The Role of Cardiac Resynchronization Therapy in Heart Failure Patients: An Expert Interview With Lynne Warner Stevenson, MD

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Interviewer: Linda Brookes, MSc

Editor's Note:
Medscape interviewed Lynne Warner Stevenson, MD, to discuss the role of cardiac resynchronization therapy (CRT) in heart failure patients.

Dr. Stevenson is Professor of Medicine at Harvard Medical School and Co-Director of the Cardiomyopathy and Heart Failure Program at Brigham and Women's Hospital, Boston, Massachusetts.

She serves on the heart failure guideline committees for the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA). Dr. Stevenson participates on advisory panels for the National Heart, Lung, and Blood Institute (NHLBI) on heart failure, cardiorenal connections in heart disease, and the role of next-generation ventricular assist devices; the Centers for Medicare & Medicaid Services (CMS); and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Dr. Stevenson's research is focused on the strategies by which therapies should be tailored to hemodynamic profiles and patient preferences for length or quality of life, and designing clinical trials that reflect the escalating severity of heart failure populations.

She was lead investigator in the NHLBI-sponsored Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) and chair of the medical management committee for the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trials. Dr. Stevenson is committed to ensuring that multiple options are developed and offered in parallel to patients with advanced heart disease.

Medscape: Electrophysiological therapies for heart failure, such as CRT and implantable cardioverter defibrillators (ICDs), have been evaluated in a number of randomized, controlled clinical trials. However, whereas ICDs have been shown to prevent sudden cardiac death while having no effect on functional outcomes, evidence for the benefits of CRT (atrial-synchronized biventricular pacing) is less clear. How do you think the medical community at large should currently view CRT?

Dr. Stevenson: CRT is the first major therapy to come along that has proven to have substantial benefit for quality of life in many recipients with advanced heart failure. Like every other advance, however, CRT is not a panacea. The way in which medical advances tend to be promoted always encourages the view of everything new that comes along as a kind of “ultimate breakthrough.” For the right patients, CRT is a terrific intervention that has meaningful benefits, including a major improvement in quality of life. Everyone agrees on that, but what we do not necessarily agree on within the professional community is who are the right patients for CRT and how many of these patients there are.

As a rough estimate, there are probably somewhere between 500,000 and 800,000 patients in the United States who have heart failure severe enough to be considered as possible candidates for CRT. We refer to that as advanced heart failure, New York Heart Association (NYHA) class III or class IV, or daily symptoms despite optimal medical therapy. Of these patients, about one third will have a QRS duration that is sufficiently prolonged to qualify them as real candidates for CRT. These parameters are the general fence around the ballpark.

However, an additional parameter is that at this time, only about two thirds of patients who appear perfect for the procedure will derive benefit. As we are trying to sort out who these patients are, the benefits of CRT have been so widely recognized that physicians are doing the procedures in additional patients who are at the borders of the accepted indications, to see whether they may benefit.

So CRT has moved from being a tightly controlled investigational procedure with very good results to one that is frequently being done in patients who are probably not suitable for the procedure, either because they do not have the ventricular activation sequence that will respond or because they are too well or too sick. We are seeing an arc of the pendulum swing in which the improvement that was remarkable initially is now being diluted by a lack of improvement in patients who were not very likely to improve in the first place.
**Medscape:** How were the criteria for appropriate implantation of a CRT device established?

**Dr. Stevenson:** The criteria currently recommended for the procedure are similar to those for enrollment in the various randomized clinical trials that have demonstrated the efficacy of CRT. However, as with many trials, the entry criteria did not necessarily describe the typical patient who was actually enrolled. The enrolled patients had an average QRS duration of > 160 mseconds, and those who showed the most benefit in the trials were those with a QRS > 150 mseconds -- although 120 mseconds, or in some cases 130 mseconds, was the threshold enrollment criterion.

As a general principle, the population of patients who actually take part in a controlled clinical trial is often much more restricted than the population who could have been recruited into the trial. So we have to be careful not to assume that the entry criteria for these trials necessarily define exactly the people who actually went into the trial.

**Medscape:** What are the generally accepted benefits of CRT in the patients who it is assumed will benefit the most?

**Dr. Stevenson:** Improved quality of life is the dramatic benefit of CRT. There is a small and now statistically robust improvement in survival associated with the procedure, but that is not why most clinicians want to do it. We aim to achieve a clinically significant improvement in quality of life and function for patients who are very limited. The fact that there is a statistically significant improvement in survival is not nearly as compelling as the clinically significant improvement in quality of life. The patients themselves are also most concerned with the quality of daily life.

**Medscape:** So the trials and meta-analyses that showed an improvement in all-cause mortality with CRT are not so important?

**Dr. Stevenson:** I accept those numbers, but that finding is not compelling to me compared with the quality-of-life benefit.

**Medscape:** Looking again at the usual criteria for CRT, these are that a patient should have NYHA class III or IV (moderate-to-severe) heart failure, be symptomatic despite stable, have optimal medical therapy (diuretics, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs], and beta-blockers), have ventricular dyssynchrony as demonstrated by a QRS duration >/= 120 mseconds on electrocardiogram (ECG), and have severe left ventricular systolic dysfunction (ejection fraction ≤ 35%). Are these criteria likely to change in the future?

**Dr. Stevenson:** A lot of work is currently being done in patients with narrower QRS intervals, between 120 mseconds and 150 mseconds, looking at other measures of dyssynchrony that would predict whether a patient would do better when the contraction of the heart is better coordinated. These are all small studies, each one with a slight variation of how to measure dyssynchrony. At the moment, as a clinician, I do not see anything from that set of analyses that is compelling. In other words, although there are many different ways of looking at dyssynchrony, the only thing that we really have good data on is the QRS duration.

Prolongation of the QRS is a very gross marker, however. There are patients who have a long QRS who do not have obvious dyssynchrony and patients who have dyssynchrony who do not have a long QRS, so the current situation is confusing. I do not think that we have the best definition of dyssynchrony, but to date, QRS is the only sufficiently validated definition of dyssynchrony in terms of showing benefit. Other questions that need further study are what benefit could be expected for the patients with current right ventricular pacing and those with atrial fibrillation.

In the patients who have significant dyssynchrony but still feel well, the question of whether early CRT could improve their prognoses is being addressed in the ongoing RESynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study.

**Medscape:** When general physicians see patients who fulfill the current basic criteria, should they be thinking of referring them for CRT?

**Dr. Stevenson:** There are a couple of major points that should be emphasized here. One is that just because a patient is prescribed the appropriate drugs for heart failure does not mean that the patient is on optimal medical therapy. There are many patients who are on the correct drugs, who still have symptoms, and yet who could be successfully managed if their medications were adjusted more carefully. It is not enough just to be on the drugs; they have to be monitored, adjusted, and titrated to the individual patient.
One of the first things that I would say to the general practitioner is that if you have a heart failure patient who continues to have symptoms that limit his/her routine daily activity, that patient's overall regimen deserves very close scrutiny. The scrutiny should first be directed toward how better to use the medications. The most common error is not to adjust the medications appropriately for volume status. Often when the volume status is adjusted appropriately, patients feel much better. Then I would look at the other medications -- the ACE inhibitors and the beta-blockers -- and decide whether those are the best doses for this individual patient; those should basically be the tolerated doses that are as close as possible to the doses shown to be effective.

Medscape: Could an ARB be used in patients who are ACE inhibitor-intolerant?

Dr. Stevenson: If they are ACE-intolerant due to cough, an ARB should be prescribed, yes. Then, after adjusting what can be adjusted, I would ask the patient again what is bothering him/her the most, because sometimes it turns out that it is something relatively small that can be addressed. Maybe the patient is getting dizzy after the medication and you need to change the timing of his/her medication, or maybe it turns out that it is really related to a myocardial ischemia equivalent, pulmonary disease, arthritis, or perhaps something else. So I would focus very carefully on what is the limiting symptom and try to attack that.

Having done that, if the patient continues to have symptoms with routine activity, then we look for other interventions that may improve the patient. At this point, I think that it is time to consider CRT. The reason I would not consider CRT initially at the time of referral of the symptomatic patient is that the benefit of CRT has been shown only in the setting of expert doctors adjusting heart failure regimens before and after device implantation. That is not often the focus of a busy practice where heart failure is only one of many cardiology diagnoses, and the heart is only one of many organ systems requiring attention. So we have to be very careful before we assume that we can translate these results into usual practice.

Medscape: Do you mean that management of heart failure should be the focus of a general office or should patients be referred to a setting where it would be the focus?

Dr. Stevenson: It depends a great deal on where the practice setting is. Approximately three quarters of patients with heart failure are cared for in a general practice. That is reality. There are not enough heart failure specialists even to come close to caring for all the patients with heart failure, so most patients are never going to visit a center specializing in heart failure management. In addition, most patients who have heart failure also have other diseases that are well managed in a general office. So I think that we have to accept the reality that most of these patients will be managed in a general office, and we have to work out how that can best be done.

General physicians work exceedingly hard and have to keep track of a great deal more information about more diseases than specialists do. I think that they face a very difficult task. General practices do not usually have their own nurses who are trained in heart failure to help them manage the patients. Evidence clearly shows that these expert heart failure nurses improve outcomes and quality of life for patients enrolled. We need to figure out how to train and export these physician extenders to provide support in the communities.

Medscape: How should general physicians proceed with potential CRT candidates?

Dr. Stevenson: After they have all the information and they have optimized medical therapy as much as possible in their practice settings, they should consider referral to a specialist who does devices. There are currently more options for implantation of heart failure devices than for dedicated heart failure management, which requires more time for much less reimbursement.

At this point, we face an increasing problem in the United States, which is already apparent in other countries where healthcare resources are more strictly monitored: We need to think very carefully about how our healthcare resources should be spent. Ideally, where this level of resources is available for expert implantation of high-level technology, it should be in conjunction with commensurate resources devoted to expert heart failure evaluation at the same site. Unfortunately, at least in the United States, it is much easier to find a place to implant a $30,000 device than to find a place where someone trained in heart failure can spend an hour with a patient over several visits for less than 1% of that billing price.

Medscape: Returning to an earlier point that you mentioned, the number you hear quite often is that a significant percentage, around 25% to 30%, of patients who are considered suitable candidates and receive a CRT device do not actually get any benefit. Is that an accurate picture?
Dr. Stevenson: That is correct, and there are many reasons for that. One is that, for whatever reason, it may not be possible to restore synchrony in that particular patient. I think that the most common reason, however, is that the patient does not have his/her medical therapy optimized, and if it is not optimized, nothing else will benefit the patient. For example, if the patient is carrying 4 L of extra volume, no electrical device is going to make the patient feel better. So both the need and the benefit of the device are in the context that the other therapy is truly optimally adjusted, not just prescribed.

Medscape: Is there really such a big a problem with diuretic therapy? Diuretics have been available for a long time.

Dr. Stevenson: The diuretics are the most commonly ineffectively used drugs, I believe. The interesting thing about heart failure is that each individual is very different and may need different doses.

Medscape: Some prominent thought leaders have suggested that the same results seen in some of the clinical device trials could have been achieved simply by adjusting the patients' pharmacologic therapy.

Dr. Stevenson: That is true for some patients but not most. Having been involved in the early trials of CRT, I remain quite impressed by the potential of CRT to improve symptoms beyond what we can do with medicines. I am a very ardent advocate of this procedure for the right patient, but I am also relatively conservative in wanting to keep it for the right patient in whom other therapies have not been effective enough.

Medscape: After patients have had CRT, how should they be monitored if there are not enough specialists for heart failure?

Dr. Stevenson: The specific device has to be checked regularly in a device clinic, but the device clinic will not have any pretensions to adjusting the rest of the therapy. A problem that we are seeing here, again because general physicians are very busy, is a tendency to think that once a patient has been referred for CRT, either it works or the patient is at the end of the line as far as treatment is concerned. There is a failure to recognize that there is still an ongoing management and adjustment of the medical therapy that needs to be made. So in some ways it is kind of a handoff, which is not the intent, but it may turn out that way.

Medscape: What should happen, ideally, at this stage? Does CRT have a long-term beneficial effect?

Dr. Stevenson: From the study data that we have, the benefits of CRT clearly last up to 2 or 3 years. I do not know how much longer after that we will see the benefits persist, but I am not seeing a rapid falloff. However, it certainly does not confer immortality; one expects that the heart failure will continue to progress, albeit after a delay. I do not know that I have a solution. The way that technologies are introduced is determined primarily by how they are developed and how they are tested, not how they would best be implemented.

So the technology is here; now the question is, what to do? If we were designing this from the beginning, I would have liked to see this technology integrated into heart failure management, such that all patients referred for CRT were enrolled in a heart failure program that included a specialized nurse who would help them keep track of their medications and educate them. That is the way in which I think I would optimally want to see this viewed.

Medscape: Do patients then tend to remain on their pre-CRT "optimal medical therapy" after CRT?

Dr. Stevenson: Yes. Again, in the trials, it was all done very carefully, with ongoing evaluation, but in the real world, where everyone is so busy, it is harder to make sure that it happens that way. I would like to add that if we started right now with a bank full of resources and asked what we should spend them on in terms of heart failure, by far and away the greatest benefit that we could get right now would be to train a cadre of nurses in how to take care of heart failure, how to manage heart failure, and to send them out to all the busy practices that have a fair number of heart failure patients but not enough to justify their own heart failure programs. Those nurses would ensure that the prescribed therapies were optimal and ensure that the patients were educated about what they can do to help their own health -- and then for those patients who continued to have symptoms, despite all of the support, we would provide the resources for evaluation at centers where both devices and other therapies were considered.

However, we never know at the beginning how effective a technology will be. Effective ones are implemented as soon as the benefit is clear, not when all the groundwork for optimal utilization has been laid. It remains very important not to let the excitement and the apparent finality of a device replace other things that we know are very important. We are always
looking for a quick fix, such as a pill or a device, but in fact heart failure is a very complex disease that requires a lot of different components to be integrated together to make patients feel as well as they can for as long as they can.

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**References**