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Advances in Electrical Therapy for Heart Failure: Proceedings from the International ADVANCE CRT Summit

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ADVANCES IN ELECTRICAL THERAPY FOR HEART FAILURE: PROCEEDINGS FROM THE INTERNATIONAL ADVANCE CRT SUMMIT

Cardiac resynchronization therapy (CRT) has substantially altered the natural course of congestive heart failure (CHF), exerting its physiological impact through favorable ventricular remodeling, with a reduction in left ventricular volumes and an increase in ejection fraction. This in turn has resulted in long-term clinical benefits with improved quality of life and functional capacity, and a concomitant decline in hospitalization for heart failure and overall mortality. The standard indications for biventricular pacing – which initially included patients with advanced heart failure and evidence of systolic dysfunction (ejection fraction <0.35), with conduction tissue disease and marked cardiac symptoms (NYHA class III and IV heart failure) – has now expanded to include even the mildly symptomatic patient (NYHA Class I and II).

Despite the successes of resynchronization therapy and the recent expansion of its role in the treatment of patients with CHF, there remain many inherent limitations to the technology and its delivery. A significant proportion of patients continue to remain non-responsive to this pacing strategy. More important, even within the responder population, it is uncertain if we are doing enough to maximize response.

On October 16 and 17, 2010, 30 internationally renowned experts in CRT from 9 countries convened in Philadelphia, Pennsylvania, for the ADVANCE CRT Summit. This multidisciplinary forum comprised experts from within the field of heart failure, electrophysiology, cardiovascular imaging, health policy, and stem cell therapy. The summit was conducted with the intent to:

- Clarify the current state-of-the-art/best practices in assuring CRT response
- Establish consensus for best practice pertaining to treatment guidelines and enhance the "continuum" of CRT response
- Identify critical unanswered questions limiting the understanding of CRT response
- Think beyond resynchronization therapy for treating the failing heart, such as newer forms of electrical treatment (ie, neuromodulation), mechanical therapy, and stem cell approaches

This supplement highlights some of the critical issues presented and discussed at the Summit. The articles included in this issue come from leaders in the field of device therapy for heart failure. These scholarly pieces highlight CRT in its present form, while elaborating on strategies to enhance response, as well as outlining future trends and synergies towards maximizing the potential benefit of cardiac resynchronization therapy.

Jagmeet Singh, MD, DPhil
Guest Editor
Chair, ADVANCE CRT Summit

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BACKGROUND, CLINICAL TRIALS, RESPONSE MEASURES, GUIDELINES, PRESENT AND FUTURE TARGET POPULATIONS

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Abstract: The incidence of chronic heart failure (HF) is increasing rapidly in the developed world, yet despite optimal pharmacologic treatment, the prognosis for these patients remains poor. Left bundle branch block (LBBB), a surrogate marker for left ventricular (LV) mechanical dyssynchrony, is present in between 25% to 50% of patients with HF and is associated with increased morbidity, mortality, and sudden cardiac arrest. Cardiac resynchronization therapy (CRT) was introduced in the early 1990s; based on electrical stimulation of the left ventricle, CRT corrects intraventricular dyssynchrony and improves acute hemodynamic variables, systolic efficiency, and diastolic function, all without increasing the heart rate or the consumption of oxygen. To date CRT has been evaluated in >4000 patients in landmark randomized controlled trials in NYHA class III-IV HF patients. These trials, including MUSTIC, MIRACLE, CONACT-CD, and MIRACLE ICD, have demonstrated consistent improvements in quality of life, functional status, and exercise capacity with CRT, while also providing strong evidence for reverse remodeling (the ventricle gets smaller and stronger) and diminished functional mitral regurgitation, resulting in reductions in both HF hospitalizations and all-cause morbidity and mortality. Nevertheless, although virtually every study so far has demonstrated a benefit for CRT, there remains a consistent 30% of patients who receive CRT but do not respond. More important, there is a lack of consensus as to how to define “success” for CRT. A recent analysis by [Fonarow et al] found that 17 different criteria were used to define a positive response with CRT: 8 of these were echocardiographic, 8 were clinical, and one was based on a combination of both echocardiographic measurements and symptom status. Applying these criteria to the PROSPECT cohort, the result was that the proportion of patients who responded to CRT varied between 32% or 91%, depending on which criteria were used. An important result of this uncertainty is that there is not yet a good sense of what the optimal rate of CRT implantation should be. That is the reason for Advance CRT Summit and the papers in this supplement. We are convinced that we can do a better job at identifying patients who are likely to respond to CRT, and increase the percentage of responders by individualizing therapy.

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THE TALE OF NON-RESPONDERS TO CRT: LESSONS LEARNED FROM ONCOLOGY

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Abstract: It is a widely recognized statistic that cardiovascular disease (CVD) is the number one cause of death in the world, with morbidity and morality rates that are higher than for all the most important forms of cancer combined. The differences in the level of attention that CVD and cancer receive, however, tends to run in the opposite direction in terms of public awareness and funding campaigns. This disparity in perception has an important consequence in the perception of treatment efficacy. The cardiac resynchronization therapy (CRT) that is the subject of the Advance CRT Summit is often criticized for 2 reasons: initial cost and a 30% nonresponse rate. These criticisms need to be reconsidered, however, when they are compared with other treatment results. For example, in CVD the well-known SOLVD trial, proving the efficacy of angiotensin-converting enzyme(ACE) inhibition in treating left ventricular (LV) hypertrophy, the statin trials in treating dyslipidemia, and antiplatelet trials in ACS have all been reported as successes, although they seldom approach the 40-50% benefit seen in ICD and CRT trials and have reported similar failure rates for patients who still had events while on optimal study therapy. In contrast, many cancer trials report results for costly therapies where success is measured in days or weeks, not months and years, of life extension in far less than 100% of the patients. As discussed in this article, the successes shown by oncologists in promoting the importance of the disease state they treat and the latest treatment options they offer need to be considered and perhaps emulated by HF specialists and electrophysiologists when they are considering how they can promote the efficacy of CRT as a treatment option.

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UNDERSTANDING THE CARDIAC SUBSTRATE AND THE UNDERLYING PHYSIOLOGY: IMPLICATIONS FOR INDIVIDUALIZED TREATMENT ALGORITHM

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Abstract: The clinical presentation of heart failure (HF) is evenly divided between systolic and diastolic (or HF with preserved systolic function). In a significant number of patients with systolic HF, an abnormality in the heart's electrical conducting system results in electrical activation that results in dyssynchronous LV mechanical activation. Left bundle branch block (LBBB), as a surrogate marker for LV mechanical dyssynchrony, is present in between 25% to 30% of patients with systolic HF and is associated with a substantial increase in morbidity and mortality and sudden cardiac arrest. The interplay of the substrates of the HF (ischemic versus nonischemic) of electrical conduction abnormality (LBBB versus right bundle branch block, RBBB), and of the resulting dyssynchrony (interventricular versus intraventricular) is complex, and requires a sophisticated degree of understanding to diagnose and treat, as discussed in this article. With the advent of cardiac resynchronization therapy (CRT) in the early 1990s, clinical trials were based on the QRS interval from the ECG as a marker for dyssynchrony. Subsequently, mechanical dyssynchrony has been a focus of a great deal of study, generally based on sophisticated echocardiographic criteria, using tissue Doppler or more recently speckle tracking with mixed results. Although a consensus has not been reached regarding utility of echocardiographic dyssynchrony, study continues. The precise diagnostic criteria remain a subject of evolving definition, although the markers of QRS >120 msec, LVEF <0.35, and NYHA class III-IV HF have been fairly standardized in both the US and European guidelines. Recent data has suggested expanded indications of CRT to NYHA class II or even I, in particular with LBBB. The principal remaining questions as they relate to the substrate of systolic HF are whether CRT will have benefit in patients with a narrow QRS (≤120 msec) but evidence of mechanical dyssynchrony, and this is currently under further investigation.

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CONTEMPORARY AND FUTURE TRENDS IN CRT PACING TO ENHANCE RESPONSE

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Abstract: Although biventricular (BiV) pacing, or cardiac resynchronization therapy (CRT), has established an unbroken record of statistically significant benefit in a series of randomized clinical trials, an underappreciated aspect of this therapy is that many challenges remain to defining “treatment success.” Some of these questions were resolved in the COMPANION trial, which established the additional mortality benefit of adding automatic cardioverter defibrillation (ICD) to CRT (CRT-D), but the question of whether the CRT (or CRT-D) is successful in an individual patient remains a challenge for physicians. As discussed in this article, these questions include whether a “best pacing site” exists, the relative advantages of an epi- versus an endocardial lead placement strategy, and the importance of avoiding the “scar” in an ischemically damaged left ventricle. It is also necessary to appreciate monitoring parameters such as dP/dt, whether a second left ventricular lead is an advantage, and optimizing device programming. Finally there the question of personalized pacing strategies such as consideration of CRT in patients with a narrow QRS interval ($\leq$120 msec), in early-stage heart failure (NYHA class II or even I), or with concomitant atrial fibrillation.

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THINKING BEYOND RESYNCHRONIZATION THERAPY IN THE FAILING HEART: OPTIMIZING THE CLINICAL RESPONSE FOR RESPONDERS AND NONRESPONDERS

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Abstract: As heart failure progresses, not only do symptoms get worse but more and more organs become involved to the point where patients that are end stage have a truly systemic illness. The endpoint therapy for HF is heart transplantation; for many reasons, however, the number of heart transplants worldwide has remained constant for the last 15 years (e.g. 2500 per year in the United States). In this context left ventricular (LV) assist devices which were originally seen as a bridge to transplantation, have now evolved to the role of serving as destination therapy. The results of the REMATCH trial published in 2001 established that the benefit with LVAD's was far superior to that of optimal drug therapy in patients with advanced HF. Since then the next major advance has been the introduction of continuous-flow pumps design. The results of 2 large randomized trials with the HeartMate II LVAD's have confirmed the hemodynamic and clinical superiority of the continuous flow approach as compared to pulsatile devices. Newer, smaller devices, such as the Synergy Micro-Pump, which are the size of an AA battery, provide flow of 2-3 L/min and result in partial support that is less invasive for patients who are at earlier HF stages. This may prove to be the trend, with the NIH moving toward application of LVAD's in patients who are late stage C, early stage D HF, and not yet at the systemic stage of HF, before the requirement for continuous intravenous inotropes.

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MULTISPECIALTY APPROACH: INTEGRATION INTO HEART FAILURE DISEASE MANAGEMENT

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Abstract: Cardiac resynchronization therapy (CRT) has been proven in clinical trials to be very effective therapy in appropriate patients. However with its broad adoption, the existing fragmentation of care has provided some challenges in maximizing this otherwise invasive but potentially beneficial intervention in the complex heart failure patient. Furthermore, considerations of costs as well as appropriate delivery of follow-up care continue to challenge the optimal application of these devices, particularly when evidence to support multidisplinary approaches are lacking. The challenge begins with identification of appropriate candidates for CRT, which is an evolving concept due to emerging new data from new studies with a wide range of inclusion and exclusion criteria coupled with oversight from providers or even logistical hurdles from patients. There are no uniformly-accepted post-implant management protocols, no innovative interdisciplinary co-management among specialists and general practitioners, nor any careful research to identify the best practices following implantation. This has resulted in heterogeneous post-implant CRT care, and inadequate transitions of care among electrophysiologists and other cardiology specialists, and between specialists and general practitioners. The concept of “non-responder” remains largely subjective and is variably defined in the literature, and the lack of understanding of the underlying mechanisms of “non-response” continued to challenge the long-term management of CRT even with the development of advanced sensor technologies. Therefore, further investigations into pre- and post-CRT heart failure disease management with a multispecialty approach are warranted.

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MANAGING ATRIAL FIBRILLATION IN THE CRT PATIENT: CONTROVERSY OR CONSENSUS?

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Abstract: According to the European Heart Surveys, heart failure (HF) is present in 34% of patients who have atrial fibrillation (AFib), and conversely, AFib is present in 42% of patients with HF. Furthermore, as the average age of populations throughout the world increase, the number of patients with HF and AFib will continue to increase. The physiologic mechanisms by which one condition leads to the other is something of a chicken and egg discussion, however, and the question of which to treat, or how to treat both conditions, represents a challenge for physicians. As discussed in this article, the thesis is that AFib has a deleterious impact on HF status and prognosis and that restoration of sinus rhythm (as opposed to simple rate control) is of benefit in this situation. Antiarrhythmic drug therapy has not been demonstrated to be an attractive option for restoration of sinus rhythm. On the other hand, a recent meta-analysis has found that in patients with left ventricular (LV) dysfunction and AFib, catheter ablation, using pulmonary vein isolation (PVI) in preference to atrioventricular (AV) node ablation followed by RV pacing, results in improved LV function and HF symptom status. As a management strategy, therefore, PVI in patients with AFib and LV dysfunction merits further investigation in randomized trials.

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