July 24, 2019

Agency for Healthcare Research and Quality
Technology Assessment Program
Supplemental Evidence and Data for Systematic Reviews Guidelines
5600 Fishers Lane, 7th Floor
Rockville, MD 20857

RE: ***Use of Cardiac Resynchronization Therapy: Technology Assessment Report***

Submitted electronically to epc@ahrq.hhs.gov

To Whom It May Concern:

The Heart Rhythm Society (HRS), the American College of Cardiology (ACC) and the Heart Failure Society of America (HFSA) appreciate the opportunity to submit joint comments to the Agency for Healthcare Research and Quality's (AHRQ) Technology Assessment (TA) Program as it assesses the use of cardiac resynchronization therapy (CRT) in the Medicare population. These comments are supported by literature reviews and dialogue with device manufacturers.

HRS, ACC and HFSA reiterate the information provide by HRS to AHRQ in March 2019. As stated in the letter from HRS to AHRQ:

> "The role of CRT in the management of patients with heart failure with depressed left ventricular systolic function and significant conduction delay to the left ventricle is well established. While majority of clinical trials conducted had both safety and efficacy end points, these efficacy end points have evolved from measurements of heart failure functional status, to including measurements of ventricular function and reverse remodeling, to finally improving survival among the recipients of these devices. These devices have improved the quality of life of thousands of patients with heart failure, prevented them from progressing to needing advanced heart failure therapies (like heart transplantation of assist devices), and extended the lives of many. In addition to these remarkable benefits, these devices have reduced hospitalizations and healthcare cost of caring for thousands of patients with heart failure. "

March 2019
In March 2019, the following questions were raised by HRS for AHRQ's consideration:

1. How can we improve our ability to measure CRT outcomes?
2. What is the role of non-invasive electrocardiographic mapping combined by radiographic data in optimizing CRT response?
3. What is the role of alternative pacing approaches (such as epicardial or endocardial LV lead implantation or His bundle pacing) among patients who fail endovascular coronary sinus LV lead implantation?
4. How can we optimize the care of CRT recipients after the implantation of the device?
5. How can we maximize the benefits of remote monitoring among CRT recipients?
6. How can we maximize the benefits of the diagnostics capabilities of CRT devices?

July 2019

HRS, ACC, and HFSA appreciate the comprehensive nature of AHRQ June 2019 technology assessment report but feel that the report does not capture the evolving nature of the technology. In posting the questions raised in March 2019, HRS was prompting the AHRQ evidence review to not only examine the current available evidence but do so in the context of rapidly evolving technology and our understanding of the appropriate clinical protocols to ensure appropriate patient care. These questions remain pertinent to the review, and failure to address these key questions will result in a report that is not as useful and relevant to clinicians and our patients as it should be. Therefore, to ensure that the evidence report provides a comprehensive review of the technology and is an aid to clinicians and our patients, we encourage AHRQ to use this opportunity to look at the future of the appropriateness of CRT with or without a defibrillator in the Medicare population and not limit the review solely to past technology utilization.

In this letter, HRS, ACC and HFSA reiterate the important questions that were posed in March 2019 and add one additional, critical question.

1. How can we improve our ability to measure CRT outcomes?

The report does not address this important question. It is increasingly recognized that categorizing CRT outcomes into responders and non-responders is too simplistic in assessing the impact of these devices. In clinical practice, we see the super responders (almost back to normal cardiac function) and responders, but we also see patients who are believed to be non-responders but in fact the CRT has slowed or halted their progression or deterioration. This is evident at times of system extraction of CRT devices for different reasons with clear evidence of clinical and echocardiographic deterioration in the LV function after losing biventricular pacing, even among patients who were previously thought to be non-responders. Differentiating true non-responders from the "non-progressors" is a challenging question to answer but hopefully will be the focus of future studies.

2. What is the role of non-invasive electrocardiographic mapping combined by radiographic data in optimizing CRT response?

The report does not address non-invasive mapping. The criteria for CRT eligibility remain limited to QRS duration, type of intraventricular conduction delay, LV ejection fraction, and symptoms. We agree with all the key questions listed for the update to better understand the efficacy of CRT among different candidates and its relation to the other variables listed (e.g., age, gender, nature of cardiomyopathy, QRS morphology and atrial fibrillation). Emerging technologies may help guide the physicians to target optimal sites for lead implantation or even after the implantation by choosing the right LV electrode to pace from that would achieve the maximum yield from re-synchronization of the cardiac chambers.

3. What is the role alternative pacing approaches (such as epicardial or endocardial LV lead implantation or His bundle pacing) among patients who fail endovascular coronary sinus LV lead implantation?

As noted, the report cites His bundle pacing, but does not address novel techniques including LV endocardial pacing. Historically, patients who are candidates for CRT and are unable to undergo coronary sinus endovascular LV lead implantation are usually referred for surgical LV epicardial lead implantation. In addition, the questions listed in the update about the role of His bundle pacing

versus CRT, a targeted question about the role of His bundle pacing versus surgical epicardial LV lead placement among patients who fail endocardial coronary sinus LV lead implantation is significant.

4. How can we optimize the care of CRT recipients after the implantation of the device?
There is limited information in the draft report regarding the CRT optimization process. Almost 20-30% of CRT recipients are "non-responders". While some reasons behind the lack of response are not modifiable, others are. Sub-optimal programming, confounding arrhythmias, lower percentage of biventricular pacing, and suboptimal lead position are all potentially modifiable factors that could yield targeted benefits from CRT. Novel ways in providing care for CRT recipients including the concept of a CRT optimization service can provide the opportunity to maximize the benefits of these devices.

5. How can we maximize the benefits of remote monitoring among CRT recipients? The draft report does not provide no information about remote monitoring. Remote monitoring of CIEDs improves clinical outcomes, minimizes healthcare cost and potentially improves survival among recipients of these devices. Despite this, adoption rate for remote monitoring has remained sub-optimal. The technology has evolved from depending on land lines to using cellular network and most recently the patient's own smart device (for certain pacemakers and CRT pacemakers). For the first time, patients can potentially have access to some of their device data. This might provide many opportunities to advance the care of CRT patients by engaging them in their own care.

6. How can we maximize the benefits of the diagnostics capabilities of CRT devices?
The report does not address other diagnostic capabilities of those devices. CRT devices, whether defibrillators or pacemakers, are equipped with many diagnostic algorithms for arrhythmias, in addition to others to monitor activity levels and some measurements that act as surrogates for the volume status of the heart failure patient. Non-rhythm related diagnostics can help the heart failure specialist or cardiologist manage the patient's heart failure. Lack of access to these diagnostics and the inability to triage the right measurements to the right specialist have limited the multidisciplinary approach to the care of the heart failure patient implanted with these devices. The advancement of technology has not been matched with advancement of handling the data and disrupting the traditional silos we have in clinical practice.

7. As the field gains further understanding of infection control, including the role of the antibiotic envelope, best practices to minimize hematomas, and better battery life, it is worthwhile to consider an additional question: How can long term complications after CRT implantation be minimized?
CRT recipients undergo several device procedures over their lifetimes for multiple reasons including generator changes for battery depletion or lead revisions, or others. Each procedure exposes the patient to potential complications including infection, bleeding, hematomas, or lead damage. This might jeopardize the CRT system. Proper anticoagulation management can minimize the risk of hematoma and therefore avoid infection. Recently published the Prevention of Arrhythmia Device Infection Trial (PADIT)[1] trial showed no significant benefit from incremental use of antibiotics. The

[1] Krahn AD, Longtin Y, Philippon F, et al. Prevention of Arrhythmia Device Infection Trial. *J Am Coll Cardiol.* 2018 Dec 18;72(24):3098-3109. PMID: 30545448

Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT)[2] study showed benefit from using antibiotic envelope in minimizing infection after cardiac implantable electronic device (CIED) procedures in select group of patients, specifically among patients undergoing ICD or CRT-D secondary procedures.

HRS, ACC and HFSA appreciate the opportunity to provide AHRQ with these comments. As noted, we strongly urge AHRQ to use this opportunity not only to update the earlier technology assessment report published in 2015 but also look to the future and raise important questions about the technology's forthcoming potential. Therefore, we urge AHRQ to expand the report and address the key questions presented in March 2019 and as part of this letter. Failure to include these critical issues will likely result in a report that is unable to fully assist clinicians and our patients.

If you have questions regarding these comments or if the societies can be of support to you, please contact Laura Blum at lblum@hrsonline.org.

Sincerely,

Andrea M. Russo, MD, FHRS
President
Heart Rhythm Society

Richard J. Kovacs, MD, FACC
President
American College of Cardiology

Randall C. Starling, MD, MPH, FHFSA
President
Heart Failure Society of America

Attachment A: HRS March 2019 Letter

[2] Tarakji KG, Mittal S, Kennergren C, et al., Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med* 2019 May 16;380(20):1895-1905. doi: 10.1056/NEJMoa1901111. Epub 2019 Mar 17. PMID: 30883056

March 4, 2019

Agency for Healthcare Research and Quality
Technology Assessment Program
Supplemental Evidence and Data for Systematic Reviews Guidelines
5600 Fishers Lane, 7th Floor
Rockville, MD 20857

RE: ***Use of Cardiac Resynchronization Therapy: A Systematic Review Update***

Submitted electronically to epc@ahrq.hhs.gov

To Whom It May Concern:

The Heart Rhythm Society (HRS) appreciates the opportunity to provide comments to the Agency for Healthcare Research and Quality's (AHRQ) Technology Assessment (TA) Program as it assesses the use of cardiac resynchronization therapy (CRT) in the Medicare population.

HRS is the international leader in science, education, and advocacy for cardiac arrhythmia professionals and patients as well as the primary information resource on heart rhythm disorders. Founded in 1979, HRS represents more than 6,400 specialists in cardiac pacing and electrophysiology, including physicians, allied professionals, scientists and their support personnel. Cardiac electrophysiology is a distinct sub-specialty of cardiology. Most electrophysiologists are eligible for board certification in clinical cardiac electrophysiology and cardiology through the American Board of Internal Medicine. Cardiac electrophysiologists implant and manage patients with cardiac implantable electronic devices (CIEDs); perform electrophysiology studies to determine the mechanisms of rhythm disorders; and perform curative catheter ablations to treat and prevent a variety of cardiac arrhythmias. The discipline of electrophysiology has undergone significant change in recent years, creating significant advances in the diagnosis and treatment of some of cardiology's most challenging diseases such as sudden cardiac death, atrial fibrillation and heart failure. As these enhancements occur, HRS remains committed to improving the quality, safety, and efficiency of patient care.

Value of Cardiac Resynchronization Therapy

The role of cardiac re-synchronization therapy (CRT) in the management of patients with heart failure with depressed left ventricular systolic function and significant conduction delay to the left ventricle is well established. While majority of clinical trials conducted had both safety and efficacy end points, these efficacy end points have evolved from measurements of heart failure functional status, to including measurements of ventricular function and reverse remodeling, to finally improving survival among the recipients of these devices. These devices have improved the quality of life of thousands

of patients with heart failure, prevented them from progressing to needing advanced heart failure therapies (like heart transplantation of assist devices), and extended the lives of many. In addition to these remarkable benefits, these devices have reduced hospitalizations and healthcare cost of caring for thousands of patients with heart failure.

Evidence Since 2014

The growing evidence of the benefits of CRT has been matched by significant improvement of implantation techniques of these devices. New delivery tools have enabled electrophysiologists to have better success rates in implanting CRT devices. The introduction of quadripolar leads has improved the success rate of implantation of coronary sinus LV leads providing physicians with multiple options to achieve better capture thresholds while avoiding phrenic nerve capture and stimulation of the diaphragm.

Despite the advancement of the technology, the response rate to CRT varies and continues to be influenced by the nature of cardiomyopathy, the type and duration of the conduction delay (left vs right bundle branch block), gender (female vs male gender), and the presence of other arrhythmias including atrial fibrillation and premature ventricular contractions (PVCs).

In addition to the improvement in the implantation techniques, there has been simultaneous interest in the care of CRT recipients after the implantation. In order to achieve the full benefit of CRT, the device has to accomplish maximum percentage of biventricular pacing. Different algorithms have been developed to achieve this by targeting the optimal activation timings between the atria and the ventricles (AV timing) and between the right and left ventricles (VV timing). In addition to emphasis on treating certain arrhythmias (atrial fibrillation, and PVCs) that might negatively affect the percentage of biventricular pacing.

Additional Considerations

In addition to the key questions listed for the update, HRS recommends that AHRQ include the following additional questions:

1. **How can we improve our ability to measure CRT outcomes?**
   It is increasingly recognized that categorizing CRT outcomes into responders and non-responders is too simplistic in assessing the impact of these devices. In clinical practice, we see the super responders (almost back to normal cardiac function) and responders, but we also see patients who are believed to be non-responders but in fact the CRT has slowed or halted their progression or deterioration. This is evident at times of system extraction of CRT devices for different reasons with clear evidence of clinical and echocardiographic deterioration in the LV function after losing biventricular pacing, even among

patients who were previously thought to be non-responders. Differentiating true non-responders from the “non-progressors” is a challenging question to answer but hopefully will be the focus of future studies.

2. **What is the role of non-invasive electrocardiographic mapping combined by radiographic data in optimizing CRT response?**
   Criteria for CRT eligibility remain limited to QRS duration, LV ejection fraction, and symptoms. We agree with all the key questions listed for the update to better understand the efficacy of CRT among different candidates and its relation to the other variables listed (age, gender, nature of cardiomyopathy, QRS morphology and atrial fibrillation). New technologies, including non-invasive mapping using multi-electrode vest that collects chest ECG signals combined with imaging data can create non-invasive 3D mapping that would help delineate the electrical activation of the cardiac chambers. This can help guide the physicians to target optimal sites for lead implantation or even after the implantation by choosing the right LV electrode to pace from that would achieve the maximum yield from re-synchronization of the cardiac chambers.

3. **What is the role alternative pacing approaches (such as epicardial or endocardial LV lead implantation or His bundle pacing) among patients who fail endovascular coronary sinus LV lead implantation?**
   Historically, patients who are candidates for CRT and fail coronary sinus endovascular LV lead implantation are usually referred for surgical LV epicardial lead implantation. In addition the questions listed in the update about the role of His bundle pacing vs CRT, a targeted question about the role of His bundle pacing vs surgical epicardial LV lead placement among patients who fail endocardial coronary sinus LV lead implantation is of significant importance.

4. **How can we optimize the care of CRT recipients after the implantation of the device?**
   Almost 20-30% of CRT recipients are “non-responders”. While some reasons behind the lack of response are not modifiable, others are. Sub-optimal programming, confounding arrhythmias, lower percentage of biventricular pacing, and suboptimal lead position are all potentially modifiable factors that could yield targeted benefits from CRT. Novel ways in providing care for CRT recipients including the concept of CRT optimization clinic can provide the opportunity to maximize the benefits of these devices.

5. **How can we maximize the benefits of remote monitoring among CRT recipients?**

Remote monitoring of CIEDs improves clinical outcomes, minimizes healthcare cost and potentially improves survival among recipients of these devices. Despite this, adoption rate for remote monitoring has remained sub-optimal. The technology has evolved from depending on land lines, to using cellular network and most recently the patient's own smart device (for certain pacemakers and CRT pacemakers). For the first time, patients can potentially have access to some of their device data. This might provide many opportunities to advance the care of CRT patients by engaging them in their own care.

6. **How can we maximize the benefits of the diagnostics capabilities of CRT devices?**
   CRT devices, whether defibrillators or pacemakers, are equipped with many diagnostics targeting arrhythmias, in addition to others reflecting activity levels and some measurements that act as surrogates for the volume status of the heart failure patient. Non rhythm related diagnostics can help the heart failure specialist or cardiologist manage the patient's heart failure. Lack of access to these diagnostics and the inability to triage the right measurements to the right specialist have limited the multidisciplinary approach to the care of the heart failure patient implanted with these devices. The advancement of technology has not been matched with advancement of handling the data and disrupting the traditional silos we have in clinical practice.

HRS appreciates the opportunity to provide AHRQ with these comments. We look forward to the review of the draft report. If you have questions regarding these comments or would like to discuss our initiatives, please contact Laura Blum at lblum@hrsonline.org.

Sincerely,

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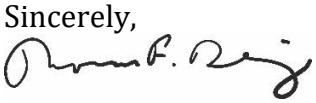

Thomas F. Deering, MD, FHRS
President