endpoint was an intention to treat analysis of survival at two years free of disabling stroke, which was at least 3 of the modified Rankin's stroke scale, or reoperation to replace or remove a malfunctioning device. And you can see that at two years there was a greater number of persons in the HeartMate 3 who reached the primary endpoint compared to the HeartMate II.

If we'd look at some of the forest plots, we can see that the HeartMate 3 was superior than the HeartMate II across a number of categories, including younger and older persons, men and women, race, and intended use, whether it was bridge-to-transplant, or for destination therapy, or so-called lifelong support. Not only did the pump improve survival, it also improved functional status and quality of life, which is critically important, because if you're going to help someone live longer, they better be living better as well.

And importantly, it decreased the incidence of stroke, and most of the improvement was reduction in the lesser degrees of stroke, so, modified Rankin stroke scale of less than 3. However, overall, there were fewer strokes seen in those patients who had the HeartMate 3.

But really what was most striking was that this technology completely eliminated one of the previous adverse events and that was pump thrombosis. Essentially, all the patients with the HeartMate 3 were free of pump thrombosis at two years, not so for those patients who received the older axial flow pump.

And let me just wrap up, because I know time is drawing to a close, to talk about heart transplant. This still remains my passion, which is cardiac transplantation. The first heart transplant was performed just over 51 years ago by Dr. Christiaan Barnard.

However, for those of you who are interested in medical history, this is a fantastic book called *Every Second Counts,* which talks about the race to perform the first transplant. So the honor of that belongs to Dr. Barnard, but really all the praise should go to Dr. Norman Shumway who was at Stanford University. And it is because of Dr. Shumway and his team that cardiac transplantation started, and more importantly, that it continued throughout the 1970s when the outcomes were really dismal, but he and his team continued to persist with their belief that this was the way to go.

Now, one of the things that they developed was the bioptome to allow endomyocardial biopsy. And by biopsying patients frequently, they could see whether or not the allograft was being rejected. They could taper corticosteroids so that would subsequently decrease the risk of infection, or they could increase immunosuppression if need be. However, between you and me, at some point we will look back on this and say, this is absolutely barbaric that we give people a heart, and then we take it away, one piece at a time.

And so as a result of that, we're trying to come up with non-invasive ways of diagnosing or excluding rejection. And so one of those is to use gene expression testing. And the idea here is that there are certain genes which are either up-regulated or down-regulated in the setting of acute cellular rejection that can be detected by looking at peripheral blood mononuclear cells.

Now, this is a commercially available test. We draw the blood. We spin it down. We send it out to California, and what we get back is an ordinal score. And if this score is below a certain threshold, we can be about 99% certain that a patient is not rejecting. If their score is above that threshold, we can't say that they are rejecting, we just can't say that they are not rejecting, and they would have to go on to do a biopsy.

Now, the utility of this test has been now tested in hundreds, if not thousands, of patients in a number of clinical trials, including the original derivation, CARGO and CARGO II trials; the IMAGE trial, which looked at the ability of this test to perform in a non-inferior way to rejection surveillance using into endomyocardial biopsy; and then a similar study, the Early IMAGE trial, which did the same thing, but early after transplant, between three months and six months-- three months and one year after transplant.

But one downside to it is it only can exclude acute cellular rejection. It can't tell us whether or not someone is experiencing antibody-mediated rejection.

Now we're moving into a new phase of molecular diagnostics, looking at something called donor-derived cell-free DNA. Now, all of us have circulating within our bloodstream free-floating DNA, and this is DNA that gets into the bloodstream due to natural cell turnover, or due to either programmed cell death, apoptosis, or injury to ourselves, but the DNA is released.

Now, if you think about an organ transplant, an organ transplant is also a DNA transplant. And we can sample cell-free DNA, and we can determine what percentage of that DNA is from the donor allograft, and what percentage is from the recipient. And what is remarkable is that the basal rate of producing cell-free DNA in a human is very, very constant. And as a result of that, any increase in the proportion of donor-derived cell-free DNA to recipient DNA is a sign that the allograft is being injured.

So these are data that were published from Stanford, doing some preliminary work looking at donor-derived cell-free DNA, showing that in the setting of antibody-mediated rejection or acute cellar rejection, you see a sudden increase in the ratio of donor-derived cell-free DNA. So this is just one example. This is one patient. Early after transplant, there were higher levels of donor-derived cell-free DNA, which makes sense, because you've just sewn in the allograft, and there was some ischemic damage. But within a couple days, it clears, and remains low and constant for a long period of time.

However, take a look at example in panel B. This is someone who had the same pattern, and then right around a year after transplant, there is this sudden increase in the ratio of donor-derived cell-free DNA. When they biopsied that heart, they saw that there was significant allograft rejection. Not only that, it was so severe that the person had to be retransplanted. And when they got retransplanted, same pattern developed. There was a drop in the ratio of donor-derived cell-free DNA until about six months after transplant, when there was-- oh, here we go. This is same slide, but you can see here is the repeat transplant, and then it goes back down very quickly to basal levels.

So this is true not only for acute cellular rejection but also for antibody-mediated rejection. Anything that injures the allograft can cause this increase in donor-derived cell-free DNA.

So we are participating, have been participating, in a registry looking at not only gene expression profiling, but also the use of donor-derived cell-free DNA. And we're about to launch a prospective evaluation of donor-derived cell-free DNA here at Mount Sinai. We're one of about 12 sites across the country that are going to be piloting this. We're very excited about its ability, in combination with gene expression profiling, to non-invasively exclude both acute cellular rejection, as well as antibody-mediated rejection.

So I took you through a lot of different things. Matt had told me to go deeper than broader. And you know, I could have gone a lot broader, and I compromise somewhere between the two. But I hope that you can tell that there's a lot of enthusiasm from our clinical and our research group in heart failure. This is, once again, a very, very active area of research. We're really excited to partner with you in looking for patients who are eligible for these therapies. We're always available on a consultative basis, if you have any questions about managing clinical heart failure.

I want to thank you again for giving me this opportunity to speak with you, and I hope we left a few minutes for questions. So thank you very much.

[APPLAUSE]

MATT: I think we have time for a few questions.

AUDIENCE: In the MITRA-FR and the COAPT trials, these were studies with heart failure with reduced ejection fraction?

DR. SEAN PINNEY: Yes.

AUDIENCE: Yet the average age of the group in the MITRA-FR was 70, I think you mentioned. So are there any study-- is this mitral syndrome that you describe significant in heart failure with preserved ejection fraction? And if so, are these devices of any help, and is it being studied?

DR. SEAN PINNEY: So in the setting of preserved ejection fraction, I would think of it less as functional or secondary mitral regurgitation, and probably more primary or degenerative mitral regurgitation. So in that setting, if you do have significant mitral regurgitation and the valve looks anatomically appropriate for clipping, the device is currently approved for primary mitral regurgitation, so I would expect that there would be some benefit.

AUDIENCE: Has that been studied?

DR. SEAN PINNEY: It has been studied, yes, in EVEREST is the name of trial. Everest.

AUDIENCE: Is the HeartMate 3 associated with less acquired von Willebrand disease than the HeartMate II?

DR. SEAN PINNEY: No. And that's the fascinating thing. So, all of the continuous flow pumps, just about every patient acquires von Willebrand disease. There is still degradation of the multimeric form of von Willebrand factor, but not everyone bleeds. About 25% of patients bleed, even with the HeartMate 3. And we don't really fully understand why.

Yes, sir?

AUDIENCE: So you showed that in comparing MITRA-FR with COAPT, that there is some difference in the patient groups who are being done. But I want to go to a different area. In any new procedure, there's usually a learning curve. So was there any difference between those who did the procedure, in terms of maybe prior experience inserting various things, or with the specific procedure that was being done?

DR. SEAN PINNEY: That's a fantastic observation and an appropriate question. There were a limited number of practitioners who had performed the device implantation in France. However, it was a new device to them, so one has to assume that there was more of a learning curve. And I think that's reflected in the outcomes.

So in the MITRA-FR group, there was a greater degree of residual moderate mitral regurgitation. Also, a higher percentage of patients required two or three clips in order to get rid of the mitral regurgitation, which would speak to basically that the deployment of a new technology in a group that still had a learning curve, as compared to the United States, where the technical success was higher than in MITRA-FR, and where the practitioners had had more prior experience in deploying the device.

Yes?

AUDIENCE: Sean, that was a great talk. I was wondering if you could just share with the audience kind of some of the calculus that goes into when you consider someone for percutaneous mitral valve intervention or advanced therapies, because we always grapple with that as a group.

DR. SEAN PINNEY: So that's a great question. So Dr. Mitter's question is, how do you decide between selecting someone for a MitraClip or a percutaneous mitral device, versus escalating care to advanced therapies? And there, the short answer is consult the heart failure group.

[LAUGHTER]

But I think it gets to one of the observations that was made comparing MITRA-FR to COAPT, and that is, one has to be really tuned into what's driving the clinical outcomes in a particular patient. So is it someone who has a severely remodeled ventricle, and has more advanced heart failure, where one expects the mortality to be a lot higher? Or is it someone who's more symptomatic from mitral regurgitation, but still has relatively preserved, or has some degree of contractile reserve, or other parameters that would suggest at least a two or three year survival? So one example of that would be a performance of a cardiopulmonary exercise test with a higher or a preserved peak oxygen consumption. Others might be the performance of dobutamine echocardiography to look at the degree of contractile reserve.

And then the last part is the part that Dr. Mitter and I, and Dr. Barghash, Dr. Moss, everyone who is here in the audience practice every day, which is really taking a look at the patient, and being very precise in patient selection. I think one of the things that will eventually emerge from these mitral trials is that although it was focused on mitral regurgitation, these were really heart failure trials. And so I think we need to do a better job of defining not the population that that will or will not benefit from the device, but the individual person.

That gets back to that observation about the Kaplan-Meier curves. You know, they didn't separate out until about 9 or 12 months. And the way I interpret that is that the patients who are going to die, are going to die with or without the device. But then after about a year, you will see that that group of persons emerge who have benefited from the LV remodeling and the increasing guideline-directed medical therapy. So being able to turn the clock back at the time of implant, and make an educated guess or educated decision as to who is the person who's going to die with or without a MitraClip, versus who is a person who's going to benefit, becomes still a little bit of an art.

I've had some discussions with the primary investigators about how we can do that analysis based on the COAPT data. Since we were an enrolling center for COAPT, we should be able to get that. We're really doing deep clinical phenotyping of those individuals, and define what a person who benefited from the device looks like.

MATT: OK, let's thank Dr. Pinney, again.

[APPLAUSE]