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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Optimizing Outcomes in Chronic Heart Failure: New Thinking, New Choices

Narrator:
Welcome to CME on ReachMD. This segment: Optimizing Outcomes in Chronic Heart Failure: New Thinking, New Choices, is jointly sponsored by the University of Cincinnati and Core Medical Education and supported by an educational grant from Novartis Pharmaceuticals. The target audience for this educational activity includes physicians and other healthcare professionals who manage patients with chronic heart failure. Your host is Dr. Matt Birnholz, and our guest today is Dr. James L. Januzzi. Dr. Januzzi is the Hutter Family Professor of Medicine at Harvard Medical School and the Roman DeSanctis Endowed Clinical Scholar at Massachusetts General Hospital in Boston, Massachusetts.

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Dr. Birnholz:
Currently, the human and financial burden of heart failure in the United States is substantial and growing. This condition represents the most common cause of hospitalizations and readmissions. With the aging of the population, these numbers are poised to grow significantly over the coming years. While hospitalization rates have declined over the past decade, the management of this patient population is far from optimal. This program will outline the prognostic factors, considerations for individualizing treatment, and the short- and longer-term benefits of newly approved treatment approaches in chronic heart failure.

And as a reminder to our audience, an outline tool kit supplement is available to clinicians to download as a specialized resource on ReachMD.com/CME.

So, Dr. Januzzi, welcome to the program.

Dr. Januzzi:
Thank you very much. It's great to be joining you.

Dr. Birnholz:
Great to have you with us. So, just to start, a basic question but one that will help provide a framework: How serious of a problem is heart failure today, and who's most at risk for developing it?

Dr. Januzzi:
Well, it's a really great question. What we know about heart failure presently is that approximately 6 million people in the United States have symptomatic heart failure, but that number is probably a gross underestimation of the number of people who actually have the syndrome but are still yet unaware. The other problem is that the frequency of heart failure is projected to increase substantially, partially due to the fact that the population is aging, as well as the fact that we are able to successfully save patients from other cardiovascular diagnoses, including myocardial infarction, severe hypertension, and other medical disorders that increase the likelihood for heart failure.

We see that heart failure is the only diagnosis in cardiology that is currently rising in incidents in 2016, and it's thought that about 1 in 10 deaths in cardiology are thought to be related to heart failure or complications from heart failure with that number growing as well. You

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get the sense, therefore, that this is a very morbid diagnosis, and indeed, unfortunately, about half of the patients that have heart failure die within 5 years of diagnosis. And depending on the age of the patient and the cause of heart failure, that number may be even higher with elderly patients having, in particular, a rather poor prognosis.

Indeed, when we think about the natural history of heart failure, we think of it, unfortunately, as somewhat of an inexorably downhill course. We'd love to believe that the therapies that we have can somehow stabilize the progressive myocardial remodeling that follows the initial myocardial injury and then episodes of decompensated heart failure, but unfortunately, the usual course for patients with heart failure over their journey, if you will, is a relatively turbulent one in many cases with frequent hospitalization and worsening functional capacity. So, unfortunately, this diagnosis is both complicated in terms of its risk; it's complicated in terms of the burden that it puts on the healthcare system; and as a consequence, we worry very much about how we can improve the care of our patients and prevent hospitalizations, for example.

Dr. Birnholz:
Those are certainly some staggering and sobering statistics that you bring forward, but why don't we examine the relationship between hospitalization and mortality in chronic heart failure?

Dr. Januzzi:
So, as I said, the course of a patient with heart failure is marked by this periodic destabilization that often requires hospitalization, and in the context of hospitalization, we not infrequently see worsening renal function, we see worsening myocardial function, we may see myocardial injury from volume overload and stress on the heart. And so, while hospitalization is clearly a nuisance for the patient and clearly something that we worry about in terms of hospital burden, it's also associated with worsening prognosis. So, when we look at the prognostic blemish of heart failure hospitalizations, we see that the mortality risk essentially doubles with each hospitalization, such that as the patient is admitted once, twice, 3 times, even 4 times within a year, we see this doubling of risk for mortality with each hospitalization.

Now, of course, to some extent this is intuitive. Patients that are sicker are ultimately going to be hospitalized more frequently. But again, there are things that occur at the time of decompensation that may ultimately add to the likelihood for future decompensation. So, this has really led us in the heart failure community to realize that we need to target our therapies for heart failure more aggressively in order to improve the outcomes of patients so treated.

Dr. Birnholz:
Can you talk a little bit more broadly about what are the biggest goals of therapy for these patients?

Dr. Januzzi:
Sure, and that's a good way of thinking of it, sort of the tide of hospitalizations, which essentially are a presage of something bad coming in the future. So, if we can improve therapeutic management of our patients with chronic heart failure, recognizing the diagnosis earlier, understanding that a patient may not be stable even if they feel fine and optimizing their therapies to achieve guideline-directed targets for their medical and nonmedical therapies, I think, is really the goal. And we must, of course, think about quality of life; we must, of course, think about lifestyle and how the patient treats themselves -- self-care is very important -- but ultimately, it comes down to how we medically and non medically manage these patients from a therapeutic perspective. And not all heart failure is treated the same, and I think it's important that your listeners understand that fully 50% of patients with heart failure actually have an ejection fraction 50% or greater, and these patients, the so-called heart failure with preserved ejection fraction, unfortunately don't have a guideline-directed list of therapies that we can reach for to help reduce symptoms and improve prognosis. Individually, of course, we can look at patients on an individualized level and obviously treat the reasons for their heart failure, whether it be hypertension, tighter control of their blood pressure, whether it be atrial arrhythmias, tighter control of arrhythmia, but unlike those patients with reduced ejection fraction who have a very clearly articulated list of therapies, patients with preserved ejection fraction are more individualized in their care. And when we manage patients, whether they are reduced or preserved in their ejection fraction, we have certain goals of therapy that we aim for.

We think a lot about patients in terms of their stages and their symptom severity, so we think of the American Heart Association, American College of Cardiology staging, which has stages A, B, C and D, and the ACC/AHA stages are divided in this way so that we can emphasize where prevention is better applied, so patients in stage A, for example, are patients at risk for heart failure. But then once we get structural heart disease, stages B, C and D, we start thinking about using medications to not only control symptoms but to reduce cardiac remodeling, improve quality of life and prevent those hospitalizations that I mentioned. And, of course, when we get to stage D, which is the end of the road, the endstage heart failure patient, that's when we think start thinking about things like transplantation or ventricular assist device therapy. So, depending on the stage, there is somewhat of a different approach to the patients, but by and large, when we think about heart failure, we think of the symptomatic patients at stages C or D.

Dr. Birnholz:

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So, let's zone in on that for a little bit, the staging used for treatment approaches. I imagine these are guideline-directed, but you alluded to guideline-directed targets in therapy. Can you talk about what the most recent guidelines recommend and whether they represent any major shifts in treatment options over time?

Dr. Januzzi:
Sure. So, the heart failure guidelines are a living document. They continue to evolve, and we are currently in between the major rewrites of the ACC/AHA heart failure guidelines, but there actually was just a focused update, because indeed, as your question implied, there are some new things coming up from a drug therapy perspective that it was felt necessary to add as a focused update to the guidelines.

But first, let's talk about the foundational therapies. What are the treatments that we give now that are currently in the guidelines and are important to consider? Well, the guidelines are very clear in articulating Class I support for inhibition of the renin-angiotensin aldosterone system, which is really the foundational sort of pathway that has a number of derangements leading to worsening cardiac function and worsening remodeling in patients with reduced ejection fraction heart failure. So, blockers of the RAS system include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, so ACE inhibitors and ARBs. Everyone knows that these drugs are of benefit for patients with reduced ejection fraction heart failure, but it's necessary for the guidelines to once again rearticulate this point. Of course, beta blockers are a very, very important aspect of care for our patients with chronic heart failure. Mineralocorticoid receptor antagonists, also known as aldosterone antagonists, including spironolactone and eplerenone are also very important agents for those patients with symptomatic heart failure with reduced ejection fraction. These drugs are typically added to an ACE inhibitor or ARB, as well as beta blockers. So, our triple therapy for reducing mortality prior to the recent guideline update was an ACE or an ARB, a beta blocker and a mineralocorticoid receptor blocker. Now, as I hinted at, there has been an update to the guidelines which really sort of turns everything a bit upside down, and we'll get to that in a second.

There are other drugs in the guidelines that one needs to keep in mind. Of course, loop diuretics are important to minimize symptoms, but they do not prolong life, and in fact, if anything, the dose of loop diuretic is linearly associated with mortality. So, we worry about the overuse of loop diuretics. And particularly, when a patient may have relatively little blood pressure to spend on the therapies that we give, what we've said in the guidelines is to really try to maximize the therapies that reduce mortality in this diagnosis, in particular, RAS agents, beta blockers, aldosterone antagonists, and to try to minimize diuretic doses.
Historically speaking, digoxin has been used in heart failure, but DIG has really fallen off in terms of its use, largely because its use has never really been well systematically examined in the beta blocker era, and really DIG is only used these days, in my world at least, for controlling atrial fibrillation rates in patients with very low blood pressures in chronic heart failure. And lastly, a very, very important guideline-directed medical therapy choice, particularly for African-Americans, is the combined use of hydralazine and nitrates, which in the A-HeFT trial was shown to reduce mortality, actually, in patients of color.

So, we have a pretty good armamentarium already in terms of current therapy options, but as I made mention, there are actually some newly approved treatment options in the guidelines that have really changed how we think about the order and the choice of guideline-directed medical therapy, and these include a medicine called ivabradine, which is designed to reduce heart rate, as well as a combination agent called sacubitril/valsartan.

Dr. Birnholz:
Let's talk about these two drugs that have recently been approved beyond the foundational therapies. I'm interested in learning about the data, for instance, regarding the use of ivabradine and maybe some background information about the mechanism of action, efficacy, safety in patients.

Dr. Januzzi:
Yes, sure. It's really a time of great change in the heart failure space, and so understanding these new therapies, I think, is really important, because actually, the focused update for heart failure guidelines really takes a pretty deep dive, in particular, with respect to its support of sacubitril/valsartan, but it's important for the audience to understand that both are in the focused update. Ivabradine has been given a Class IIa, so the class of recommendation is a IIa, which is the level of support is that it can be beneficial, with a level of evidence B-R, which means that there's one randomized trial. It doesn't mean that the study was a bad study. It doesn't mean that the quality of evidence isn't good. It's just that when you see B-R, it just means that there's one randomized trial to support its use. So, a Class IIa B-R, which states that ivabradine can be beneficial to reduce heart failure hospitalization for patients with symptomatic heart failure with reduced ejection fraction. And they make the point that these patients should be receiving guideline-derived evidence-based medical therapy, including a beta blocker at maximum tolerated dose and who are in sinus rhythm. And I'll go into why the guidelines are worded this way for ivabradine. In a similar fashion, the guidelines incorporated sacubitril/valsartan. This is a combined drug that is an angiotensin receptor blocker, neprilysin inhibitor, or ARNI, and I'll explain what that is in just a little bit. And similar to ivabradine, the guidelines have integrated sacubitril/valsartan but gave it an even more profound recommendation. Sacubitril/valsartan received a Class

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I level of evidence B-R stating in patients with chronic symptomatic heart failure and reduced ejection fraction who can tolerate RAS inhibition, replacement by an ARNI is recommended. So the guidelines actually recommend changing patients from ACE or ARB if they are stably taking those drugs over to the ARNI.

And I'll go into both drugs, because I think it's important to understand why we use these agents and how they may be best deployed. First, ivabradine, ivabradine belongs to a class of drugs called HCN channel blockers. It's a hyperpolarization-driven ion channel blocker that blocks something called the funny current, the IF current, which is involved in heart rate in the sinus node only in patients that are in sinus rhythm. So, inhibiting the IF current causes a pure effect to reduce heart rate in those patients in sinus rhythm, and as such, the drug was actually developed initially as an anti-anginal. As you can imagine, reducing heart rate seems like a good idea in patients with chronic coronary disease, but it was also examined in patients with heart failure, and really some interesting data came from that.

Dr. Birnholz:
Let's talk about that data a little bit. I'm interested in what this data shows regarding the efficacy, safety, and effect on outcomes for patients who were taking both ivabradine and also looking at that in the same light with sacubitril/valsartan.

Dr. Januzzi:
Sure, it's really interesting to see. They both get a level of evidence B-R in the guidelines because for both drugs there was one large, in both cases, multicenter trial supporting their use. And so, for ivabradine, the SHIFT study focused on the use of ivabradine for the management of patients with chronic heart failure, and SHIFT included a fairly typical type of patient with reduced ejection fraction. These are adult patients with Class II through IV symptomatic heart failure, reduced ejection fraction, but these patients had to be in sinus rhythm. Again, I remind the audience that the IF current is only inhibited in patients with sinus rhythm, so they had to be in sinus rhythm for the majority of time. Patients with paroxysmal atrial fibrillation or intermittent pacing were actually eligible for the trial but only if they were in sinus rhythm for the majority of the time, so greater than or equal to 60% of the time. Also, they needed to have a heart rate greater than 70 beats per minute. And in this study patients were randomized to receive ivabradine 5 mg twice a day and then ultimately up titrated to 7.5 if tolerated, and if it wasn't well tolerated, it could be down titrated to 2.5 mg b.i.d. considering the heart rate effect that you get from the drug versus placebo. And these patients were actually well treated. They received typical guideline-directed medical therapy. Although, some of the criticism of the trial was that the beta blocker dose used in the study might have been a bit better than was seen in the trial, but regardless of what was seen, when looking at the efficacy of the drug in terms of its ability to reduce heart rate, we see that ivabradine caused a significant and prolonged reduction in heart rate across the duration of the study, and with this there was a significant reduction in the primary composite endpoint of cardiovascular death, or heart failure hospitalization. And this reduction was largely driven by reduced hospitalization rates for those patients treated with ivabradine. Although, it's necessary to emphasize that at the higher heart rates, we did, in fact, see an impact on mortality, actually, such that patients had very high heart rates. There was a substantial impact of ivabradine, not only on the hospitalization point but also on the outcome of CV death.
Considering prespecified subgroups in the study, the drug was largely effective across most groups, including those patients taking beta blockers versus those not taking beta blockers. Again, I think it's important to emphasize for the audience, maximizing the beta blocker dose is crucially important before adding ivabradine, but if a patient remains with a heart rate above 77 beats per minute, which is sort of the magic number that was found in the SHIFT study, despite excellent guideline-directed attempts at achieving beta blocker dosing, then ivabradine is a very reasonable choice to help improve the risk for hospitalization.

What we do when we start ivabradine in the clinic, if we really feel as if we've maximized beta blocker doses, and by and large our patients fall in to one of two categories; there are patients who are clearly on the highest doses of beta blocker. You know, we have people that are on 200 mg or more of metoprolol succinate or 50 mg twice a day of carvedilol, and they still have a heart rate above 75, 77 beats per minute. We will add ivabradine starting at 5 mg twice a day, and then we bring them back in about a week or two and look at their heart rates, and if their heart rate remains above 60, we up titrate them to 7.5 mg. If they're between 50 and 60, we leave them at 5 mg. And if they're really too slow, we will then split the dose and reduce to 2.5 twice a day. The other group of patients where we use ivabradine are those patients who are flagrantly intolerant of higher beta blocker doses. So, we do our due diligence, we try to get the beta blocker increased, but some patients simply cannot tolerate higher doses, and at that point we'll add ivabradine to the mix.

Dr. Birnholz:
So, Dr. Januzzi, just to help us understand the data behind sacubitril/valsartan, compared to usual care, what does that data show regarding its efficacy, its safety and especially its effect on outcomes?

Dr. Januzzi:
Yes, that's a really important question, probably the most important question of the whole discussion, because for the guidelines to essentially say that this drug should be switched in place of an ACE or an ARB, the results must be really profound, and indeed, the PARADIGM-HF study was the one trial that looked at this question. And in PARADIGM, patients were treated after a run-in period with either sacubitril/valsartan or enalapril to highest tolerated doses, and indeed, the primary endpoint of the trial, which was a composite of

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cardiovascular death and heart failure hospitalization, showed a profound reduction in the risk for either endpoint in patients treated with sacubitril/valsartan. So, whether one looks at cardiovascular death or even all-cause mortality, two very important endpoints in patients, as well as heart failure hospitalization, everything was reduced by about 20% by the addition of the drug to usual care.

Curiously, you would think that a vasodilator would reduce the risk for death from worsening heart failure alone, but indeed, sacubitril/valsartan also reduced the risk of sudden death in the trial, which was very interesting. And it came with a very reasonable safety profile. Patients treated with sacubitril/valsartan, of course, were more likely to have symptomatic hypotension because the drug is a bit more powerful with respect to its vasodilating effects, as it's a combined agent, but generally speaking, the drug was extremely well-tolerated, and indeed, discontinuation of the drug for an adverse event was actually lower with sacubitril/valsartan compared to patients treated with enalapril. Now, one very important aspect of treatment with this drug that I think clinicians need to remember is that neprilysin inhibition from sacubitril has a significant effect to block the breakdown of BNP. Now, we measure BNP frequently in our patients with heart failure to monitor their symptoms and their risk for future events, but in patients treated with sacubitril/valsartan in the PARADIGM study, a significant rise in BNP was seen in those patients treated with the drug. So, it's important for people to remember if their patient is taking this very important Class I guideline-directed medical therapy, concentrations of BNP are going to be hard to interpret. In contrast, NT-proBNP, which is not a substrate for neprilysin, falls very smoothly in parallel with the benefits of the drug.

Dr. Birnholz:
Fascinating. How about the way in which you would consider dosing for these patients given it's combination therapy?

Dr. Januzzi:
So, since it's a combination drug that has a couple of effects, it does have a little bit more of an effect on blood pressure, and so when we start the drug, much like with ivabradine, we typically bring patients back every 2 to 4 weeks and monitor their blood pressure as we up titrate. Now, there's a lot that goes into this. I'll tell you how we choose the doses and how we titrate, and then maybe we can talk a little bit about why, what are the data that support the use of the drug? Since this drug contains a neprilysin inhibitor, there's an unwanted interaction between ACE inhibitors and neprilysin inhibition, so anyone that's taking an ACE inhibitor needs to be off the drug for at least 36 hours before starting sacubitril/valsartan, and that side effect that we worry about is something called angioedema, which is swelling of the mucous membranes in the oropharynx. So, anyone taking an ACE needs to be off it for at least 36 hours, and then we start the drug and up titrate based on the person's tolerance for vasodilators. So people that are taking large doses of ACE inhibitors, we start at the intermediate dose and up titrate to target, which is essentially 200 mg total twice a day of the drug. For those patients at lower doses of ACE inhibitor, we start at the lower dose after the 36-hour washout and then titrate slowly. For those people taking an ARB, there's no washout needed, of course, and so there we can just start the drug depending on the dose of ARB that they take and up titrate, once again, to try to reach goal, 200 mg twice a day of sacubitril/valsartan. If a person is not taking either an ACE or an ARB, we typically start them at lowest dose just because we don't know what their tolerance with respect to blood pressure is going to be. We typically measure renal function as well as serum potassium in patients that have the drug initiated, and often what we find when we add the drug and up titrate it is that if blood pressure gets a bit soft, we can dial off the loop diuretic to help buy a little bit more blood pressure to allow us to get the drug up to a level that would help us to reduce risk in chronic heart failure.

Dr. Birnholz:
Well, Dr. Januzzi, you've given us a lot of important take-home messages for us regarding chronic heart failure, the emerging and, of course, current therapeutic avenues. Anything that you'd like to summarize as some important points for our audience?

Dr. Januzzi:
Sure. Thanks for asking, and thanks for having me. I think that the audience really needs to recognize heart failure is reaching epidemic proportions and will continue to worsen, and our patients with heart failure have a very high risk for morbidity and mortality. The risk for adverse outcomes, the risk for these bad things happening to our patients, however, may be substantially reduced, particularly with achievement of so-called guideline-directed medical therapy for heart failure. And for those patients with reduced ejection fraction, we now have new treatment options that are very exciting, because they either add to existing GDMT, or in the case of sacubitril/valsartan, replace existing GDMT to improve their outcomes. Now, I'll remind the audience that treatment with ivabradine is indicated for those patients who are on maximally tolerated beta blocker therapy. This is not a drug to just casually throw on without doing due diligence to get the beta blocker to target, but if you've gotten the patient to as high a beta blocker dose as you can and their heart rate remains elevated, then therapy with ivabradine may be beneficial to reduce the risk for hospitalization.

Treatment with sacubitril/valsartan is an even more huge undertaking in the sense that so many patients are eligible for this drug and should be switched over, but the effort is worth it. This is now indicated as a replacement for ACE or ARB, it's a Class I indication, and it's not only to reduce hospitalization but also to reduce mortality. The PARADIGM-HF study really indicated quite clearly that this drug is a major leap forwards for the care of patients with chronic heart failure and reduced ejection fraction.

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Dr. Birnholz:
Well, with that I very much want to thank our guest, Dr. Januzzi, for helping us better understand the current burden of heart failure disease, foundational therapies and, of course, new treatment paradigms to help us optimize outcomes in chronic heart failure.

Dr. Januzzi, thanks so much for your time.

Dr. Januzzi:
My pleasure. Thank you.

Narrator:
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