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Improving Pump Function in Heart Failure with Reduced Ejection Fraction

Announcer:
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Dr. Felker:
Hi, and welcome to CME on ReachMD. I’m your program chair, Dr. Michael Felker. I’m Professor of Medicine, Vice-Chief for Clinical Research in the Division of Cardiology, and the Director of Cardiovascular Research at the Duke Clinical Research Institute at Duke University School of Medicine in Durham, North Carolina. I’m really happy to be – today to be joined by two good friends Dr. Nancy Sweitzer and Dr. John Teerlink. I’ll be speaking with them each individually about the current use of inotropic therapy, along with the latest evidence on improving systolic function of the heart, a key potential therapeutic target in heart failure. Our discussion will start with Dr. Nancy Sweitzer, who is Professor of Medicine, Chief of Cardiology, as well as the Director at Sarver Heart Center at the University of Arizona in Tucson, Arizona. Nancy, welcome to the program.

Dr. Sweitzer:
Thanks, Mike. It’s great to be here with you and John.

Dr. Felker:
So, just so we’re all on the same page in regards to terminology, we use this term, “inotrope” a lot, but what exactly do we mean when we use the term “inotrope”?

Dr. Sweitzer:
Great question, Mike. So, an inotrope is a drug that alters contractility, or force of contraction of the heart. And we talk about positive inotropes, which are drugs that increase contractility, and negative inotropes, which are drugs that decrease contractility of the heart. If you remember the pressure volume curves from medical school as pressure increases on the X-axis stroke volume goes up and this is, you know, the classic Frank Starling law – is you increase the preload on the heart, stretch those sarcomeres, the heart contracts harder. When you have an ionotropic reaction, or an ionotropic drug onboard, you actually change contractility curves, so for any given left ventricular and diastolic pressure, your stroke volume will be greater because the intrinsic contractility of the heart has increased.

Dr. Felker:
So, for the years that you and I have been practicing cardiology, there’s been more or less a constant interest in this idea of inotropy as a potential therapeutic approach for heart failure, so what do you think underlies that? Why is it such a fundamentally appealing idea to try to increase inotropy in patients with heart failures, specifically patients with heart failure reduced ejection fraction?

Dr. Sweitzer:
Well you’re absolutely right, Mike. Since the 1980’s in fact, we’ve been trying to find a drug that would increase the contractility of the hearts of our patients with heart failure with reduced ejection fraction, or HFrEF, in particular. Because the fundamental problem in

HFrEF is a failure of contractility of the left ventricle, typically due to some sort of injury, and the neural hormonal activation worsening that problem and we're dealing with hearts that just are not contracting sufficiently to support all of the activities of of the person's life that they would like to do. You know, so whether from scarring secondary to myocardial ischemia, or genetic alterations leading to dilated cardiomyopathy, inflammatory infectious damage related to myocarditis, the left ventricle can't generate the normal amount of force due to a combination of myocyte loss and neurohormonal activation. And so, we're storing force generation in this damaged myocardium, or heart, would, it seems, improves the condition and it's intrinsically a very appealing concept.

Dr. Felker:
Yeah, if you think about our effective therapies, you know we don't often think in this way, but really they're all targeting various secondary phenomenon, and not really the intrinsic problem of of impaired contractility, so we've kind of been lucky in that a lot of the things that have worked have dealt with some of these secondary issues, and not the primary issue. So, given how fundamentally attractive this idea of inotropy is, can you tell us about some of the prior attempts to develop inotropic therapy for our chronic heart failure patients? Were they successful? What's the history here?

Dr. Sweitzer:
Well I think the longest history for inotropic therapy clearly goes back to William Withering and digoxin, which we've had for a long time, and which has some positively inotropic effects. That said, the first randomized clinical trial of digoxin was published in 1997, and as you know, there was no mortality benefit to digoxin therapy in heart failure, although there was a reduction in hospitalizations by about 10% in that trial. You know, the IV inotropes dobutamine and dopamine were studied in the 1960's and 1970's, and most of the studies were hemodynamic studies. And clearly the hemodynamics of the dysfunctional heart improve when you infuse these drugs. These drugs, at the time, had less arrhythmia than isoproterenol, epinephrine or norepinephrine, other inotropically active drugs that were being used, and so they became more widespread in their use. And then, you know, there's a whole range of beta agonists that have been tested, and all of them clearly have hemodynamic benefits, with improved cardiac output. But then, over the subsequent decades, it became clear that there's excessive mortality, with almost all of these drugs, and I think the investigative history is most clear with the phosphodiesterase inhibitor drugs which activate the beta adrenergic pathway in a different way, but are positively inotropic. And again, all of these drugs improve hemodynamics of the dysfunctional heart, particularly cardiac output, which is a very appealing number to doctors. We like that number to be higher. And all of these drugs, interestingly, prolonged life in rat models of heart failure. But when they were tested in humans, beginning with amrinone in 1984 we saw an increased mortality, increased arrythmia, interestingly thrombocytopenia with that drug. Milrinone – the randomized trial was published in 1991 – potentially accelerated underlying disease processes with a 30% mortality increase over six months of treatment, compared to placebo patients. And interestingly, milrinone in the trials performed least well in the sickest patients. The sickest patients died at the highest rate in that trial. And then we had a whole series of drugs with slightly altered mechanisms – pimobendane, flosequinan, vesnarinone – all of them increased mortality. But interestingly, most of them improved quality of life, which probably relates to the hemodynamic improvement. So, you know, we clearly know, after decades of working on this that beta adrenergic stimulation is arrhythmogenic and potentially dangerous in our patients. It contributes to disease progression, we know that from the beta blocker trials, actually, that if we stimulate the beta adrenergic system chronically in the heart, it's probably contributing to ongoing disease progression. And so, while improving cardiac output is an appealing concept, it doesn't really actually address the underlied – lying disease pathology and has really, so far, failed pretty miserably.

Dr. Felker:
Yeah, it's really striking when you run through this list of trials, the disconnect between drugs that as you said, actually improved hemodynamics, but but they all impair mortality. It's notable, you know, a lot of these trials also predated ICD therapy, so you wonder if if the mechanism of risk is potentially erythrogenic, whether that might be different in a more contemporary population.

Dr. Sweitzer:
Yeah, absolutely, although none of us want our patients' defibrillators firing, either, so…

Dr. Felker:
Definitely true. So you've done a great job of outlining some of the risks that come with this class of drugs, but as you know well, we continue to use IV inotropes like milrinone, dobutamine in selected patients in clinical practice every day. What do you see in sort of the contemporary landscape as the appropriate use of these agents? How should we be approaching them?

Dr. Sweitzer:
Of course we use these drugs, because we're dealing, often with patients in cardiogenic shock, who are in the process of dying before our eyes, and you use anything and everything you can to keep people alive to so that you can apply more effective therapies that we have available, such as ventricular assist devices and other mechanical circulatory support, hopefully stabilize them and get them on guidelines-based therapy, which we know does save lives. So I think, clearly, temporizing patients in cardiogenic shock or advanced

heart failure, until more definitive therapy is available, is a very common and appropriate use of inotropic therapy. Palliation, all of these drugs typically make patients feel better and when patients are at the end of life, making them feel better is typically our primary goal. We're not really trying to prolong life. And as you mentioned, many of our patients do have ICDs, making potentially palliation with these drugs more palatable. And then, you know, bridge therapy under carefully controlled conditions – I think you've seen this, we've all seen this with the new allocation system. In heart transplantation, we're using inotropes a little bit more to try and get patients to transplant without having to stop at another surgical therapy such as an implanted circulatory support device. But I think, clearly, because of the data about increased mortality, these drugs are not appropriate for intermittent infusion therapy which was for a while, a way we used these drugs. And there's really no role for chronic outpatient infusion, other than palliation for these drugs, because of the risks.

Dr. Felker:
Great, Nancy. That was a tremendous summary. For those who are just joining us, this is CME on ReachMD. I'm Dr. Michael Felker, and I now have the pleasure of speaking with my friend, Dr. John Teerlink, who's Professor of Medicine at the University of California, San Francisco, and the Director of Heart Failure at the San Francisco Veterans Affairs Medical Center. John, welcome to the program.

Dr. Teerlink:
Thanks, Mike, and it's great to join you and Nancy on this discussion.

Dr. Felker:
Now John, you've just heard Dr. Sweitzer provide some background about the history of inotropic therapy and some of the current uses. I'd like to turn and ask you a few questions about an investigational therapy, called omecamtiv mecarbil. Can you tell us about the mechanism of action for this first in class drug and how it was developed?

Dr. Teerlink:
Yeah, well, thanks to Nancy's beautiful summary of kind of the inotropes that have already been tested, we've now looked at different classifications of inotropes, and different ways to actually improve the cardiac performance. And the agents that Nancy discussed so eloquently, we now term "calcitropes". And those are agents that improve cardiac function by influencing the calcium flux within the cardiomyocyte. Omecamtiv mecarbil is the first in class of myotropes, or drugs that improve cardiac function by directly acting on the cardiac sarcomere. With each heartbeat the chemical energy from ATP is converted into mechanical force, through the interaction of myosin with the actin filaments, and this produces a power stroke, or contraction of the myocyte. However, in a normal heartbeat, not all of the activated myosin heads actually attach to the actin filament to generate this power stroke. Omecamtiv mecarbil is a novel, selective cardiac myosin activator, and it stabilizes the myosin in this pre-power stroke state, allowing it to increase the number of myosin heads that actually bind to actin to produce greater force. So in effect, omecamtiv mecarbil treatment sort of results in more myosin hands pulling on the actin rope, with each heartbeat. And this mechanism of action avoids all of the deleterious effects of the calcitropes that Nancy discussed, such as the beta adrenergic agonists and the phosphodiesterase inhibitor drugs. So basically, this is a really unique and novel approach to improving cardiac function.

Dr. Felker:
Yeah, a really interesting and novel mechanism, as you said. Can you talk a little bit about some of the data in the development of this drug that helped set the stage for the Phase 3 trial, GALACTIC, which we'll talk about here in a bit?

Dr. Teerlink:
Yeah, you know, I think omecamtiv mecarbil may be the only drug that was specifically designed for heart failure with reduced ejection fraction, and this journey started 20, 30 years ago. And then advanced very rapidly into early clinical studies, which showed an improvement in cardiac function, and these were illustrated in early echocardiographic studies, one of which was led by Professor John Cleland. And then these studies provided the background for the COSMIC-HF trial. This enrolled 448 patients with stable, chronic, symptomatic heart failure, with ejection fractions less than or equal to 40%, and randomized those patients to either placebo or two dosing strategies of omecamtiv mecarbil, treated for 20 weeks. And in this study, in the COSMIC-HF study, omecamtiv mecarbil improved systolic function and compared to placebo, with increased systolic ejection times, increased stroke volumes, as well as improvements in left ventricular fractional shortening and ejection fraction. And then consistent with that improvement in left ventricular systolic function, omecamtiv mecarbil also reduced LV systolic dimensions and volumes. Importantly, LV diastolic dimensions and volumes were also reduced, suggestive of benefits for reverse cardiac remodeling, during that 20 weeks of therapy. So then, in addition, a small reduction in heart rate, suggestive of sympathetic withdrawal, and a significant decrease in NT-proBNP, consistent with reduced left ventricular wall stress and greater decongestion, were also noted. And also importantly, their adverse events in these early clinical trials were, of omecamtiv mecarbil were similar to placebo. And these findings all provided the basis for the Phase 3 GALACTIC-HF study.

Dr. Felker:

Great, John. That's a great summary of the early phase data. Can you talk now a little bit about the design and the primary results of the GALACTIC-HF?

Dr. Teerlink:
Yeah, GALACTIC-HF tested, and I think this was for the first time, the hypothesis specifically improving cardiac performance can result in improved clinical outcomes in patients with HFrEF. The participants in GALACTIC-HF had symptomatic, chronic heart failure, with EF's less than or equal to 35%, elevated natriuretic peptides, who were receiving standard heart failure therapies, and because we wanted to do a broad patient population, they were enrolled from both inpatient and outpatient settings. The patients in the trial were randomized one-to-one, to omecamtiv mecarbil, using a pharmacokinetically-guided dosing REV strategy, or placebo. GALACTIC-HF enrolled 8,256 patients, and only one patient was lost to follow-up for vital status. Patients were followed for a median of about 22 months. And these patients in GALACTIC-HF represent one of the broadest ranges of heart failure with reduced ejection fraction patients enrolled in contemporary heart failure trials, with a mean ejection fraction of 27%, about half with New York Heart Association functional class III or IV, and half with ischemic etiology. Also of note, the baseline systolic blood pressures and renal function were lower, and the NT-proBNP concentrations were higher than in most other heart failure trials. Patients in GALACTIC-HF also had among the best heart failure therapies, at baseline, of any contemporary heart failure trial. So that's kind of the design and where we and the baseline characteristics of the patients. So in addition, the primary endpoint of GALACTIC-HF was met, with a significant 8% reduction in the risk of the composite outcome of time to first heart failure event or cardiovascular death, with a P-value of 0.025. And thus, these results confirm that hypothesis that selectively increasing cardiac function can, in fact, improve clinical outcomes in patients with heart failure and reduced ejection fraction. Now we looked at other endpoints in this trial. We looked at the risk of first heart failure event, which was the predominant drive or the primary outcome, which was also reduced by 7% in the omecamtiv mecarbil treated patients, and noted that the risk of cardiovascular death, which was both a component of the primary outcome as well as secondary endpoint was not significantly different between omecamtiv mecarbil and the placebo groups. Another thing that we looked at was the effect of omecamtiv mecarbil on symptoms. And so, we evaluated the change in the Kansas City Cardiomyopathy questionnaire total symptom score, from baseline to week 24, and the overall statistic, doing our testing strategy, was 0.028, but this did not meet the hierarchical, multiplicity controlled threshold of 0.02 that we had pre-specified, so this was not met. However, interesting to note, in the inpatients, which were more symptomatic, omecamtiv mecarbil resulted in a 2.5 point improvement in their KCCQ total symptom score, with confidence boundaries excluding zero. So that's a potentially intriguing finding. Then we also looked at prespecified subgroups, and across the board, pretty much the analysis of these subgroups showed that the primary composite outcome was consistent with beneficial treatment of omecamtiv mecarbil across the board. Though, if you look at and there are lots of caveats in looking at subgroups, there did also appear to be a trend toward better outcomes with omecamtiv mecarbil in patients with evidence of more advanced heart failure. In one subgroup in particular, the baseline ejection fraction demonstrates significant heterogeneity in the treatment effect, with an interaction P-value of 0.003. And so, when we looked at this a little further, this subgroup of 4,400 patients who had an EF less than 28% had a nominal, 16%, reduction in that composite primary endpoint. And given omecamtiv mecarbil's mechanism of action, which is to increase cardiac function, there is actually a lot of biological plausibility. There may be a greater benefit in patients with more severely reduced systolic function, and suggests that these patients may actually derive a better – a greater benefit, if you will. Then we also, obviously need to look at adverse effects, and how – what happened to the patients when they were treated with omecamtiv consistent with this mechanism of action, as well as the multiple prior studies. There was no significant effect on systolic blood pressure, potassium levels, or renal function – suggesting that omecamtiv mecarbil could be readily incorporated into our contemporary heart failure treatment algorithms, and it would not compete with the initiation or dosing of established heart failure therapies. Just like in previous trials, there was small reduction in heart rate, consistent with sympathetic withdrawal, and reduced natriuretic peptide levels, consistent with improved ventricular wall stress and decongestion. A minor increase in cardiac troponin I was also noted in this study. There was no imbalance in adverse events or serious adverse events including those adjudicated by you and the clinical events committee specifically related to cardiac ischemia, and no difference in ventricular arrhythmias, as was seen with all the calciotropic agents. And the overall adverse event profile was similar to placebo, so we really have a drug here that seems to provide a clinical benefit in terms of reducing heart failure events with an adverse event profile that's very close to placebo.

Dr. Felker:
So John, great summary of a complex set of data. Can you talk a little bit about what you see as the main take home messages?

Dr. Teerlink:
Yeah, I think – you know, harkening back to bit, what Nancy was suggesting, you know, adrenalin and those agents were discovered in, you know, the turn of the century, in 1900's. And so, GALACTIC-HF in some ways represents the culmination of this journey that started over this one century ago. And it demonstrates it's selectively targeting the cardiac sarcomere with omecamtiv mecarbil. This first-in-class myotrope is a novel approach to improving cardiac function and clinical outcomes, and that we were able to show a statistically significant reduction in the risk of a primary composite outcome of first heart failure event or cardiovascular death. And so, I

think we're very excited to be able to advance the field by providing this new approach to the treatment of heart failure with reduced ejection fraction. And clearly, we'll want to do additional analyses, to see whether there are specific patient populations that will derive even greater benefit from this new approach to treating heart failure.

Dr. Felker:
Great. So, now I'd like to bring Nancy back into the discussion, and my final question really is meant for both of you. So, given the data we've talked about, what role do you see for omecamtiv mecarbil in the treatment of patients with heart failure reduced ejection fraction? If the drug becomes commercially available in what patients could you foresee using this drug or ex – how would it fit into the sort of overall armamentarium? And Nancy, I'll start with you first.

Dr. Sweitzer:
Yeah, thanks. So, it's – you know, the – these data are really interesting and quite new. I think we're still all absorbing them, and figuring them out, and looking forward to additional analyses to help us be more intelligent about where we might use this drug in our patients. I think clearly we are in a time of incredible richness for treatment of our patients with reduced ejection fraction heart failure. The SGLT2 inhibitors, the RNEs have really, you know, transformed care in the last five years of these patients, and we have so many options. But despite that, we do have patients who still progress to advanced heart failure, and I think, you know, it's wonderful to have some potential drug therapy options for those patients, because previously, we've really had only surgical options with mechanical circulatory support and transplant. But if you have a patient, for example, who is not currently a candidate for those therapies, or who may never be a candidate for those therapies and in whom you wanna, perhaps reduce morbid events, such as hospitalizations, I think omecamtiv mecarbil may be a very reasonable choice in that population of patients. We also have vericiguat, which was tested in a very similar advanced heart failure population, and again, seemed to do better in the sicker patients. So I think with these very ill heart failure patients with high highly adverse outcomes being predicted based on their clinical characteristics, I think it'll be interesting to see how this drug performs, and I'm really intrigued by these data that suggest the lower EF, the better the drug performed, because it may really be a nice choice for our very sickest patients who don't have a lot of options.

Dr. Felker:
Thanks, Nancy. John, I'll ask you the same question. And you probably know this data better than anyone about what clinical role you foresee, based on what we know so far with omecamtiv mecarbil?

Dr. Teerlink:
Yeah, so based on the data that we have so far, I think I'd remind folks that actually, everybody who had, you know, the patient population in general in GALACTIC-HF benefited from omecamtiv mecarbil. And given that it doesn't seem to affect blood pressure or adversely affect heart rate or potassium or renal function, it can be added pretty much at any time in the course of a patient's care who has an EF less than 35%. Interestingly, unlike some of the newer agents which do affect, such as vericiguat, which affects blood pressure, at the time where other therapies may be being withdrawn, which are these advanced heart failure therapies, omecamtiv mecarbil should be readily able to be added to these patients, without complicating their regimens. So I anticipate that it can provide a modest benefit to the general heart failure patient population with reduced ejection fraction less than 35%, and then will provide even a greater benefit to specifically targeted, advanced heart failure patients within that group.

Dr. Felker:
Yeah, I think it's a really important point about the fact that this drug does not lower blood pressure, does not alter heart rate, does not change renal function, a lot of the things we worry about especially as our patients with heart failure get sicker. Well, with that, I'd like to thank both my guests. This has been a great discussion. Thanks to Dr. Nancy Sweitzer and Dr. John Teerlink for speaking with me and our ReachMD audience. It was great having you both on the program today.

Dr. Teerlink:
It's been great to be here. Great to be here, Mike. Thanks.

Dr. Sweitzer:
Thank you for having me, it was a great discussion.

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