SPEAKER 1: [INAUDIBLE] Dr. Anu Lala-Trindade [INAUDIBLE]. Her medical degree from [INAUDIBLE] and School of Medicine. She completed her internal medicine [INAUDIBLE] here at Mount Sinai, followed by an [INAUDIBLE] at NYU School of Medicine. [INAUDIBLE] medical school.

Dr. Lala [INAUDIBLE] as an assistant professor of cardiology. She serves as the director of heart failure research and [INAUDIBLE]. She was also selected as the 2016 American Heart Association [INAUDIBLE] honoree for her commitment to education and cardiovascular health awareness. Please join me in welcoming Dr. Lala.

[APPLAUSE]

ANURADHA LALA-TRINDADE: Good morning. Thank you so much, Rachel. Thank you, Dr. Murphy and vice chairs of medicine for inviting me to speak to you this morning. 10 years ago, I was sitting back there. I was a second-year resident doing a research project with Dr. McLaughlin and Dr. Penny in an effort to try and match for a cardiology fellowship.

So it's very sort of humbling to be on the opposite side of this podium. It's with a lot of pride and a lot of gratitude and humility that I look forward to holding your attention over the next 45 minutes.

So talking about acute heart failure is an enormous undertaking. And I obviously can't touch on all of the salient points that I would like to in acute heart failure given the time restriction over the next 45 minutes, but what I thought I would do is cover a sort of top 10 list of things that I would hope that you could take home after this session.

So if it seems a little piece-mealed, forgive me. It's for the purposes of making these 10 points that may not all be connected.

So the first point-- and we'll come back to each one of these over the course of the next hour-- the main reason for acute heart failure admission is clinical congestion. Hemodynamic congestion, which is somewhat related but distinct, precedes clinical congestion by days and up to weeks and can persist even after the relief of symptoms.

Half of the patients hospitalized with heart failure have heart failure with preserved ejection fraction, so that's an injection fraction over 50%. And these patients have similar outcomes to those patients who have a reduced ejection fraction.

80% of patients already have a history of heart failure, so these are not de novo heart failure admissions. And comorbidities are extremely common in heart failure-- and these include coronary disease, hypertension, atrial fibrillation, diabetes, lung disease, sleep disorders, depression, and chronic kidney disease. And these need to be addressed when taking care of patients with heart failure.

Positive troponins and elevated natriuretic peptides are associated with a poor prognosis, but they may not necessarily be modifiable. They may, in fact, just be markers of disease severity. Other markers of poor prognosis include low blood pressure, low serum sodium, high natriuretic peptides, as I mentioned, and worsening renal function.

And again, it's important to distinguish between markers and targets of therapy. And we'll get more into this later. Pharmacotherapies for heart failure with reduced ejection fraction for which we have evidence-based therapies are highly underutilized, and we need to use the hospitalization for heart failure to our advantage to improve the way we treat these patients.

The post-discharge phase is an extremely vulnerable one that is characterized by a deterioration in clinical status and is associated with unacceptably high rates of morbidity and mortality. 50% of readmissions following heart failure hospitalization are non-heart failure related. And finally, many patients unfortunately do not receive sufficient education or appropriate follow up after acute heart failure hospitalization in that very vulnerable phase.

So we're going to touch on each one of these 10 points. And we'll come back to them at the end to come full circle. And hopefully you'll be able to take these home with you today.

So let's start by talking about what congestion actually is. So a patient goes from having no symptoms with a backdrop of having abnormal LC function, whether that systolic, or diastolic, or most commonly both, and then there's some sort of trigger on this backdrop of abnormal LV function, be it dietary indiscretion, medication such as NSAIDs or negative inotropes like calcium channel blockers, noncompliance, of course, infection, ischemia, arrhythmias, uncontrolled hypertension, and endocrinopathies that ultimately lead to an elevation in LVEDP or Left Ventricular End Diastolic Pressure.

And there is impaired volume regulation, which coincides with increases in the renin-angiotensin aldosterone system, reduced cardiac output in certain cases, activation of endothelium, inflammation, altered adenosine signaling. All of which contribute to a very complex process that's sort of simplified in the term of fluid redistribution.

What does all of this lead to? Well, put quite simply, it leads to increased filling pressures. So that's an increase in the LA pressure, the pulmonary capillary wedge pressure, increase in your pulmonary pressures that ultimately lead to the increase in right-sided filling pressures as well. And this is what leads to a patient actually decompensating and developing symptoms.

So I think we're all pretty familiar with what clinical congestion is. And that's often synonymous or used synonymously with acute heart failure. So the signs of heart failure, we're all familiar with.

These include elevated jugular venous pressure, edema, pleural infusions, pulmonary edema on X-ray or rails-- which we note most commonly, and perhaps that's because we can see radiographic evidence of this, but it's not necessarily specific for heart failure-- ascites, and elevated natriuretic peptides.

But it's actually what the patient feels that brings them in to be seen, right? So these are symptoms. And the most common of these symptoms is dyspnea, followed by fatigue, early satiety, nausea, edema, and then also a term that's becoming more popular, which has been bendopnea, which is essentially feeling short of breath when you bend over to tie your shoes.

So what is hemodynamic congestion then? How is that distinct from clinical congestion? Well, put quite simply, this is just elevated filling pressure.

So you can see here on the left, this is ischemia of a patient, hypothetically, with elevated filling pressures on pulmonary arterial catheterization, an RE of 15, and a pulmonary capillary wedge pressure of 30. So grossly elevated filling pressures. So it would be no surprise to us that this patient would have symptoms of congestion, signs and symptoms of congestion, which we referred to on the previous slide. And that patient would have clinical congestion as well.

But it's when you have evidence of increased filling pressures and the absence of signs or symptoms of heart failure that you have, essentially, just hemodynamic congestion. And this is important, because it's becoming an increasingly hot area of interest-- in that, if we can potentially target increased filling pressures before the patient develops clinical symptoms, perhaps we can improve some of the outcomes in the readmissions we're seeing with heart failure patients.

So why does it matter? Well, very obviously, clinical congestion, or heart failure, or acute heart failure is what brings people to be seen. They seek urgent evaluation for relief of their symptoms.

We all know that heart failure is a major cause of morbidity and mortality in the United States and globally. And it's characterized by exceptionally high rates of admission and readmission. So over one million admissions for heart failure in the US alone per year, a 25% readmission rate at 30 days alone, which if you think about it, is extremely high, and over 50% in some studies at six months and one year.

The number of decompensation events predicts mortality independent of some of the factors that we know are associated with poor prognosis, like age and renal function. And the costs for taking care of heart failure patients are just staggering. It's over $30 billion per year in the US alone.

So before we go back to our top 10 list, let's talk a little bit about how we actually relieve congestion. So one of the most obvious answers is, obviously, diuretics, right?

And unfortunately, because it's not an incredibly sexy topic, it's not highlighted, I think, as much as it needs to be. The DOSE trial, which was published in *The New England Journal of Medicine* now six years ago looked at exactly how we should best go about diuresing patients.

And essentially, what they did is they took 400 patients and randomized them in a two-by-two factorial design to high dose versus low dose IV diuretics. So the high-dose arm was 2.5 times the daily oral dose in IV form, so really high doses, things that we don't see in routine clinical practice. And then also bolus versus continuous drip.

And what they found was that the high-dose arm seemed to be more effective in decongesting patients. And it was associated with a transient change in renal function, but that renal function change or that worsening renal function was mitigated at 60 days.

So it was safe. It was well-tolerated. And it was probably better at decongesting patients. There was no difference, however, in using a bolus dosing strategy versus a continuous drip strategy.

I'll make a quick plug for some of the other loop diuretics, bumetanide and torsemide. Bumetanide and torsemide have better bioavailability. It's a one-to-one oral to IV conversion. Longer half life than furosemide.

And torsemide, in particular, is associated with having an antifibrotic effect, reduced aldosterone production, and potentially reduced sympathetic activation, and is now the subject of a NIH trial comparing torsemide versus burosemide, which we hope to participate in.

What about diuresing patients with vasodilator onboard? Does that help you? Does that allow for better decongestion?

So the ASCEND-HF trial was the largest acute heart failure trial to date, which looked at patients getting standard therapies for decongestion versus standard therapies plus a nesiritide. And unfortunately, neither dyspnea relief nor post-discharge outcomes were improved. And, in fact, there was more hypotension and a trend towards worsening renal function in patients who received nesiritide.

Similarly, a much smaller study done by the Heart Failure Network looked at whether adding low-dose dopamine or low-dose nesiritide-- such that you wouldn't cause the hypotension that you saw in ASCEND-HF-- to see whether those strategies would allow for enhanced decongestion, and that was also a negative study.

There was no improvement in renal function and no improved sort of levels of decongestion with those strategies either. So where we stand right now is high-dose diuretics really work. And we're probably underutilizing them.

What about ultrafiltration? We always hear about that. Someone comes in massively volume overloaded. We say, oh, they're not responding to diuretics. Let's just ultrafiltrate them.

So ultrafiltration is the removal of plasma water across a semi-permeable membrane, potentially preserving intravascular volume. So the theory behind-- or the hypothesis is that it would allow for better renal function. But that's if the fluid removal from the intravascular space does not exceed the interstitial mobilization from extravascular space to the intravascular space.

Ultrafiltration has now been studied in three sort of semi-large randomized controlled trials. These were UNLOAD, CARESS, and AVOID HF. In UNLOAD, there was a signal towards more weight loss, more fluid loss, but this was at a 48-hour endpoint. But there was no change in dyspnea relief for these patients.

CARESS looked at patients with cardiorenal syndrome, randomized to ultrafiltration versus that high-dose strategy studied in DOSE. And patients-- in fact, ultrafiltration was found inferior to high-dose diuretics due to worsening renal function.

So this was followed by AVOID HF where the rates of ultrafiltration were actually modifiable and individualized, which was one of the main criticisms of the CARESS trial. And unfortunately, even though there was a signal towards less hospitalization in the ultrafiltration arm, this study was stopped early by the sponsors, and so we don't have that verdict out yet.

So what's the take home for ultrafiltration? As it stands right now, if diuretics are unsuccessful, we can think about ultrafiltration, but we have to keep in mind that this requires vascular access. It requires additional nursing support. It's associated with higher costs and also a bleeding risk, because these patients require systemic anticoagulation.

What about other therapies used to decongest patients? And acute heart failure, unfortunately, is just getting worse and worse of a rap, because it is associated with more and more negative trials. But it's not that we're not learning from those negative trials.

So the first of one of these is a vasopressin antagonist, so looking at tolvaptan and conivaptan to promote aquapheresis. This was studied-- tolvaptan, in particular, was studied in the EVEREST trial.

This was 4,000 patients. And there was no difference in all-cause mortality or the composite cardiovascular endpoint. So we really restrict these to sick patients who are profoundly hypernatremic, generally a sodium less than 130, and it's really approved only for short-term use.

What about mineralocorticoid receptor antagonists? So we use those in our liver disease patients all the time. It's helpful sometimes in the setting of diuretic resistance.

And this was formerly studied in the ATHENA-HF trial just earlier this year. And what we saw was high-dose spironolactone was studied versus placebo. And this was in 360 patients. And though spironolactone was safe, there was no difference in natriuretic peptide levels, a congestion score, or dyspnea.

Finally, two other large studies that deserved mention were the RELAX-AHF studies. So these looked at serelaxin, which is a synthetic analog of relaxin, which is normally found in the body and is upregulated in pregnancy. And this compound mediates vasodilation. It's involved in endothelian pathways and has positive effects on collagen and fibrosis pathways as well.

And though the first study of roughly 1,000 patients improved dyspnea and decreased hospitalizations, RELAX Acute Heart Failure II, which was a larger follow-up study as mandated by the FDA before approval, failed to show improved efficacy for improving cardiovascular death or worsening heart failure.

And finally, published just a few months ago in *The New England Journal* was the TRUE acute heart failure study that was 2,150 patients looking at ularitide, which is a natriuretic peptide or a vasodilator. And these patients had an IV infusion of this compound versus placebo for 48 hours based on the fact that vasodilation acutely in heart failure was thought to be-- thought to reduce wall stress. And unfortunately, this did not pan out to prove its primary outcome either, so there was no difference in cardiovascular death.

So to be a little bit more negative and add to that story, many patients are still discharged with congestion. And I think that gets back to the point that I was mentioning before that we are underutilizing how we use diuretics and other decongestive therapies.

So this was a small analysis we did of the DOSE and CARESS trials from the Heart Failure Network of 500 patients. And congestion in this study was defined as patients with orthopnea and edema. And we found that 50% actually still went home with orthopnea and edema.

And these were in specialized heart failure centers. And these trials were aimed purely at decongestant patients. So these numbers are pretty staggering.

I will point out on the right, however, that it's important to note that even when you were decongested, event rates post-discharge were still exceptionally high. So heart failure hospitalization itself bodes a poor prognosis, and we need to do whatever we can to improve those outcomes.

How do we know if someone is adequately decongested? How do we know if our therapies were actually successful? Well, all of these things have been associated or linked to decongestion and thereby linked to improved outcomes.

So resolution of signs of heart failure is always something that we look at. Relief of symptoms, the most common reason. Weight loss has been associated with improved outcomes.

Fluid loss is also looked at, but is less consistently seen to be associated with improved outcomes compared to weight loss. Improved renal function-- some reports say worsening renal function. Hemoconcentration is a marker of decongestion and is associated with better outcomes and reduction in natriuretic peptides.

But to be honest, we don't really have a great definition of what it means to decongest a patient appropriately. Sometimes you can see resolution of signs and symptoms of heart failure, but persistently elevated natriuretic peptides and maybe no change in weight.

So how do we put this all together? And that's still an area of ongoing investigation. So let's come back to our top 10 list.

Hemodynamic congestion precedes clinical congestion by days and up two weeks and can persist after the relief of symptoms. So this is that same patient I showed you with elevated filling pressures.

We essentially diurese this patient or use our decongestive therapies. And now they have lower filling pressures, but they're still not normal. But at this point, the patient says, hey, listen. I don't feel bad anymore. I don't have any dyspnea at rest. I want to go home. And so we discharge this patient. But perhaps we're discharging these patients with still persistently elevated filling pressures or hemodynamic congestion, and this is playing a role into why we see such high rates of readmission.

So I will make a plug here that just because your patient is saying they feel better, try and provoke them. See whether they're able to walk around without feeling shortness of breath. See whether they're actually able to lie flat in front of you and not complaining of shortness of breath. Really sort of test where they are, because, obviously, everyone wants to go home.

So can we prevent this clinical congestion? Well, I've already sort of alluded to the fact that filling pressures continuously rise until they reach a critical threshold, and that's where decompensation occurs. But if we catch patients before that decompensation occurs, perhaps we can prevent some of these hospital admissions.

So this is where the PA pressure monitor, or what's commonly referred to as the cardio MEMS device, comes into place. So this is a pressure sensor that lies in the pulmonary artery.

And it was studied in the CHAMPION study published in 2011 where they took over 500 patients who had pretty severe heart failure, so Class III heart failure and a prior hospitalization in the past one year. Importantly, this included heart failure with preserved ejection fraction and reduced ejection fraction.

And what they saw was a close to 30% reduction in heart failure hospitalizations at six months in the arm that had the PA sensor and physicians and health care practitioners could act upon those readings. So that's all good if that's clinical trial data, but the skepticism came from, well, does this really translate into real life. And what we've seen over the past several years is that it actually does.

So this is a study that was just published in *Jack* earlier this year looking at Medicare beneficiaries, over 1,000 patients. And what they saw were those patients with a PA sensor monitor had reduced hospitalizations for heart failure at both six months, which is here on-- this was panel A-- and at one year. And as one might expect, this was associated with a reduction in costs of about $7,500 per patient.

So as this becomes more utilized, it's possible that we might be able to use it in our acute heart failure patients who were hospitalized to see where they are from a hemodynamic perspective. And just so you guys know, Dr. Noah Moss in our group is the one who's actually implanting these cardio MEMS devices.

So another case or another clinical context-- this is a 72-year-old woman with obstructive sleep apnea, diabetes that's not very well-controlled. She's a prior smoker with COPD.

She has single vessel coronary disease. She has chronic kidney disease, Stage III, with a creatinine of close to two. An ejection fraction of 55%. And two prior heart failure hospitalizations in 2017 alone. She's on Lasix, Albuterol, JANUVIA, Lipitor, and diltiazem.

So I ask you, and I won't ask you to raise hands, because no one ever answers those or participates in those. But think to yourself-- would you think about this patient any differently if she had an ejection fraction of 30%? And is this a typical patient? Do heart failure patients have so many comorbid conditions?

So let's talk a little bit about heart failure and ejection fraction. So when I think about heart failure, we think about preserved ejection fraction, which is defined by our guidelines as an EF over 50%. And reduced ejection fraction, which is defined by an ejection fraction less than 40%. And both of these can present in the chronic phase and the acute decompensated phase or the acute heart failure phase.

Somewhere in between is the intermediate ejection fraction, 40% to 50%. And this is a little bit of a black box. We don't exactly know what outcomes are for these patients.

But it's important to remember that a majority of patients are "wet" and "warm." This is 80% of the people that we're seeing. So, of course, we have a different vantage point being the advanced heart failure team because we're seeing many of the underperfused patients.

But for the purposes of this talk, it's important to realize that these patients can be decongested. They do respond to diuretic therapy. And we need to do that. And this applies to heart failure with reduced ejection fraction and preserved ejection fraction in the same way.

So what about survival? Well, we always think, and we're so numerically obsessed as human beings that we think, OK, higher ejection fraction means better prognosis, better outcomes. And that's not necessarily the case.

So this study blew everyone's mind. And this was published now over 10 years ago. And that was over 2000 patients in Canada who were hospitalized for heart failure. And what we found was the hazard ratio for survival was essentially not statistically significant in that there was no statistically significant difference between patients with preserved ejection fraction and reduced ejection fraction.

In a more contemporaneous cohort looking at "Get with the Guidelines Registry," we see similar results in that heart failure with preserved ejection fraction and reduced ejection fraction have the same outcomes. So that brings us to point number 3. Half of our patients have an EF over 50%. And outcomes for HFpEF are similar to HFrEF.

So what about these comorbid conditions we were alluding to in the previous case? A majority of heart failure patients have multiple chronic conditions. And this is more and more true as our population ages, and more and more elderly patients are living with heart failure.

Heart failure with preserved ejection fraction patients have more comorbidities in general than heart failure with reduced ejection fraction. But it's almost crazy to think about the fact that almost 50% of patients with HFpEF have four or more comorbid conditions. And these data come from Olmstead County in Minnesota.

This is from roughly 1,300 patients. And you can see here that men and women both have a number of comorbid conditions. But you see that more in the HFpEF group than the HFrEF group.

And this data is just showing what we know about the typical patient who presents with acute heart failure. This comes from our Adhere registry, the Euro heart failure registry, and the OPTIMIZE-HF registry, so thousands and thousands of patients which tell us that the mean age is over 70. So these are increasingly older patients.

It's about 50/50 men and women. Most of these patients, as I mentioned previously, have a history of heart failure. It's 50/50 in terms of ejection fraction-- preserved and reduced ejection fraction, as I already mentioned.

Up to 2/3 of patients have a history of coronary disease. A majority have a history of hypertension. About 40% have a history of diabetes. A fib is seen in about a third of patients, as is renal insufficiency.

There's a nice article in *JACC,* which summarizes the differences in comorbid conditions stratified by HFpEF and HFrEF. And this is really just reiterating the comorbid conditions that this hypothetical patient I presented to you has-- so chronic obstructive pulmonary disease; anemia, which is potentially modifiable by iron infusions, which have been shown to improve outcomes. Diabetes is becoming an increasing area of interest, especially as SGLT1 and 2 inhibitors are improving outcomes in the chronic setting. Renal dysfunction, sleep-disordered breathing, and obesity.

And we just looked at over 750 patients hospitalized for acute heart failure and found that over 20% of those patients had a BMI over 40. And we wanted to call the title of that article which was published in *JACC-HF* "40 Is the New 30." But it didn't really get a lot of approval there.

[LAUGHTER]

So again, that's now take-home point number 4. Comorbid conditions are common and need to be addressed while we're treating the heart failure. What about biomarkers?

So natriuretic peptides and troponins, we've become obsessed with these. And because heart failure is not as easy sometimes to diagnose, we rely on some of these more objective markers to help guide our management. Unfortunately, this hasn't panned to be very helpful.

So there's no absolute BNP threshold or value that actually signifies congestion. It may be helpful to get a BNP level when patients are "wet" on admission, and then compare it to how they are after therapy, and see a reduction in BNP. But that's also wrought with error.

So really where we stand right now in terms of what the guidelines tell us is that it's a Class 1A recommendation to order a BNP level to prognosticate but not to guide therapy. And this is on the right. And this is really only applicable to chronic heart failure with reduced ejection fraction patients.

But it did surprise the heart failure field in that a BNP-guided strategy did not improve outcomes for patients with chronic heart failure and reduced ejection fraction. So I think more and more we know that it's associated with a poor prognosis. But not that we should use our therapies based on these levels.

What about troponin? Well, troponin signifies myocyte damage. And it may reflect a coronary event. But more commonly in heart failure, it reflects global myocardial stress and accelerated apoptosis.

So this is a nice study that was done from a biomarker subset from the ASCEND-HF trial. And what we've found here was that cardiac troponins were elevated above the 99th percentile in up to 50% of acute heart failure patients. And it was associated with outcome-- you can see here in unadjusted analysis-- so death at 30 days. And that was significant.

But once it was adjusted for other factors, it was no longer significant. And you can see here, interestingly, cardiac troponins were elevated in patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy, and slightly more commonly in patients with reduced ejection fraction as opposed to preserved ejection fraction. So take-home point number 5-- positive troponins and elevated natriuretic peptides are associated with worst prognosis but not necessarily used to guide therapy.

So another patient, Mrs. Jones, is 53. She is AHA/ACC stage C, heart failure with reduced ejection fraction, EF of 24% and ischemic cardiomyopathy, NYHA Class II symptoms, who presents to the emergency room with dyspnea, and bendopnea, and orthodema, which is a combination of orthopnea and edema, after dietary indiscretion while she was on vacation. She takes 40 milligrams twice a day of Lasix.

So you treat her according to the DOSE algorithm. You give her 200 IV Lasix. That's 100 IV BID. That's 2.5 times her oral dose IV. And she's responding beautifully.

But unfortunately, her creatinine goes from 1.2 to 1.9. And she still has orthopnea, and edema, and an elevated jugular venous pressure when you examine her. Should you reduce the dose of your diuretic therapy? OK, good, we have some participation. Good.

So worsening renal function is often the bane of our existence. It's very common in acute heart failure. And it's been associated with worse outcomes.

And it scares us. We see the creatinine go up-- oh, this person is probably overdiuresed. We should stop. We should pull back the diuretic and hold it for a few days.

And then what happens? The patient develops congestion all over again. You sort of end up in an in-between state. And that's why perhaps readmission rates are as bad as they are.

But what we're learning now is that transient worsening renal function may not affect the post-discharge outcomes. And this was seen in the DOSE trial. So higher doses of diuretics, again, were associated with better dyspnea relief and fluid loss.

And that change in worsening renal function was mitigated at 60 days. So in fact, worsening renal function may just be a trade-off for decongestion. And it's probably worse to have patients go home congested than with a change in their renal function.

So this patient, the same patient-- her creatinine now is 2.1. She doesn't have any edema anymore. You don't see any jugular venous distention. But she's orthopneic when she lies down. And her systolic blood pressure now is in the 80s.

And this is just a quick plug for the utilization of the right heart catheterization. Clearly, it doesn't have a role in everyday "warm" and "wet" patient. But it does have a unique role in identifying high-risk heart failure patients with persistent hemodynamic abnormalities. Our guidelines currently tell us that it's a Class 1 to have a PA catheterization in a patient with respiratory distress, low perfusion suspected, or if their intracardiac filling pressures are unclear.

And here more relevant-- it's a Class 2 for a patient who has persistent symptoms despite therapy. Their fluid status is uncertain. Their systolic blood pressure is low.

The renal function is worsening with therapy. Or you think that they may require a parenteral vasoactive agent. And, of course, we use it commonly in the evaluation for advanced therapies, such as LVAD or transplant.

So what are some of the other markers of poor prognosis and acute heart failure? Low systolic blood pressure has time and time again been shown to inversely correlate with in-hospital and post-discharge mortality. Coronary artery disease, which I showed you, is seen in up to 2/3 of patients. The extent and severity of it is a predictor of poor prognosis.

Troponin release we already spoke about, as did we speak about elevated natriuretic peptides. Ventricular dyssynchrony, so a wide QRS-- this occurs in up to 40% of heart failure with reduced ejection fraction patients and is associated with higher in-hospital and post-discharge mortality. So if you're seeing the patient with a wide QRS, think about cardiac resynchronization therapy to improve outcomes.

Hyponatremia is certainly associated with poor outcomes. And it occurs in up to a quarter of acute heart failure patients. Clinical congestion at the time of discharge we've spoken about. We've also spoken about a similar post-discharge event rates for ejection fraction, whether it's preserved or reduced.

And importantly, like I mentioned before, it's nice if we're able to provoke these patients to see if they're symptomatic, if they are restricted in what they're able to do in their functional capacity. And we spoke about renal impairment as well. Though these are markers of poor prognosis-- it just froze-- there we go-- it's important for us to distinguish between markers and targets for therapy.

So these unfortunately just may be markers of poor prognosis and may identify higher-risk patients, patients who need more frequent follow-up and maybe more home care, other resources. So point number 7-- use the heart failure hospitalization to ensure that patients are actually on good medical therapy. So despite excellent medical therapy that is available for heart failure with reduced ejection fraction, patients are still being discharged without being on these medicines.

An example is, mineralocorticoid antagonists, such as spirininolactone, are used in less than a third of patients with acute heart failure in the US. And compared to Europe, it's used in about 60% there. So still suboptimal there, but even worse in the United States.

The pre-discharge implementation of carvedilol in the IMPACT-HF study was safe. It was well tolerated. And it improved short-term compliance with medicines.

So we always think, oh, beta blockers, we need to take those off. A person is hospitalized with acute heart failure. And that's actually not been the case. In fact, initiation during hospitalization or on discharge has been associated with improved adherence and survival.

So again, use the hospitalization to assess the medical regimen. Add appropriate therapies-- so ACE inhibitor, Arb, or Entresto for heart failure with reduced ejection fraction; and evidence-based beta blockers, such as metoprolol-XL, or carvedilol, or bisoprolol; mineralocorticoid antagonists. And increase those doses to target.

So take-home points 8 and 9-- the post-discharge phase is a vulnerable one. It's associated with a deterioration in clinical status, with unacceptably high rates of morbidity and mortality. And we've spoken a little bit about that already.

But it's also important to note that because we're getting dinged by CMS for readmissions post heart failure, 50% approximately of readmissions following a heart failure hospitalization are non-heart failure-related. So we did a simple analysis of close to 800 patients in the Heart Failure Network trials. And you can see here the causes varied a little bit by timing. And we only had 60-day follow-up for these trials.

But you can see here at less than 30 days, heart failure hospitalizations were 50%. And if you went out further, they were slightly higher than that but still not an overwhelming majority. It was near 60%. And in fact, this is where the management of comorbid conditions becomes relevant in that we need to address them when patients are actually hospitalized. Because it's often these comorbid conditions that bring them into the hospital after discharge.

And last, many patients do not receive sufficient education or appropriate follow-up after acute heart failure. I'm going to use the next few minutes to talk a little bit about some of the efforts that are being made at Mount Sinai to improve outcomes and to address this fact. So we screen, obviously, pre-admission for patients who can benefit from certain resources that we have at the Mount Sinai Health System, whether it be the MACT program, visiting docs, or certain EMS initiatives like community medicine.

And what's important is, we want to reduce the variation in care when someone is hospitalized with heart failure. So I'm going to talk a little bit about the pathway that's been created for patients admitted with heart failure. And then pre-discharge, we want to optimize transitional planning. And our team along with many members of the hospital, along with you and the house staff really make an effort to optimize this phase. And so this is patient education, really going over their medications, trying to optimize their medications, and then link them up to other resources that we have available.

We in that pre-discharge phase also make sure that they have early and close post-discharge follow-up. So that includes a phone call in less than three days generally after discharge, a rapid follow-up appointment within a week to 10 days of admission, and then potentially also involving the IMA PACT Clinic. And then post-discharge and long-term, of course, we're looking to improve outcomes in the chronic heart failure setting.

So what about our heart failure pathway at Mount Sinai? So this is just snapshots, basically, of Epic and the CHF pathway that's been created. And this pathway, essentially, is really just an order set, the Epic, by which, once activated, a series of interventions occur. So you can see here, once you activate or click that a person is on the CHF pathway, of course, we're going to collect vital signs. You're going to notify appropriate physicians, make sure that you get appropriate imaging and studies, that you have an EKG, of course, physician consults, either to the advanced heart failure team in specific scenarios, palliative care when it's advanced, or the EP service, ancillary consults, respiratory interventions, daily labs, and then a very comprehensive list of medications.

And you can see, once you've checked that off, it essentially comes up on your Epic screen, on the snapshot screen, that the patient is on the CHF pathway. And this triggers a number of other interventions that you may not necessarily be aware of. And quite frankly, sometimes, I haven't been as well.

So this triggers that the patient definitely gets weighed. It triggers that the patient gets a folder and an information booklet. It triggers that a nurse visits the patient and tries to educate the patient about certain resources available, that they get a scale with this. And Jen Allman, who allowed me to take a picture of her yesterday, along with many other members of our team and health care practitioners across the health care system have worked very hard to try and improve ways of cohorting these patients and ensuring that they are seen appropriately in hospital, but even more importantly, as they transition to the outpatient setting.

So I'm going to end with a few slides about our team. It is an absolute honor and privilege to work with this team of individuals. And this is just the physicians slide. I'll show you our nurse practitioner and nurse slide following this.

Dr. Sean Pinney is our director. Dr. Ani Anyanwu is going to be doing a transplant this afternoon as our surgical director of mechanical circulatory support and heart transplant. Dr. Amit Pawale is the director of acute mechanical circulatory support.

We're very privileged to have world-renowned Dr. Donna Mancini, who has really defined how we can assess for advanced heart failure by way of cardiopulmonary exercise testing and is a leader in the field of heart transplantation. Dr. Noah Moss-- this is, I got to get a better picture of him-- is our medical director of mechanical circulatory support. He also does right heart catheterizations for us and implants cardioMEMS devices

Dr. Johanna Contreras is the director of heart failure at Mount Sinai St. Luke's and a member of our advanced team, seeing patients here as well. I'm-- me. Sumeet-- I'm sorry I spelled that wrong-- is one of our newest members of faculty, comes to us from Northwestern. And we're looking forward to increasing our formalized study of heart failure with preserved ejection fraction with his arrival.

Dr. Maya Barghash-- we sort of share this same lineage and education. I understand that her phone number now and all the calls for her now are being directed to the Chief's office. So we apologize for that, we'll try and fix that. And Dr. Maria Trivieri was a wonderful colleague, who's the director of pulmonary hypertension and is currently working on a KL2 grant here.

It indeed does take a village to take care of heart failure patients. That was just the physicians slide. We have a whole host-- if you ever stopped by at our office on 6 West and 271, it looks like a telemarketing office. There's so many of us in one small space.

But that's because we're constantly communicating about patients, trying to improve outcomes. We have heart transplant coordinators, heart failure NPs, LVAD coordinators, and, of course, pulmonary hypertension as well. And this is all under the associate directorship of Dr. Kim-- of Kim Ashley.

So coming back to our top 10, the main reason for acute heart failure is clinical congestion. Hemodynamic congestion precedes this and can persist even after symptoms are relieved. Half of patients have HFpEF and their outcomes are similar to HFrEF. 80% of patients already have a history of heart failure. And comorbid conditions are very common and need to be addressed.

Positive troponins and elevated natriuretic peptides are associated with worse outcomes. Markers of poor prognosis also include low blood pressure, low serum sodium, and worsening renal function. But these may be markers of illness and may just highlight patients who need closer follow-up, more intense follow-up and resource utilization rather than be targets for therapies.

Pharmacotherapies, at least in the heart failure with reduced ejection fraction population, are highly underutilized. The post-discharge phase is very vulnerable. And it's characterized by clinical deterioration and high rates of morbidity and mortality. 50% of readmissions following heart failure hospitalization are non-heart failure-related.

And many patients don't receive sufficient education or appropriate follow-up after acute heart failure. So please take that last point to heart and utilize some of the resources that we have instituted here. And we are ever willing to communicate, and educate, and learn from you as well to improve outcomes for this epidemic, essentially. I want to thank you very much for your attention. And I'd love to take any questions.

[APPLAUSE]

SPEAKER 2: Questions.

AUDIENCE: On your medicine list, don't you think you should have Entresto, in view of the PARADIGM study, as a valuable treatment for heart failure, which is really underutilized because of prior authorizations?

ANURADHA LALA-TRINDADE: You're absolutely right. Thank you so much for bringing up that point. So as everyone knows in the audience, Entresto was studied in nearly 8,000 patients in the PARADIGM-HF study.

These were heart failure with reduced ejection fraction patients, in the chronic setting, mainly Class 2 and Class 3 patients. The investigation of Entresto for acute heart failure is ongoing. And that's being studied in the PIONEER heart failure study. And we are participating in that clinical trial.

So if you have a patient with decompensated heart failure who is hospitalized and not yet on Entresto, please notify us and our clinical research team. These are patients that we need to study. And we need to understand the utilization of Entresto in the acute heart failure population. So thank you for that point.

SPEAKER 2: So I have a question. I just want to point out something. Case number 2, diabetic [INAUDIBLE]. So I'd say that I'm not too picky.

ANURADHA LALA-TRINDADE: No, absolutely.

SPEAKER 2: But to point out the important relationship between the kidney and the heart. Not just the fact that you have increased [INAUDIBLE] declining renal function, that you have increased volume opener, [INAUDIBLE] with heart failure. But the importance of preservation of renal function because of the effects of declining renal function organically on the heart as a result of increasing [INAUDIBLE], et cetera, [INAUDIBLE]. So really again the importance of the relationship between the heart and the kidney, and the importance of preservation of renal function, and the impact that that would have on the heart.

ANURADHA LALA-TRINDADE: Absolutely. No, thank you so much. And that's quite commonly seen. We see that all the time that patients are not necessarily on an ACE inhibitor [INAUDIBLE].

SPEAKER 2: So I guess the point is that you actually get nephrologist to co-manage your patients when they have--

ANURADHA LALA-TRINDADE: Very frequently.

SPEAKER 2: Frequently.

ANURADHA LALA-TRINDADE: Frequently.

[LAUGHTER]

SPEAKER 2: We'll leave it at that.

ANURADHA LALA-TRINDADE: There's always room for improvement.

AUDIENCE: Hi, and a great talk. You point out the importance of clinical assessment because you're saying, we should be diuresing people, certainly in the hospitalized setting, until they're more euvolemic. And yet following the BNP is not so evidence-based. And diuresing until renal failure, renal insufficiency isn't going to be that accurate either. Do you think we do a good enough job training clinicians in terms of clinical assessment, [INAUDIBLE] history, exam, JVD? What's your sense on it?

ANURADHA LALA-TRINDADE: That's a great question. I think no, I don't think we spend enough time on the physical exam. And I don't want to maybe date myself or sound, quote unquote, "old school," but absolutely. I think in my heart failure training, every single day we had to do a manual blood pressure-- Maya knows this.

We had to do a Valsalva maneuver to elicit and estimate pulmonary capillary wedge pressure. We had to provide an exact number on jugular venous pressure. And I will say that though it can be painful as a trainee, at 6:00 in the morning especially, doing a manual blood pressure on everyone, it's proved to be invaluable to me since graduating and since entering the real world. I can't emphasize enough how important it is to really get a gauge of where these patients are.

And so any one of you who rotate with us on our service, you'll always see us really being nitpicky about, OK, I saw JVD. What does that mean? What was the patient doing?

Were they lying flat? Were they sitting up? What would you estimate the JVD to be at? And though it's wrought with some errors and limitations, at least it's allowing you to get back gestalt.

SPEAKER 2: Dr. [INAUDIBLE] one of his favorite questions and topics, the JVD. Yes.

AUDIENCE: The follow-up on [INAUDIBLE] point. Are there any functional studies that you could do prior to discharge that could better predict non-readmission than JVD, blood pressure with the standard set that you use.

ANURADHA LALA-TRINDADE: Yeah. I mean that's really what everyone is hoping to do. Everyone's trying to understand how we can better predict who's going to be readmitted and who's not. So I did bring up the point of the importance of performing a functional assessment before they leave.

I think that's critically important. And we don't do it. We just say, oh, the patient's feeling better, their kidney function looks OK. The labs are OK.

They should go home. We're worried about length of stay, et cetera. But we don't provoke these patients.

And there are some small studies that have looked at six-minute walk test to essentially stratify those patients that will do better versus worse post-discharge. I can't say that I do that formally in every patient. But I definitely try to walk them around. And you'll sometimes see us doing that with patients on 7 Center, in 7 West, in 7 East. And certainly in the clinics, we'll walk them up and down in GP1 Center really to understand what their functional limitations are.

AUDIENCE: [INAUDIBLE] physical sign of bendopnea been studied in any detail [INAUDIBLE] sensitivity, spasticity, how it should be performed [INAUDIBLE] common usage?

ANURADHA LALA-TRINDADE: Right, so Mark Dresner, who's at UT Southwestern studied with my mentor Lynn Stephenson, and coined this term. And everyone is trying to coin cuter terms-- orthodema, bendopnea, et cetera. He actually did evaluate the symptom of bendopnea

And if you start to ask your patients, you'll be surprised as to how many people say they feel fine, they don't have orthopnea. But when they bend over to tie their shoes, they're short of breath. So it is an important question.

And what he did is he looked at actual PA catheter tracings. And what he did find is that independent of abdominal circumference, those patients with bendopnea had increased filling pressures. And that's now been studied in subsequent populations and associated with worse outcomes and worsening functional capacity by CPAT as well.

AUDIENCE: Following up the last two comments, and in the interest of team-based care and also not demanding more of our trainees at 6:00 AM in the morning, I'm wondering if some of these things-- the bendopnea and the orthodema-- can be done by the nursing team, and if that's being considered for the pathway, particularly for just the typical floor patient?

ANURADHA LALA-TRINDADE: I think that's a great point. I think heart failure is one of the prime examples of how closely we work with our nursing colleagues. We would not be able to do anything that we do without them. And especially in the transition role from acute heart failure hospitalization to the outpatient setting, they're instrumental.

I think Jen does a lot of work as do other members of our team in trying to educate the nurses and then having that translate to education of the patients. But you bring up a really good point, I think. Doing more of that, having more integrated rounds like this can only help facilitate that.

SPEAKER 2: One last question

AUDIENCE: The BNP thing, not using it for therapy is very counterintuitive. And when you read these papers, they don't really tell you exactly how they use the BNP, how they respond for the number. And then at the end, they lump all the patients together.

So they never [INAUDIBLE] patients to see if there's subgroups where it actually is helpful. So I just think it's too early to bury the BNP as a test. It doesn't seem to be tested properly yet.

ANURADHA LALA-TRINDADE: You're absolutely right. By no means do I mean that we should bury natriuretic peptides. I think they're important. We know that they're involved in the pathophysiology of heart failure and congestion.

For example, a post hoc analysis of [INAUDIBLE] showed that those patients with heart failure with preserved ejection fraction and low natriuretic peptides seemed to respond to spirininolactone more effectively than those with high natriuretic peptide levels. So we're seeing that it's stratified in groups, no question. How we should act upon it yet is not entirely clear.

The space where we do think that it is useful is to try to use it to optimize therapies for heart failure with reduced ejection fraction that we know work. To be honest, we should be doing that anyway. We should be treating patients with optimal target doses of Toprol XL, bisoprolol, carvedilol, ACE, Arb, Entresto. We're not doing it.

So could we potentially use natriuretic peptides to do exactly that? Yes. And I think that's where we're seeing-- like the PROTECT-HF study, that's what was seen. The most recent study that I cited to guide it, which is close to 900 patients in chronic setting, where that strategy did not improve outcomes, those patients were not optimized on medical therapy in a differential way.

So the placebo group were optimized on medical therapy almost the same as the natriuretic peptide strategy arm was. And that's perhaps why we didn't see that difference. So it kind of goes back to the original point-- as we have medicines, we know they work, we know they improve outcomes. And we're not doing a great job of putting patients on them.

SPEAKER 2: Thank you very much.

ANURADHA LALA-TRINDADE: Thank you.

[APPLAUSE]