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## Heart Failure Grand Rounds: 3 Things You Need to Know About Cardiac Contractility Modulation

### Announcer:

Welcome to CME on ReachMD. This activity, entitled "Heart Failure Grand Rounds: 3 Things You Need to Know About Cardiac Contractility Modulation" is provided by **Meditelligence**.

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### Dr. Butler:

Device-based therapy may benefit some patients with heart failure. But more than 70% of the patients with reduced ejection fraction are ineligible for cardiac resynchronization therapy, or CRT. Enter cardiac contractility modulation, or CCM. This therapy improves symptoms, exercise tolerance, and quality of life while reducing the rate of heart failure hospitalizations. So what is CCM, what patients will benefit from it, and how can we as physicians facilitate this benefit for our patients?

This is CME on ReachMD, and I am Dr. Javed Butler.

### Dr. Abraham:

And I'm Dr. William Abraham.

### Dr. Butler:

Bill, absolutely great to have you here today and to learn from your experience and expertise. But before we get into CCM, let's just first discuss a little bit about pathophysiology of heart failure and how it relates to guideline-directed medical therapy. We have had a lot of positive clinical trials, a lot of advances in the management of patients with heart failure and reduced ejection fraction [HFrEF]. So is there any residual need for newer therapies, devices, or drugs for patients with heart failure?

### Dr. Abraham:

Yeah, absolutely, Javed. Despite our currently available guideline-directed drug therapies for the treatment of heart failure, morbidity and mortality remain poor. And many of our patients remain highly disabled by their symptoms. The residual risk is really quite striking in these patients. And we really need to get to, and no pun intended here, the heart of the matter. And that is an impairment in cardiac function, both in inotropy or contractility, and in lusitropy.

### Dr. Butler:

So what about the issue of mortality/morbidity that we have really focused on a lot in clinical trials, but more patient-centered outcomes, functional capacity, quality of life? Can you just put that a little bit into perspective for our listeners?

### Dr. Abraham:

Sure, I can. And it's a really important topic, because I think oftentimes, as clinical trialists, we see the most important outcomes to be morbidity and mortality, particularly death. Whereas many of our patients place symptoms above clinical outcomes. They want to feel better; they want to be able to perform more activities of daily living. So improvement in quality of life and functional status and exercise ability are quite important to our patients, and I think should be important to us as clinicians as well.

And in this regard, while our drug therapies for heart failure can reduce morbidity and mortality, they really have quite modest effects on improving patient-centered endpoints. For example, on average, when one looks at the improvement in quality of life score, using either the Minnesota or the Kansas City quality of life questionnaires, our drug therapies improve quality of life by maybe a couple of points. Whereas, as I'll mention later, emerging therapies such as cardiac contractility modulation have a very, very large and clinically meaningful effect on improving patient-centered endpoints.

**Dr. Butler:**

Can you briefly describe what exactly is CCM, how it works?

**Dr. Abraham:**

Yeah, CCM is a device-based therapy which delivers an electrical stimulus impulse to the heart during the absolute refractory period of the cardiac cycle. So unlike traditional cardiac pacing, it's not intended to electrically capture or pace the ventricle. But what these electrical signals do is that they fundamentally affect the underlying biology of the heart in a way that improves contractility without increasing myocardial oxygen consumption or myocardial work.

And in fact, it's been shown both in animal models and in humans, that CCM produces a switch, reversion of the fetal program of gene expression seen in the failing human heart to a more adult program of gene expression, which favors an improvement in contractility. I'll mention parenthetically that that switch has only been shown with 2 other therapies for the treatment of heart failure, and those are beta-blockers and cardiac resynchronization therapy. So in that regard, CCM is in good company with other therapies that share some similarity and underlying mechanism of action and have been associated with striking improvements in our heart failure patients.

**Dr. Butler:**

What about its impact with longer-term use on improvement in ejection fraction or remodeling? Does that do that for patients with heart failure and reduced ejection fraction?

**Dr. Abraham:**

It does. And it does it similarly to what we see with beta-blockers and CRT in the treatment of heart failure. That is, these effects on the molecular biology of the heart and in protein levels and phosphorylation and all of the magic of CCM that leads to this improvement in contractility is, over the long term, associated with an improvement in cardiac structure and function, what we call reverse remodeling of the heart. So we see with CCM as we see with other effective therapies in heart failure, improvements in LV ejection fraction, reductions in left ventricular systolic and diastolic volume, all indicative of improvement in the heart. This reverse remodeling has been associated in the CCM studies with improvements in symptoms and exercise capacity and quality of life. And while yet unproven in a properly powered, prospective, randomized control trial, certainly the totality of emerging evidence suggests the potential for improvements in clinical outcomes as well.

**Dr. Butler:**

So can you tell us – a couple of related questions to you, Bill. One is what patients have been tested in the clinical trials with CCM? And second, what benefits were seen, what were the results of those trials?

**Dr. Abraham:**

The trials have focused predominantly on New York Heart Association functional class III patients. The reason for that is that it represents a large segment of the heart failure population with a large unmet need. These are highly symptomatic patients who are sick but not yet sick enough for an LVAD [left ventricular assist device] or a transplant, but they're not doing well enough to be satisfied with their current care; they need something else.

In addition, from some of our earlier studies, we noted that the patients who are most likely to respond best to cardiac contractility modulation therapy are those with ejection fractions ranging from 25% to 45%. So let's call those patients with, you know, moderately reduced LV ejection fractions and not severely reduced LV ejection fractions. And in that population of patients, the trials have demonstrated significant improvements in exercise ability, measured by both metabolic exercise testing or the peak VO<sub>2</sub> as well as by the 6-minute hall walk distance, have demonstrated improvements in quality of life and finally improvements in New York Heart Association functional class ranking.

And again, to put some of these results into perspective, the typical or average improvement in quality of life score seen with cardiac contractility modulation is about 10 to 12 points. And remember, earlier I told you with our drug therapies, it's about 2 or 3 points. And in fact, these quality of life instruments have validated a clinically meaningful improvement being somewhere around 5 points or greater. So when you think about this, CCM produces a clinically meaningful improvement in quality of life that is about three- or fourfold that of what we see with our guideline-directed drug therapies for heart failure.

**Dr. Butler:**

For those just tuning in, you're listening to CME on ReachMD. I am Dr. Javed Butler, and here with me today is Dr. William Abraham. We are discussing the 3 things you need to know about cardiac contractility modulation and how this therapy will benefit your patients with heart failure.

So now that this therapy has been approved and has been used clinically, are there any real-world or registry data that replicate these results that you mentioned from the clinical trials?

**Dr. Abraham:**

There are. And I think we're learning quite a bit from ongoing observational and registry studies. For example, one substantial registry study has looked at clinical outcomes, real observed clinical outcomes, in patients with CCM compared to what would be predicted by a validated risk predictor score, the MAGGIC score, and demonstrated compared to expected morbidity and mortality, the observed event rates were substantially lower.

But after having said that, I want to emphasize that the real indication for using CCM today is in those class III patients with advanced symptoms, poor quality of life, impaired functional status, you know, despite guideline-directed drug therapies who we really want to make feel better.

**Dr. Butler:**

So I have a question for you for today and a question for you for tomorrow. So the question for today is how does this practically work? Are these EP [electrophysiologist] doctors inserting the device? Is this something that general cardiologists can just refer to EP?

**Dr. Abraham:**

Yeah, from a practical standpoint, really, any practitioner who touches the lives of heart failure patients can refer a patient for cardiac contractility modulation therapy. The device is implanted by electrophysiologists, cardiac electrophysiologists, or really can be implanted by anyone skilled in the implantation of pacemaker or defibrillator-type devices. But the key here is getting the patient to the electrophysiologist for the implant procedure.

So again, I think it's a very straightforward algorithm here. You know, patient on optimally tolerated – and I say optimally tolerated because we know many patients with heart failure don't tolerate maximal doses of all of our guideline-directed drug therapies. You know, make your best shot at getting them on reasonable GDMT as tolerated. And if they remain in class III heart failure, have an ejection fraction somewhere ranging from 25% to 45%, whether you'd be a primary care physician, a general cardiologist, or a heart failure specialist, you know, please consider sending that patient to the electrophysiologist for cardiac contractility modulation therapy.

And I should have mentioned one other caveat here. These are patients who are not indicated for cardiac resynchronization therapy. So if they've got a CRT indication, they should receive it. If they don't, then CCM is your alternative device-based therapy for treating these patients.

**Dr. Butler:**

Now, a question for tomorrow. Any chance that in the future there'll be some data coming out on HFpEF [heart failure with preserved ejection fraction] as well?

**Dr. Abraham:**

Yeah, for sure. This is a great area of interest for many of us. It turns out, and I think I mentioned it earlier, that in addition to supporting contractility, there is an improvement in lusitropy, that is relaxation, as well. We know that in HFpEF patients, at least many of them, they may have normal ejection fractions or near normal ejection fractions, but they still may have abnormalities and contractility, but we know they also have abnormalities in lusitropy as well. And so mechanistically it makes great sense that this therapy would work in patients with preserved ejection fractions as well.

**Dr. Butler:**

Well, thank you, Bill. This is a great 360 view of this therapy. May I ask you to share some take-home message from this discussion?

**Dr. Abraham:**

Yeah, well, I think the take-home message is that cardiac contractility modulation therapy is now a reality for our HFrEF patients. And by our HFrEF patients, I mean those with ejection fractions ranging from 25% to 45%. It is a good therapy for patients who don't have a CRT indication and despite guideline-directed drug therapies still aren't doing as well as we'd like them to be doing or as they would like to be doing as well. So please consider this now in your armamentarium of therapies to improve the lives of our heart failure patients.

**Dr. Butler:**

Well, unfortunately, that's all the time we have today. So I would really like to thank our audience for listening to this discussion. And thank you so much, Bill, for joining us today and sharing all your valuable insight. It was absolutely a pleasure speaking with you today.

**Dr. Abraham:**

My pleasure. Thank you, Javed.

**Announcer:**

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