Research Review Disposition of Comments Report

Research Review Title: *Use of Cardiac Resynchronization Therapy in the Medicare Population*

Project ID: CRDT1013

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ.

	Commentator & Affiliation	Section	Comment	Response
1.	**Peer Reviewer #5**	Structured Abstract	**Methods:** Was any consideration given to refining/restricting the search timeline? Medical therapy and the devices themselves have improved a lot since the mid-1990s…For example, strategies to reduce inappropriate shocks, aldosterone blockade (1999), and more recently quadripolar CRT leads. This makes assessing the evidence base tricky as likely older studies contribute less to the current understanding of CRT than do newer investigations. Would also clarify if the authors themselves are meta-analyzing existing data, or summarizing the work of previously-published meta-analyses. More generally, I think it is important not just in the text but in the abstract and exec summary to be perfectly clear about which statements refer to patients with mild (NYHA I-II) vs severe heart failure (IIIIV). The concluding statement (see below) requires this in particular for context. **Results:** Again, as stated the results are very hard to place in context without knowing more about the patient population (though the text clarifies this somewhat). The statement that CRT-D vs CRT-P is "uncertain" seems contrary to the results of the COMPANION study where this was evaluated – both reduced hospitalizations, but only the CRT-D improved survival. While direct comparisons between these arms may be limited, "uncertain" implies it was not studied at all which is not the case, and there seems to have been a clear winner here. (Which arm of that study would the authors have preferred to be in?) **Conclusions:** The statement that "more data are needed to determine CRT effectiveness in non-LBBB" patients is incorrect. This has been looked at in both RCT settings and innumerable subgroup analyses, all of which point in the same direction, reflected in the updated CRT guidelines. It is both biologically and now scientifically implausible to suggest that pre-exciting the LV in someone for whom it is not activated late to begin with will be beneficial, and it may in fact be harmful (Echo-CRT, for example). It struck me as an omission not to comment specifically on response/nonresponse RATES as an important and oft-debated outcome in CRT studies. Similarly, characterizing the nature, incidence and predictors of "super-response" would also be of interest in this topic and more novel perhaps than summarizing existing meta-analyses.	**Methods**: In the current review, we sought to be inclusive. We acknowledge that both implanter experience and technological improvements have occurred over the study period. However, it was the opinion of our team that these differences over time did not preclude considering the earlier studies and including all studies, rather than excluding older studies, offered a more representative view of the impact of CRT on outcomes. In terms of harms, we explicitly state the dates of the studies reported. We performed multiple meta- analyses, where appropriate. We did not integrate existing meta-analyses into the new review. However, if inclusion criteria were met, the studies in the prior meta-analyses would be captured in our systematic review. Eligibility criteria and our approach for synthesis is described in the methods section of the review and in our protocol. We agree with the reviewer on the importance of defining impact on outcomes specific to NYHA class. We now specifically define for which NYHA classes these outcomes were assessed and any respective limitations in the systematic review conclusions. We made these changes to the abstract, summary, and concluding statement. **Results:** Our opinion is that the results of the COMPANION trial comparing CRT-P vs. D were uncertain. The study was reported to not be powered to compare CRT-P vs. D and did not report analyses to directly compare CRT-P vs. D. Without this direct comparison, the impact of CRT-P vs. D is uncertain. **Conclusions:** We agree with the reviewer that subgroup analyses from RCTs cast doubt on the efficacy of CRT-D in non-LBBBs compared to ICD alone. Subgroup analyses, however, have significant limitations, especially when not pre-specified. We also acknowledge that many single center cohorts with significant limitations point to

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				non-LBBB patients responding less than LBBB patients. These studies did not compare non-LBBBs with and without CRT. What the natural history would have been without CRT in non-LBBBs is unclear. At wide QRS durations, multiple studies have shown that LV activation delay may in fact exist in some patients with non-LBBBs (particularly those with wider QRS durations). Therefore, we believe that concluding that the simple presence of a non-LBBB indicates no LV activation delay is not correct. We did not include response rates since response is defined in a myriad of different ways (which is one of the chief limitations with the CRT literature). A response rate defined by change in EF is not comparable to that defined by symptoms. Similarly, "super-response" has been defined in many different ways and not the focus of this review. We do however, report ranges for the individual definitions of response.
2.	**Peer Reviewer #1**	Executive Summary	**Page 10, line 24:** This is not consistent with Guidelines; there is no indication for CRT in patients with EF > 35%. In patients with EF ≤ 35%, NYHA II, III, IVa, without indications for CRT but anticipating frequent pacing (> 40%), CRT could be considered as a IIA indication. **Page 10:** Scope and Key Questions: appear to be somewhat different from the Objectives stated in Page 5 **Page 11:** line 16-17: how about RBBB and non-LBBB **Page 11:** line 36: how about HF hospitalization **Page 12:** line 26-28: This sentence is not clear: "No conclusions could be drawn about the association between CRT-D implant and both ventricular arrhythmias and inappropriate shocks." The think the authors intended to say " no …….. CRT-D implant and subsequent appropriate and inappropriate shocks". **Page 14, line 41:** Significant bias on age is always present when deciding on CRT therapy even in RCTs. Because of this	**Page 10, line 24:** In this particular section, we do not state that this comes from the guidelines. This statement comes directly from the discussions with key informants, commenting on implantation practices in the United States in terms of CRT-P devices. **Page 10:** Both the objectives and scope describe the purpose of our review as assessing the effectiveness of CRT and predictors of response. We, however, have assessed this in patients with an EF≤35% and a QRS duration ≥120 ms. We have added this clarification to the objectives. **Page11, Line 16:** RBBB and non-LBBB were not part of our pre-specified subgroups of interest. **Page 11, Line 36:** Heart failure hospitalizations are one of the important outcomes we assessed. **Page 12:** We have clarified this sentence to read "No conclusions could be drawn about the

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			age bias, would either delete this sentence or put a qualifier regarding how many or % of very elderly patients (> 75-80 yrs of age) were included in these trials. This is a critically important issue in clinical practice. Very elderly is the fastest growing segment of our population, yet with least amount of data is available. **Page 14, line 51-55**: This reviewer would agree with the authors' suggestions, however, 3 points/questions could be raised: 1) it is surprising to see the impact of CRT-P vs. optimal medical therapy on non-mortality endpoints were not as robust as CRT-D vs. ICD since CRT (either D or P) should have provided similar "remodeling" mechanisms, and ICD does not; 2) would it be plausible that CRT-D could have provided more survival benefit than CRT-P to "allow" more time to demonstrate benefit from other non-mortality endpoint? 3) Would it possible that the pacing by ICD (from the conventional RV apex position) accelerated the progression of the underlying condition? **Page 15, Table 1,** Column "All-Cause Mortality": This reviewer agrees with the overall conclusion although the details stated in the column are not all correct. RAFT enrolled Class II (~ 80%) and III patients, no Class I patients. There was a change of enrollment criteria during the study because changes in Guidelines for CRT in class III patients. MADIT-CRT poses further challenges in the interpretation of the data. It enrolled class I and II ischemic patients but only class II for non-ischemic patients. The overall data from class I patients is very limited (~ 15% of the total enrollment). **Page 15, Table 1:** why a functional endpoint, i.e. 6-min walk, was not included in the analysis? It is an important "surrogate" endpoint for functional capacity. Inclusion of 6-min walk or some other functional outcomes would make the CRT response analysis more complete in addition to mortality, HF hospitalization, remodeling (LVESD), and HRQOL. **Page 16, line 10**: needs editing **Page 16, line 32:** confounding factors or confounders.	association between CRT-D implant and subsequent ventricular arrhythmias and inappropriate shocks." **Page 14, line 41:** We have added this limitation, noting "However, data for very elderly patients (> 75 years of age) were limited." **Page 14:51-55:1 and 2)** We believe that these apparent differences in effect reflect the differences in the level of evidence for CRT-D and CRT-P (i.e., quantity and quality of evidence) and not necessarily differences in the effect itself. **3).** Although possible and interesting, these explanations, including possible biological mechanisms, would be pure conjecture and are thus beyond the scope of our review. **Page 15, Table 1:** We thank the reviewer for this clarification. We have reworded this section to make it clearer. In addition, we have made changes to the report as a whole, calling attention to the paucity of data on NYHA class I patients. **Page 15, Table 1:** 6-minute hall walk distance was included in this review and is described in the main report text. We limited discussion in the executive summary to critical outcomes. **Page 16, line10:** We have made editing changes. **Page 16, line 32:** We have corrected this to "confounding factors." **Page 16, Applicability**: We have included the additional comment on limited data for the very elderly. **Page 17, line13:** We have made changes throughout the document to report results by NYHA class, specifically noting limitations for NYHA class I data.

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			Page 16, subsection Applicability: agree with the conclusions on race, gender and age. Please see my earlier comments on age. Page 17, subsection on Limitations: not very clearly stated; needs editing Page 17, line 13: would even further clarify that this trial, RAFT, only included class II (~ 80% of study cohorts) and III patients. There is little data on mortality, CRT-D vs. ICD from class I patients. Page 17, subsection Gaps: this reviewer agrees with QRS morphology/non-LBBB, AF, and CRT-D vs. CRT-P are gaps deserving consideration for future studies. Elderly patients with and without multiple co-morbidities require further studies. Value and cost effectiveness will need to be critically evaluated.	**Page 17, subsection gaps**: While we agree with the reviewer that studying the effects of CRT in an elderly population would be of interest, our systematic review did not find age to be an important determinant of response. In addition, subgroup analyses from the RCTs have not shown age to be an important effect modifier. Therefore, we did not include it as a variable requiring future specialized attention in a dedicated RCT. Cost-effectiveness Is outside the scope of EPC reports. We have proofed the section for grammatical errors.
3.	**Public Reviewer #2** Barbara Veath Director, Global Health Economics and Health Policy Medtronic, Inc.	Executive Summary	On page ES-7, it is stated that ?we considered the appropriate control for the CRT-D effectiveness question to be an ICD alone and for CRT-P to be optimal medical therapy alone. We did not assess the comparison of CRT-D to optimal medical therapy.? Medtronic does not disagree with this statement; however it would be beneficial to include a detailed rationale for why this decision was made for clarity. In the executive summary Medtronic also suggests that it be updated with respect to the changes mentioned in the rest of the sections below, including recognizing any impact of: ? Including the Individual Patient Data Meta-Analyses ? Including the evidence associated with the REVERSE trial ? Conclusions drawn from reconsidering the methods and conclusions of the subgroup analyses	We thank the reviewer for these observations and have added the following to the executive summary: "In addition, we considered the appropriate control for the CRT-D effectiveness question to be an ICD alone, given the robust data demonstrating improvements in mortality with an ICD that evolved concomitantly with studies of CRT effectiveness. We considered the appropriate control for CRT-P to be optimal medical therapy alone." In the introduction the following statement is added: "With the concomitant development of the implantable cardiac defibrillator (ICD), comparisons used in the large clinical trials changed to compare patients with ICDs with and without CRT." We did not conduct individual patient data meta-analyses. The REVERSE trial was excluded due to inclusion of patients with an LVEF≤40%. Multiple pre-specified subgroup analyses, such as gender, QRS morphology, were, however, commented on throughout the report.
4.	**Peer Reviewer #1**	Introduction	Page 21, line 39: similar to my comments to the Executive Summary: there is no indication for CRT therapy in patients with EF > 35%. An "upgrade" from conventional PM to CRT is	Page 21: In clinical practice, based on input we obtained from key clinical experts in the field, CRT-P is reasonable and often placed under these

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			indicated if conventional pacing, with pacing-mediated LBBB, causes HF or decrease in EF to < 35%. Page 22, line 16: the focus is on the Medicare population, but there is no emphasis and granularity from age related issues.	circumstances. We agree with the reviewer's point as to what the guidelines state; however, the guidelines in this case are more directed to CRT-D devices and less so to CRT-P. Page 22: There is no emphasis on the granularity from age-related issues because there are no RCTs, which was our pre-specified criteria, specifically studying an elderly population. We did, however, extrapolate our findings to an elderly population. We describe this in the Applicability section of the report. We also specifically examined age in the predictors section, finding no association between age and CRT responsiveness, recognizing significant biases in this literature exist.
5.	**Peer Reviewer #3**	Introduction	In the Background, the following is not completely true: "More recently, the indications for CRT expanded to include patients with minimally symptomatic heart failure (NYHA class I-II)." The recommendation for Class I is only a Class IIb recommendation, so for all practical purposes, Class I HF patients are not included in the expanded indications. This needs to be removed from the text throughout the document and "minimally symptomatic" should be changed to patients with less advanced HF symptoms. In the following sentence from the Background: "CRT-P devices are occasionally placed in patients who wish to avoid ICD shocks or in patients with an indication for frequent ventricular pacing due to conduction disease who have an LVEF between 36-50percent", the authors should add "right" between "frequent" and "ventricular".	We agree with the reviewer and have made changes throughout the document, taking care to separate out statements made for NYHA class I from II. We made the change to specify, "right ventricular pacing."
6.	**Peer Reviewer #4**	Introduction	The authors should reconsider the use of the term "congestive heart failure" which most consider to be outdated. Many patients with heart failure do not have congestion, particularly at the time of device implantation. On the other hand, many patients who do have congestion have heart failure with preserved EF , for which there is not sufficient experience to judge CRT but many theoretical reasons that it would be less useful. To keep the designation CHF, most have changed the term to chronic heart failure (in this case with reduced ejection fraction). The use of the term "occasionally placed" for CRT-P in heart failure is very US-centric and pro-defibrillator, as many more	The reviewer makes a valid point. Throughout the report, we have changed "congestive" to "chronic" to reflect current terminology. We thank the reviewer for these comments. We recognize that in Europe, CRT-P is utilized to a much greater extent, even in the traditional CRT-D eligible population. We amended the introduction, and Discussion, in the main report to highlight the elderly as a population who may wish to avoid shocks and may preferentially choose interventions to improve quality of life rather than those focused

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			CRT-P than CRT-D are placed in Europe, where there have been calls for even less use of the defibrillator with CRT. Furthermore, there is stronger rationale for CRT-P than the authors suggest as limited to "those who wish to avoid ICD shocks" and "LVEF between 36 and 50%", such as older patients who want to enhance quality of life but do not want to have to address potential inactivation of an ICD when they are facing death that may be timely. The authors do not show enough sensitivity to this issue, which is the subject of intense discussion in the geriatric field.	on life prolongation.
7.	**Peer Reviewer #5**	Introduction	Would also note in the "more recently" comments that note only have criteria grown to include mild CHF, but also recent guidelines have adjusted the strength of recommendations according to QRS type and width in particular. Also, while the topic is important and interesting, it might be worth noting WHY this report specifically (as opposed to the guidelines, innumerable reviews and metaanalyses already done in CRT) was deemed to be important or different from current literature in this area. Somewhat later the authors note the choice of studies and controls as a unique feature of this report – would move this up front to be clear about the conclusions, as adjudicating CRT-D vs OMT is different than CRT-D vs ICD as a control in particular.	We agree with reviewer as to the changes in current guidelines reflecting QRS duration and morphology and have added the following" In addition, the most recent guidelines for CRT implantation have called to attention the importance of both QRS duration and morphology." We agree with the reviewer that the section on what separates this review from past reviews/meta-analyses is important; however, it is the belief of the authors that the flow of the document is better with that section in its current position.
8.	**Public Reviewer #2** Barbara Veath Director, Global Health Economics and Health Policy Medtronic, Inc.	Introduction	Description of Indications Relating to Frequent Ventricular Pacing: On page 1 of the introduction, there is a brief statement alluding to other applications of CRT therapy: ?CRT-P devices are occasionally placed in patients?with an indication for frequent ventricular pacing due to conduction disease who have an LVEF between 36-50 percent.? While Medtronic recognizes that these patients are outside the scope of the analyses in this document, Medtronic believes that this statement should be updated to reflect the current state of evidence. There is now a large, randomized trial published demonstrating the benefit of biventricular pacing in patients who had indications for pacing with atrioventricular block, New York Heart Association (NYHA) class I, II, or III heart failure, and a left ventricular ejection fraction of 50% or less (Curtis, et al. N Engl J Med 368;17;1585-93). The benefit shown was a significant improvement in the primary outcome composed of	We thank the reviewers for these comments. We read the BLOCK HF trial with great interest; however, it was outside the scope of this review. We revised the text in the Introduction: "Our current review differs from prior reviews in that only patients with an LVEF≤35% and a baseline QRS duration≥120 ms undergoing biventricular pacing were included. These criteria were developed in consultation with our key informants and largely mirror the current U.S. appropriate use criteria for CRT. This eliminated the REVERSE,BLOCK-HF, and HOBIPACE trials, which included patients with LVEF's >35%." Description of response to CRT Therapy: The reviewers make valid points as to the appropriate use of the word "response". Whether no improvement or even a slight worsening in remodeling endpoints could actually be a marker of

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			time to death from any cause, an urgent care visit for heart failure that required intravenous therapy, or a 15% or more increase in the left ventricular end-systolic volume index (hazard ratio 0.73, 95% CI [0.59-0.89]). These results are even more meaningful considering that the benefit ascribed to the reductions in mortality and heart failure hospitalizations alone were statistically significant (hazard ratio 0.78, 95% CI [0.61?0.99]), excluding the contributions of LVESVI. There was benefit associated with all patients enrolled in the trial, with no interaction effect found in any sub-groups. This trial not only included patients with CRT-P devices, but also CRT-D. Finally, based on the strength of this evidence, this indication for CRT therapy has been approved by FDA and included in the European guidelines for pacing and CRT (European Heart Journal, doi:10.1093/eurheartj/eht150). The FDA approval was granted on 10-April-2014 (CRT-P was P010015/S205 and CRT-D was P010031/S381), and contains the following language regarding the indication: ?NYHA Functional Class I, II, or III patients who have LVEF<=50%, are on stable, optimal heart failure medical therapy if indicated and have atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.? Again, while this is outside the scope of the analysis as defined, Medtronic thinks it is important to mention in order to be reflective of the current state of evidence. Description of Response to CRT Therapy: Regarding the topic of response to CRT therapy, the brief description on page 1 states ??it is generally estimated that between 30-40 percent of patients receiving CRT derive what may appear to be little benefit.? This statement concludes that the benefit is known and is less or meaningless for non-responders. While it is true that some derive less benefit than others, the absolute amount of that benefit is less clear without a direct comparator not receiving CRT therapy.	“response” in some patients, as they may have gotten much worse without CRT is certainly possible. For this reason, we worded this section using quotations around the terms responders and non-responders and used the terminology “what may appear to be of little benefit” as below. “While the percentage of “non-responders” to CRT fluctuates greatly, primarily based on how one defines “response”, it is generally estimated that between 30-40 percent of patients receiving CRT derive what may appear to be little benefit.”

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			This topic has been described as a ?myth? (JACC Vol. 53, No. 7, 2009, p. 608-619). It is possible that this was born from the language generally used in publications that classify patients with terms such as ?improved?, ?unchanged?, and ?worsened?. This has led to the conclusion by some that those in the ?unchanged? category have received little or no benefit from CRT therapy. Since heart failure is a progressive disease, one might intuit that a patient whose status has not changed over time actually has received benefit. There is evidence in the acute setting that cessation of CRT therapy in ?non-responders? leads to rapid deterioration of hemodynamics (Mullens W, et al. J Am Coll Cardiol 2009;53:600 ?7). There is also evidence that patients categorized as ?unchanged? do experience a mortality benefit from CRT therapy (AHA abstract number 16318 ? 2014, https://aha.apprisor.org/epsAbstractAHA.cfm?id=2). In this presentation, based on a pooled analysis of 1,609 patients from 5 clinical trials, there was a mortality improvement in the ?unchanged? patients as compared to those categorized as ?worsened? (unadjusted 18 month mortality rate 0.34 [0.18-0.65]). Because of this, Medtronic suggests a more nuanced description of the topic of response, acknowledging that there is less certainty about whether or not those in the ?unchanged? category have or have not received benefit, and that there is some current evidence suggesting that these patients experience a mortality benefit.	
9.	**Peer Reviewer #1**	Methods	This reviewer primarily provides a content review. The methodology appears to be solid and robust. Weakness of including RCTs needs to be taken into consideration Page 27, PICOTS table: one potential weakness is overlooking the exclusion criteria of the RCTs, particularly regarding predictors, i.e. predictors could not be identified if patients were excluded from the trials.	As we believe appropriate, the effectiveness questions were limited to RCTs. We do not feel that their more narrow patient population is limiting and have not made the suggested change.
10.	**Peer Reviewer #2**	Methods	Are the inclusion and exclusion criteria justifiable: Yes Are the search strategies explicitly stated and logical: Yes Are the definitions and diagnostic criteria for the outcome measures appropriate: Yes	We thank the reviewer for the comments.

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			Are the statistical methods used appropriate: Yes	
11.	**Peer Reviewer #3**	Methods	Their methods are robust. In the following: "CRT-D was found to be effective in reducing heart failure hospitalizations, inducing ventricular reverse remodeling, improving quality of life, and increasing six-minute hall walk distances compared to an ICD alone with a high strength of evidence." What about mortality (in comparison with OMT it does, but if they do not want to include this comparison, then they need to state compared with what? Under outcomes, why did the authors not look at mitral regurgitation? Why did they not look at biomarkers? Also, they present data on ventricular arrhythmias and inappropriate shocks, but they do not list these in the table of outcomes, why not? For many of their data of interest, the authors said they contacted the authors of the original citations to get the missing data. As someone who has done systematic reviews, my experience has been that the rate of response from the authors of the articles is pretty low. The authors should provide information on the response rate and completeness of the data they end up receiving from the primary authors. I would not combine data on patients with class I HF symptoms and those with class II HF symptoms. The level of evidence is very different for these 2 groups and again the guidelines lump the recommendations for patients with class II HF symptoms with those for patients with class III HF sxs not patients with class I HF symptoms and the only recommendation on class I patients is a class IIb recommendation. Why did they exclude CRT-D vs. OMT comparison? Why is ICD only not listed as a comparator of interest?	Given the current indications for ICD implantation, we did not believe that the proper control group for CRT-D was optimal medical therapy. The mortality outcome was left out of that particular statement as we determined mortality to have moderate strength of evidence rather than high. We selected what we believed to be the most clinically relevant outcomes. As such, we decided not to include changes in mitral regurgitation and biomarkers. Data on ventricular arrhythmias and inappropriate shocks were included under harms section. We contacted the authors for 24 articles but only received the information for 2 articles. We agree with the reviewer in terms of the issue of NYHA class I patients. We have made changes throughout the document separating out statements for class I vs. class II patients. We explain the comparators selected in the first part of this response section.
12.	**Peer Reviewer #4**	Methods	No problems here that I see, can't address the complex statistical methods	Thank you for the comment.
13.	**Public Reviewer#1** Laura Blum, Heart Rhythm Society	Methods	Overall, the authors employed sound methodology in their search and abstraction for assessment of risk for potential bias and ensuring that the highest possible level of evidence could be reviewed. Meta-analyses were performed when feasible. However, HRS has the following concerns:	1). The article by Goldenberg (N Engl J Med. 2014 May 1;370(18):1694-701) was after the search date for our draft report and was identified in our updated search for the final report. The study has, however, not changed our conclusions in terms of

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			1) Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT): HRS is concerned that this review did not include the post-trial analysis of MADIT-CRT that was published on March. 30, 2014. HRS believes that this study significantly changes the recommendation on survival benefit with CRT-D on minimally symptomatic heart failure patients. 2) Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial: HRS is concerned that the results of the COMPANION trial were not judged as moderate evidence. COMPANION was the largest CRT device trial ever undertaken and the first CRT device trial designed to study the composite of death and hospitalization as a primary endpoint in heart failure patients. All patients in COMPANION were on optimal pharmacologic therapy (OPT), so that the results were obtained in an already maximally medically treated population. The results of COMPANION showed that, as compared with optimal pharmacologic therapy alone, cardiac-resynchronization therapy with a pacemaker(CRT-P) decreased the risk of the primary end point (hazard ratio, 0.81; P=0.014), as did cardiac-resynchronization therapy with a pacemaker?defibrillator (CRT-D) (hazard ratio, 0.80; P=0.01). The risk of the combined end point of death from or hospitalization for heart failure was reduced by 34 percent in the CRT-P group (P<0.002) and by 40 percent in the CRT-D group (P<0.001 for the comparison with the pharmacologic-therapy group). A CRT-P reduced the risk of the secondary end point of death from any cause by 24 percent (P=0.059), and CRT-D reduced the risk by 36 percent (P=0.003). As a randomized clinical trial, COMPANION did not examine issues related to the distinction between CRT-D versus ICD; other meta-analysis supports a mortality benefit. 3) Comparison CRT-P vs. CRT-D: HRS questions the utility of the comparison between CRT-D and CRT-P within the criteria used to conduct this review. The review was conducted solely on studies that recruited patients with LVEF?35% and QRS duration >120 msec. Based on the current guidelines, all of these patients qualify for an ICD (unless patient prefers not to have one). Comparing CRT-D with CRT-P does not add any clinical value within the framework proposed by the authors. In	mortality with CRT-D in minimally symptomatic patients. The study by Goldenberg et al. reported mortality only in the bundle branch morphology subgroups and not in the population as a whole. In addition, there was significant patient drop out rate. For these reasons, while the new analysis reported in the Goldenberg paper was included, it did not elevate the strength of evidence for the outcome of mortality when assessing CRT-D. 2) The judgment with regard to weight of evidence takes more into account than statistical significance. COMPANION was rated as moderate risk of bias based on multiple factors. 2 and 3) We thank the reviewers for these comments. As the reviewer points out, the COMPANION trial was the only RCT to include both CRT-D and CRT-P arms in patients with an EF ≤35%. A comparison of these two groups was not reported, yet the Kaplan Meier curves of the two are fairly similar. In our key informant calls, there was a strong desire to further look at this comparison, as the key informants noted that the incremental benefit of an ICD on top of CRT remains uncertain.. Outside the U.S., CRT-P is implanted with much greater regularity in patients with an LVEF ≤35% (i.e. an ICD eligible population). 4) As the reviewer points out, in ICD eligible patients, CRT-P is only used in uncommon circumstances (at least in the U.S.) where an ICD is not desired. As such we determined in this situation that the best control is OMT alone. The current systematic review was designed to be comprehensive evaluating both CRT-D and CRT-P. CRT-P may be used more often in an elderly ICD eligible population based on patient preferences, such as the avoidance of shocks. 5) Adverse events: In the harms sections, both RCTs and cohort studies were considered. For the RCTs the percentages for both the CRT-D arm and

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			addition, the best level of evidence is rated ?low? and the COMPANION trial did not study this comparison. It is likely that additional studies will not be done in this area as all these patients qualify for an ICD. Evidence shows that for patient with a LVEF ? 35% and who need a CRT, CRT-D is the choice (unless patient prefers not to have an ICD) AND CRT-P should be reserved for patients with EF between 36-50%. Therefore, HRS recommends excluding the comparison between CRT-D and CRT-P from the manuscript. These comparisons, although done using robust statistical techniques, are not useful in clinical practice. 4) Comparison CRT-P vs OMT: A similar argument can be made for the comparisons between the CRT-P and medical therapy. Since the inclusion criteria were LVEF ? 35% and QRS >120 msec, all those patients should be receiving an ICD except for patient preference. As such, HRS recommends that comparisons between CRT-P and medical therapy should follow the use of CRT-D in New York Heart Association (NYHA) III-IV patients. 5) Adverse Events: HRS has some concerns about the reporting of adverse event percentages. In Table 18, only the total percentage of complications is currently listed. HRS believes that it may be more appropriate to list the differences in outcomes, especially in RCTs that compared the CRT-D and ICD group. There is wide variability in adverse event reporting that is difficult to comprehend from a clinical and practical standpoint. On one side, the authors comment that CRT-D may have a higher infection rate compared to CRT-P. However, when examining the adverse event profiles comparing CRT-D to ICD vs. CRT-P to medical therapy, CRT-P implantation appears to have significantly higher adverse events, especially with respect to pocket hematoma, infection and lead dislodgement. The current reporting of adverse events highlights two issues: a. The authors did not consider the improvement in LV lead technology and implant delivery systems over the past decade. Most of the CRT-P studies are older whereas the CRT-D studies considered are more recent (within the past 5-6 years). As with many learning curves, complication rates improve until physicians become proficient with the new technology.	ICD alone arm are reported. For the cohorts with a single CRT-D arm, just the total complications are reported. Including both study designs we believe to be important to provide a better sense of what the true complication rates are in the general populations (not just those included in RCT's). In terms of the reporting of harms for CRT-P and the outlier studies (e.g., the 17% dislodgement rate was seen in a cohort of 21 patients), we reported both the dates of the studies and total number of patients. The size of the studies was taken into account when making our assessment of the data 6) We thank the reviewer for this comment. The follow up times for the harms studies are reported in the tables and allow the reader to assess adequacy of follow-up time. 7) Our opinion is that total hospitalizations could be misleading. The CRT population is a sick population, often with many concomitant co-morbidities. Hospitalization for other causes would surely get captured in total hospitalizations. Therefore, we decided to focus on harms likely to be directly related to the CRT implantation. 8) We agree with the reviewer that a mechanistic discussion of the predictors would be interesting; however, we believe this falls outside the scope of this systematic review. 9) We thank the reviewer for these comments. 10) As the reviewer cites, a pacing myopathy is often determined after the fact when a patient with frequent RV pacing improves with CRT upgrade. Defining patients who clearly have a pacing myopathy prior to CRT (e.g. as opposed to having a worsening NICM) is challenging and beyond the scope of this report. Therefore, such an attempt to specifically examine this population was not made. 11) We appreciate the reviewer's comments.

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			b. The reporting difference between larger RCTs and smaller cohorts were independent validation (like a steering committee) of adverse events is not present. It is doubtful that a 17% lead dislodgement rate still exists in the present day, given the advances in lead technology and delivery systems. These should be mentioned as a potential issue in adverse event reporting; and as such, these data reported should be approached with caution. 6) Short Follow-Up Period: The design of the studies also captures few CRT replacements due to their short follow-up period. If the trials had been extended past the typical battery longevity, patients would have likely needed procedures related to generator changes with their associated risks for complications. Fortunately, the latest generation CRT LV leads and generators seem to have enhanced battery longevity. 7) LV Lead: Published literature has demonstrated that there is a clear increased rate of complications from the left ventricle (LV) lead. Unfortunately, the draft report only examines hospitalizations related to heart failure complications despite the need for repeat procedures or repeat hospitalizations related to complications of the LV lead. The analysis of total hospitalizations might have shown a less positive result. This explains why clinical guidelines recommend caution in LV lead placement for patients who are less likely to benefit (Class I vs Class II-III or less likely to respond). 8) Additional Explanation Needed: It would be beneficial to provide the explanation of the potential mechanisms as to why females, LBBB, and NICM have superior outcomes as this would be very useful for the reader. 9) Limitation of Existing Data: We applaud the authors for commenting on the limitations of existing data in making any definite conclusions on several predictors such as right bundle branch block (RBBB), Interventricular Conduction Delay (IVCD), variable QRS duration, as well as atrial fibrillation (AF) and chronic kidney disease (CKD). Although LBBB and normal sinus rhythm (NSR) patients have been shown to do better, the converse is not necessarily true and additional data is needed to have a better handle on the predictors.	We believe that including our opinions as to possible mechanistic reasons for the predictors is outside the scope of this systematic review. Number needed to harm could not be calculated since no meta-analysis could be performed for the harm outcomes. For the few meta-analysis for the effectiveness outcome that were performed, we did not feel adding NNT would provide significant value.

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			10) Missing Data from the Report: Unfortunately, no data is presented to address pacing induced cardiomyopathy and role of CRT in those patients. HRS believes that this is an important aspect of CRT use and should be addressed in such a comprehensive manuscript. 11) Additional Items for Consideration: a. It would be beneficial for the authors to list information on number need to treat (NNT) or number needed to harm (NNH) whenever applicable as that adds to the practical applicability of the data. b. It would be important for the authors to discuss potential mechanisms behind the favorable (for example: Female sex) and unfavorable predictors (for example: non-LBBB morphology) for the reader. Data Inaccuracies	
14.	**Peer Reviewer #1**	Results	Page 36, table 5: the CARE-HF primary study was published in 2004 Page 37, table 7, line 46: survival data from class I patients is either Low or Insufficient, CRT-D vs. ICD. Page 40, subsection Participant Characteristics: a detailed dissection of the age groups will be critically important to address CMS questions. Page 47, last paragraph: the discussion is not granular enough. The authors continue to group class I and II patients together in this discussion. There are major differences between MADIT-CRT and RAFT. MADIT-CRT enrolled class I patients with ischemic HD only (~ 15% of the study cohorts). RAFT enrolled class II and III patients; there were no class I patients. Page 52, figure 7a: it is not surprising HRQOL was not significantly affected since these patients were minimally symptomatic at baseline, i.e. what is there to improve from the patients' point of view? Page 58, table 12, last column on All-Cause Mortality: again, RAFT did not enroll class I patients.	Page 36, Table 5: fixed Page 37, Table 7: fixed Page 40: In all of our patient characteristics sections for the various key questions, patient age is the first variable specified with age ranges given. Page 47: We agree with the reviewer and have amended statements on NYHA class I vs. II throughout the document. Page 52, figure 7a: The majority of minimally symptomatic patients had class II symptoms; therefore, improvement could be possible. We believe it was important to include outcomes important to patients, including symptoms. Page 58, table 12: We recognize RAFT did not include NYHA class I patients. We changed the wording here to make this clearer. Page 85, second paragraph: For meta-analysis, only data from one report for each study was included.

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			Page 85, second paragraph: all of these studies were from CARE-HF reported from different follow up duration. This poses an interesting question: were these reports from the same RCT taken as a single study or multiple studies for the meta-analysis? Page 99, line 39: “by 3 months”?? 3 days? Page 99, table 32: same study listed twice in the table? How could pneumothorax occur in medical therapy patients? The authors probably did not understand the nature of these different therapies. Page 101, table 33: hematoma is only a concern during the short term post op period (hours to days). It is not a concern at 6 or 12 months follow up. I believe the Gras’ study is again reference twice while the medical arm should not have had any hematomas. Page 102, table 36: there should be no lead dislodgement for the medical therapy group!!! Page 124, table 47: Most of the information in the CRT-P vs. OMT is either irrelevant or incorrect because there is no procedure for patients randomized to OMT!!! Consequently, this reviewer worries about the overall analysis and conclusion in the entire section (CRT-P vs. OMT) Page 135, table 52: Would highlight extreme caution to draw conclusions on age due the selection bias and the very limited data from the very elderly.	The unit of analysis is the study not article or report. Page 99, line39: We clarified this to state “3 months follow-up.” Page 99, Table 32; Page 101, Table 33; Page 102, Table 36; Page 124, Table 47: The problem arises with the paper by Gras et al. In this paper, 65 patients from the “medical therapy arm of CARE-HF” actually received a CRT-P device. Therefore, there should be only one arm. The table was corrected. Page 135, Table 52: We thank the reviewer for this comment. We note this limitation and have commented on selection bias in other parts of the report.
15.	**Peer Reviewer #2**	Results	Is the amount of detail presented in the results section appropriate? – Yes, if anything too much. Are the characteristics of the studies clearly described? – Yes, mainly through the tables? Are the key messages explicit and applicable? – For the most part, yes. When you refer to predictors of response in sub-groups, do you	We thank the reviewer for the comments. The subgroups were chosen based on information from key informants in the field of heart failure and CRT. Better outcomes in women do not necessarily mean lack of response in men. We have made appropriate edits for the typographical errors.

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			mean to say that these sub-groups had greater effect sizes? Are you referring to formally test quantitative and/or qualitative interactions? In particular, when you note better outcomes with female gender, does that mean that CRT therapies are not effective in men? Are figures, tables and appendices adequate and descriptive? – Yes, note that in some places you say QRS > 120% when you mean QRS > 120 ms. Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? – Not that I know of. Some readers may be disappointed that you did not consider the trials that focused on patients with QRS < 120 ms, but I understand that this was not within the scope of your assignment.	
16.	**Peer Reviewer #3**	Results	I would not combine data on patients with class I HF symptoms and those on patients with class II HF symptoms. The level of evidence is very different for these 2 groups and again the guidelines lump the recommendations for patients with class II HF symptoms with those for patients with class III HF sxs not patients with class I HF symptoms and the only recommendation on class I patients is a class IIb recommendation.	We agree with this comment and have made necessary changes throughout the document to make this distinction more apparent.
17.	**Peer Reviewer #4**	Results	CRT-D vs CRT-P: As we have to draw conclusions from imperfect data, it would be helpful to summarize the endpoints for which CRT-D and CRT-P would be expected to be similar or different, then indicate when the data is specifically present and its strength. For instance the physiology of the disease and mechanism of the therapy would make it unlikely that CRT-D would decrease HF hospitalizations or improve 6 minute hall walk more than CRT-P if used in the same patients. On the other hand, it is possible that CRT-P might reduce death less than CRT-D. With regard to predictors of good or adverse outcome with CRT, we are unlikely to have detailed subgroup data on predictors in all groups; until/unless we do, it would be reasonable to assume that the factors that predict POOR response of usual CRT endpoints such as function and QOL with CRT-D are not likely to be associated with better outcomes in CRT-P. This is particularly important as RBBB is associated	We agree with the reviewer and have added the following to our CRT-P section: “However, of the outcomes that were assessed, the ICD function would impact only the mortality endpoint. Therefore similar conclusions as to those noted for CRT-D can be drawn for CRT-P devices for the other, non-mortality endpoints.” Page 68: We considered different harms and adverse events; complications are only one type. We believe that length of stay was an important outcome and chose to include it within the harm section, though we acknowledge the reviewer’s point that the cause of hospitalization is not specified.

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			with WORSE outcomes, particularly in patients with NYHA II disease, and should be assumed to be adverse for CRT-P as well. In fact, it would be particularly important to avoid deleterious outcomes from CRT when implanting a device with no other purpose. Page 68: It does not seem appropriate to include total number of days hospitalized together with harm in the "length of hospital stay". The thrust of this section is complications, many of which might prolong the initial hospital stay, and a few of them might cause later re-hospitalization. Total number of days hospitalized is usually an outcome for which heart failure is a dominant contributor compared to device harm. Inappropriate shocks: Table 21 should include the % of pts with inappropriate shocks in the 2 groups for each of the studies listed, clarifying the groups. This is the more important information, currently discussed above in text, please add to the table. page 156 line 17 and page 160 line 16, I think this is a pasting error, as age is in the row for QRS duration for both tables.	Thank you. We have added the details about Inappropriate shocks to the table as suggested.
18.	**Peer Reviewer #5**	Results	I am a little surprised that nothing at all could be said about inappropriate shocks, if only to summarize the data presented in the major studies. I'm surprised the authors conclude there is insufficient evidence to support a survival advantage for CRT-D in severe heart failure, particularly NYHA III. CRT-D improved survival in COMPANION. CRT-P improved survival in CARE-HF, and the weight of evidence from RAFT and other studies indicates that adding an ICD either helps or at worst is neutral on survival. Thus it seems hard to argue that there is insufficient data to make a comment on all-cause mortality. Put another way, could the authors really imagine an RCT comparing CRT-D to either CRT-P or an ICD alone in patients with NYHA III CHF, low EF, LBBB etc? I think such a study ("COMPANION-II", if you will) would be hard to sell to an IRB, let alone clinicians or patients. (Which arm of THAT study would the authors want to be in?) NYHA Class IV is another story, however, as these patients are generally not indicated for an ICD unless expected to receive a transplant. So perhaps III/IV need to be treated differently here.	In our review, the comparator for CRT-D was an ICD alone. The COMPANION trial did not have such an arm. The other studies of CRT-D in class III and IV heart failure with an ICD alone were not compelling in terms of a mortality advantage. In minimally symptomatic heart failure, RAFT showed a mortality advantage but the shorter term follow up of MADIT-CRT did not. The longer term follow up of MADIT-CRT showed a mortality advantage in only LBBB patients but did not report mortality statistics for the group as a whole. In addition, significant numbers of patients were lost to follow up. For these reasons, we determined the strength of evidence for CRT-D vs ICD alone to be moderate.

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19.	**Public Reviewer #2** Barbara Veath Director, Global Health Economics and Health Policy Medtronic, Inc.	Results	Regarding the Subgroup Analyses: In the technology assessment, the subgroup analyses are described individually. Medtronic believes that it is more appropriate to look at the interaction effect to assess for differences between groups (DOI: 10.1002/sim.1296). Sub-group analysis presented in the assessment either did not use interaction tests to assess differences in sub-groups or they were not presented. Medtronic believes these data are important to help fully understand subgroup results. It has been well documented that caution must be used when significant sub-group results are found. There are numerous examples where subgroup results are found in a study only to be later disproven. The Individual Patient Data meta-analyses (described in the comments on the Appendices) provide an excellent opportunity to assess subgroups as it combines data from multiple studies and provides greater power to assess subgroups which single studies rarely have. Regarding the text in this assessment associated with predictors of response, the conclusions seem stronger than warranted in some cases. Language characterizing response predictors such as ??were strongly predictive?? (page ES-5), and ?is predictive of? (Table 52) overemphasizes the role of the unpowered, retrospective analyses that were done to support these statements. Medtronic suggests that alternative language, such as ??is correlated with?? would be more appropriate. Regarding the Evidence of Mortality Benefit of CRT in NYHA Class III/IV: As described in the comments on the Appendices, Medtronic strongly believes that the Individual Patient Data meta-analyses should be included in this assessment. With the additional power enabled by access to the detailed data from a number of randomized clinical trials, stronger conclusions can be made. From the Cleland 2014 manuscript: ?Interactions between CRT and other covariates were not significant in a multivariable model that included QRS duration. Similar reductions in all-cause mortality were observed with CRT regardless of? NYHA	We completely agree with the authors on the limitations of subgroup analyses. For that reason, we tempered our conclusions for certain subgroups, such as patients with atrial fibrillation or those with a non-LBBB. Determining interaction effects requires patient level data, which was generally unavailable. We agree with the reviewers and have modified the language in the section on predictors of response, where applicable. We did not include past meta-analyses in our review. In addition, we decided to include RCTs alone in answering the effectiveness questions. Unavoidable confounding, in even high quality analyses as the reviewer cites, is still likely to be present and it was therefore not included. We considered the IPD analysis to be a pooled analysis of selective trials and therefore did not include it in our discussion of other systematic reviews.

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			class??. In addition, while Medtronic recognizes that the methods of the assessment limited the efficacy analysis to include only the evidence from randomized controlled clinical trials, Medtronic feels it would be helpful to acknowledge that real world evidence in large populations does add perspective on the issue. Specifically, high quality analyses from the NCDR ICD Registry have shown an association between the use of CRT-D and mortality benefit as compared to ICD therapy in patients with LBBB, regardless of gender (AHA 2014, abstract #13355; http://www.abstractsonline.com/pp8/#!/3547/presentation/48337).	
20.	**Peer Reviewer #1**	Discussion	Discussion/ Conclusion: Page 161, first paragraph: this reviewer continues to have difficulties with moderate strength of evidence for class I patients. Page 161, last paragraph: there is insufficient data to conclude on patients with advanced age. Page 163, table 60: same comments on mortality in class I patients	We agree with this reviewer and the prior ones, in terms of NYHA class I patients. The text has been modified throughout the report to reflect evidence specific to class I patients. We have also included a statement on the "very elderly", noting limited data.
21.	**Peer Reviewer #2**	Discussion	Are the implications of the major findings clearly stated? – Yes Are the limitations of the review/studies described adequately? – Yes In the discussion, did the investigators omit any important literature? – No, nothing important omitted. Is the future research section clear and easily translated into new research? – For the most part, yes. However, I wonder whether there would be equipoise when considering CRTD vs ICD alone in advanced heart failure (Table 62) when it is already established that CRT-D improves quality of life. If there is little additional harm and clear improved quality of life, how could we justify withholding CRT-D from patients suffering from advanced heart failure? I also wonder	We thank the reviewer for these comments. We recognize the mortality benefit of defibrillation and therefore included ICD, not OMT, as the comparator for CRT-D. We did not speculate on incorporating real-time imaging for CRT implantation, but is something that may be examined as the technology and literature develops.

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			about the value of research into improving response, e.g. by incorporating imaging into CRT implantation to see effects on resynchronization in real time.	
22.	**Peer Reviewer #3**	Discussion	In the Limitations, they need to acknowledge that they could not examine important determinants of response like device programming, left ventricular lead placement, type of left ventricular lead, etc.. They also could not account for variability in optimizing programming after the procedure etc.. Other gaps in knowledge that require more research are: Do patients with severely dilated left ventricle benefit from CRT? Do patients with significant right ventricular failure benefit from CRT? What are the benefits and risks of CRT in patients with advanced kidney disease? What is the effect of CRT on the risk of ventricular arrhythmias? CRT in patients with AF: do patients with AF benefit from CRT? Does CRT reduce the burden of AF? And very importantly, how could one treat non-responders?	There are potentially hundreds of reported possible determinants of response, especially if isolated technical aspects are examined. We chose to focus on those we and our key informants believed most important. We also recognize there are additional subgroups which may be examined in the future.
23.	**Peer Reviewer #4**	Discussion	Discussion/ Conclusion: Some of the comments regarding conclusions relate to data discussed above in Results. The data used to drive their conclusions regarding benefit in patients with QRS over 120 seem has been interpreted differently by others. Most patients in the major trials had QRS > 140-150, for whom benefit is appropriately assigned. Rather than concluding that there is not enough information to make different conclusions for QRS < 140, we could also conclude that there are not enough patients from the trials to convincingly demonstrate benefit for patients with QRS < 140. This is particularly important for a device which may confer additional risk compared to ICD. Table 64 and related text: the characteristics of a study to evaluate effectiveness of CRT-D in afib must specify how AV nodal ablation will be used to control rate, as the % pacing is critically important in this population. Regarding future research, the authors need to distinguish what would require	We agree with the reviewer that the evidence for effectiveness of CRT is not as strong in patients with a narrower QRS. The issue is further complicated by bundle branch block morphology which is intimately related to QRS duration. We believe the data were conflicting (again often confounded by bundle branch block morphology) on QRS duration, leading to a conclusion that more data are needed to determine that CRT does or does not benefit patients in the QRS duration 120-150 ms range. Table 64 and related text: We agree with the reviewer and have amended this table, noting the role of AV node ablation. Future research: We agree with the reviewer that a trial of CRT-D vs CRT-P in the U.S. may never occur. This is not to say that it would be inappropriate. As the reviewer points out, perhaps in an octogenarian population (a population which represents up to 30% of current implants) such a

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			randomization and what could be done with non randomized experience, such as CRT-D for non-left bundle branch block. it doesn't seem that the authors have considered carefully which randomizations are actually feasible in the U.S. For example, how could you do a study in the use that randomizes patients with low EF to CRT with an ICD or no ICD? Probably the only people willing would be patients who would be more likely to choose CRT if not in a trial, who are older with more co-morbidities, or patients unable to under stand the differences. (I do agree however that trying to understand this decision about CRT-P vs CRT-D is one of the most urgent for us to address, particularly in the elderly who clearly benefit from CRT in terms of function and QOL, but are probably less likely to have meaningful life extended with an ICD.)	trial could be done. In Europe, CRT-P is used in a much broader fashion even in younger patients who would be ICD candidates.
24.	**Peer Reviewer #5**	Discussion	Many points above apply to the discussion/conclusions. Again, I am surprised that the authors persist in advocating for "further research" regarding patients with non-LBBB morphologies. If the authors will insist on a dedicated, specific, focused RCT on every subgroup imaginable for CRT, they will continue to be disappointed. The fact is that non-LBBB morphologies SHOULD NOT respond usefully to CRT, and in fact they do not. There is no study or subgroup analysis I am aware of suggesting otherwise. This issue really seems well beyond equipoise to me, as reflected in the recent guidelines update, which go further to emphasize that the benefits of CRT are clearly concentrated in those with not simply wide (>120) but very wide (>150) QRS complexes of LBBB type. I think the most staggering research gaps left by the existing high-quality evidence are really to figure out who, from the population already defined, benefits from CRT and who does not; why, whether and to what degree "CRT optimization" (variously employed) makes a difference; whether quadripolar LV leads will make a difference in response; the value of algorithms such as adaptive CRT; and others. Would the authors really advocate for instead focusing limited resources on a trial of CRT in RBBB patients? Or those with QRS 120-130? To emphasize that further, the Conclusions as stated are basically the bottom line clinical trial results from RAFT, COMPANION, and CARE-HF (without the specificity of which	We thank the reviewer for these comments. We respectfully disagree that the issue of lack of CRT response in non-LBBB patients has been conclusively proven by the existing data. We agree with the reviewer that non-LBBB patients appear to have less benefit than LBBB patients. We also recognize that subgroup analyses from COMPANON and MADIT-CRT point to no benefit with CRT-D compared with an ICD alone in this population. We believe, however, that subgroup analyses have inherent limitations that prevent us from concluding definitively a lack of benefit. There have been multiple studies demonstrating LV activation delays in patients with non-LBBB morphologies, especially those with broader QRS durations. There are also studies suggesting that QRS duration is the driver of response (not QRS morphology). We do not advocate an RCT on every subgroup, but, for this subgroup, suggest that one is needed. Non-LBBB (RBBB and IVCD) represent up to 30% of current U.S. device implants and would be a feasible study to perform. We agree with the reviewer that the conclusions need to be changed to emphasize the lack of data for Class I patients. Changes in terms of separating out class I patients have been made throughout the report.

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			NYHA classes are included in the statements). Given the amount of effort invested by the authors in this work, I found this a surprising place to end.	
25.	**Public Reviewer #2** Barbara Veath Director, Global Health Economics and Health Policy Medtronic, Inc.	Discussion	Regarding the Evidence Associated with the REVERSE Trial: Medtronic believes that the published evidence associated with the REVERSE study (page 144) is appropriate to include in this assessment, and brings unique value to understanding the effectiveness of CRT therapy in the mild heart failure population. While a distribution of EF data was not published, an analysis of our database shows that 92.6% of patients had an EF<=35% at enrollment in REVERSE. Therefore Medtronic believes REVERSE is substantially representative of the patients that are in the scope of this assessment. In relief to the strict inclusion criteria in this assessment, consider the approach used in the recent ARHQ document ?Assessment on Implantable Defibrillators and theEvidence for Primary Prevention of Sudden Cardiac Death? (http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id91TA.pdf). While the scope of the document was for the primary prevention population, the inclusion criteria allowed for trials that had a small amount of secondary prevention patients (the trial needed to have >= 80% primary prevention patients, not 100%). This allowed the inclusion of the RAFT clinical trial, which was excluded in the initial assessment draft, to the betterment of assessing the therapy. The conclusion of one of the key questions was altered from the draft assessment to the final version as a result of this inclusion. Inclusion of the evidence associated with REVERSE will not only corroborate and strengthen the already positive assessment of CRT therapy, it will provide data that will help understand some of the current gaps. REVERSE provides good prospective data on Clinical Composite Response and LVESV, which are outcomes of interest and not otherwise available for the mild heart failure population. In addition, there is a strong retrospective analysis that can shed some light on the value of CRT-D therapy in addition to CRT-P. Specifically, multi-variable analysis comparing outcomes within the CRT-D and CRT-P cohorts of REVERSE showed CRT-D implantation to be a strong predictor of increased survival (HR=0.35,	We determined the eligibility criteria *a priori* with input from CMS, AHRQ and key informants. We chose the LVEF≤35% cutoff based on clinical guidelines and input from experts in the field. Unfortunately, this study did not meet criteria to be included.

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			p=0.003, DOI: 10.1161/CIRCEP.113.000570).	
26.	**Public Reviewer #2** Barbara Veath Director, Global Health Economics and Health Policy Medtronic, Inc.	Appendices	Regarding the Individual Patient Data Meta-Analyses: There are two significant pieces of evidence related to individual patient data meta-analysis that were excluded from consideration (page E-13). Medtronic believes that the individual patient data meta-analyses (Cleland, NICE) bring novel understanding of the effectiveness of CRT therapy, and thus should be included in this assessment. First, the patients included in the assessment meet the scope of the assessment (LVEF<=35%, QRS>=120ms). Second, though the reason given for exclusion (No original data ? page E-13 of the appendix document) can be interpreted as a valid reason, the fact that it is an ?individual patient data meta-analysis? necessarily means a new and expanded understanding of the existing data that is not readily replicated without access to the data. In fact, the AHRQ assessment acknowledges as a limitation that ??we did not conduct individual patient data meta-analysis to assess predictors meaning that our analyses may suggest that clinically relevant subgroup effects exist, but we are unable to quantify the effects reliably or precisely. ? (page E-8 of the executive summary). Finally, as mentioned in the comments earlier in this document, these meta-analyses bring novel understanding of the data that directly address outcomes of interest (e.g. mortality benefit of CRT in NYHA class III/IV) that are lacking in the current draft assessment. These are the first individual patient data level meta-analyses for CRT and provided stronger power, due to larger sample size and increased number of endpoint events, to detect differences in effect by various sub-groups. Further, subgroup-analyses had largely been limited to univariate findings. These analyses use a multivariable approach in an effort to tease out how strong the effect is with each variable. A key and novel finding of the analyses was: with more patients and more events compared to any one trial, baseline QRS morphology did not play a significant role in determining the effect of CRT, and QRS duration was the only predictor of CRT benefit.	We reviewed the IPD analysis provided and considered it a pooled analysis of selective studies and did not consider it further.

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27.	**Peer Reviewer #1**	Clarity and Usability	1. The over structure of the report is adequate. Due to size of the document, improvement is needed on the organization. For instance, the table of content is difficult to follow. There are several groups of references, etc. 2. Main points are presented rather clearly. There is very little new information while age-related issues, critical to the CMS mission, are not addressed adequately 3. Weak conclusions from less robust data will not be helpful to inform policy or practice decisions.	We thank the reviewer for these comments. The table of contents and references follow AHRQ style guidance. There are two listings of references: one following the Executive Summary and one following the main report. With respect to age, there have been no RCTs specifically examining CRT in an elderly population; therefore, all conclusions on age need to be extrapolated from younger populations. This is discussed at length in the Applicability section. This is not a unique problem to the CRT literature but rather many systematic reviews seeking to answer questions in a Medicare population. Subgroup analyses from the main trials of CRT have not shown age to be an important factor for CRT effectiveness. The studies about predictors, with many inherent biases, have also not shown age to be an important factor for CRT.
28.	**Peer Reviewer #2**	Clarity and Usability	Is the report well structured and organized? – Yes, understanding that they are using standard EPC structure. Are the main points clearly presented? – Yes. Can the conclusions be used to inform policy and/or practice decisions? – Yes, it appears that CRT-D (and in some patients CRT-P) is an appropriate, effective, and safe therapy for patients with heart failure, LVEF < 35%, and QRS > 120 ms. Compared to other technologies used in medicine, the evidence is remarkably strong.	We thank the reviewer for these comments.
29.	**Peer Reviewer #3**	Clarity and Usability	The “Objectives” stated in the abstract are vague and confusing. Which group is being compared with which group? This sentence needs to be revised: “To assess the benefits and harms of cardiac resynchronization with (CRT-D) and compared to an ICD alone, CRT without a defibrillator (CRT-P) compared with optimal medical therapy and CRT-D compared with CRT-P.” There are many typographical and grammatical errors. The document needs serious editing. If the revisions I am suggesting can be implemented, the report will improve and then it can be more effective at informing	We thank the reviewer for the comments. The document has been edited as the reviewer suggests to improve clarity.

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			policy and practice decisions.	
30.	**Peer Reviewer #4**	Clarity and Usability	Clarity and Usability: The initial summary and much of the results create confusion regarding the different comparisons and conclusions. Unlike most analyses, the tone of the conclusions here is often stronger than the presentation of the results, such that I was not sure of the thrust of each section until many pages later in the conclusion. This made me wonder if sections of results were written by someone different or at a different time than the conclusions, which seem frankly more seasoned. Do we really want to go through all the individual outcomes and predictors for each of the comparisons in such detail, versus more tables that indicate how the results are the same or different with the comparisons. If this is the assignment, it was indeed done thoroughly. The structure of the key findings in the discussion page 161 and the table format of table 60 are very helpful and could be used more effectively in the initial summary. The 2 sentences at the end of the first paragraph page 162 should be provided in the abstract and the initial summary to indicate what we could reasonable extrapolate for CRT whether combined with D or not. However the table 60 on page 163 could be further clarified by including the usual abbreviations CRT-D, CRT-P in the first column	We thank the reviewer for these comments. We attempted to synthesize the data in the most efficient way at the same time. We performed meta-analysis wherever possible and included many tables to help the reader follow along. We agree with the reviewer and have added these two sentences earlier in the document
31.	**Peer Reviewer #1**	General	General Comments in Response to the Questions: 1. The report is clinically meaningful although there is very limited new information from the current report in comparison to the data from trials and existing meta-analysis. 2. The targeted population and audience were clearly defined; however, to this reviewer's surprise, the focus on age and the Medicare population is weak and to the most extend, lacking. Specifically, one of the most critical questions regarding CRT in HF is how did the very elderly (age > 75 – 80 years) respond? This is the fastest growing segment of our population; many live with multiple co-morbidities. Medical decision is difficult beyond what Guidelines could provide. This	1) We thank the reviewer for these comments. 2) There are no dedicated RCTs on CRT in the Medicare population; hence, extrapolation from younger populations is all that is possible. This is described at length in the Applicability section. 3) We decided on our comparators after a discussion with several expert informants in the field. We did not believe that CRT-D vs. OMT was an appropriate comparison. If a patient is a candidate for CRT, they are also a candidate for ICD and it would no longer be ethical to withhold ICD.

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			weakness of the report is primarily due to the methodology limiting to RCTs only. 3. The key questions are clearly stated and comparison groups are appropriate; however this reviewer would raise a 4th question: CRT (P+D) vs. OMT. This is clinically relevant. Outcomes may be more robust than CRT-P vs. OMT alone 4. Although the methodology is robust reflecting the authors' expertise, there is evidence that clinical experience is lacking among the authors. This reviewer is particularly worried about the potential harm analysis performed CRT-P vs. OMT. In the absence of an implanting procedure among patients randomized to OMT, there should not be any pneumothorax, hematoma, infection, hospital stay, etc. Consequentially, all of the conclusions reached by the authors need to be reassessed 5. Related to #4, the authors grouped class I and II patients together as "minimally symptomatic" group in CRT-D vs. ICD comparisons. Two RCTs were included in the analysis (MADIT-CRT and RAFT). ~ 15% patients in MADIT-CRT were class I with ischemic HD; there were no class I patients with non-ischemic HD (exclusion of the trial). RAFT only enrolled class II and III patients without any class I patients. This reviewer would suggest the conclusions drawn by the authors are likely appropriate for the class II patients, but insufficient for class I patients.	The one trial we identified that included an OMT arm (COMPANION) would not be possible today as ICDS are the standard of care. 4) The issue with the harms the reviewer is referring to was an abstraction error from one study by Gras et al. in which 65 patients from "the medial therapy arm" of CARE-HF actually received devices. We thank the reviewer for identifying this error that has been corrected. 5) We agree with the reviewer on this point and changes have been made throughout the document to make this distinction.
32.	**Peer Reviewer #2**	General	Is the report clinically meaningful? – Yes, as the report deals with a common and serious condition, one associated with high mortality and morbidity, and the report discusses a critically important technological advance. Are the target population and audience explicitly defined? -- Yes, except it is not clear to me whether the authors consider completely asymptomatic post-MI patients with LVEF <35% and QRS > 120 ms. Are the key questions appropriate and explicitly stated? – Yes.	We thank the reviewer for these comments. No separation was made based on MI status.
33.	**Peer Reviewer #3**	General	The report is meaningful. The target population is explicitly defined. Under Scope and Key Questions, the authors should add the	We have not modified our review questions – these were refined and agreed upon with input from CMS, AHRQ and key informants. There are varieties of

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			following question: “What is the comparative effectiveness and safety of CRT-D versus ICD only?” They present results on this, so it should be listed as one of their key questions. Unless this is not a comparator of interest, and if so, then the results should not be included in the abstract. I personally think this is an important comparator and should be included. Under Scope and Key Questions, the authors should define “response”. If they are only referring to response pertinent to CRT, then the questions regarding predictors of response to CRT-D and CRT-P should be combined.	definitions of response in the predictors section. We captured the definition provided by the study authors.
34.	**Peer Reviewer #4**	General	Organization with simple purpose and summary tables could come earlier to help orient the reader	We have included summary tables to the extent possible.
35.	**Public Reviewer #1** Laura Blum, Heart Rhythm Society	General	The Heart Rhythm Society (HRS) welcomes the opportunity to provide written comments on the draft AHRQ Technology Assessment Report titled ?Use of Cardiac Resynchronization Therapy in the Medicare Population? dated October 21, 2014, Project ID: CRDT0913. HRS is the international leader in science, education and advocacy for cardiac arrhythmia professionals and patients, and the primary information resource on heart rhythm disorders. Founded in 1979, HRS represents specialists in cardiac pacing and electrophysiology, consisting of physicians, scientists and their support personnel. Electrophysiology is a distinct specialty of cardiology, and electrophysiologists are board certified in clinical cardiac electrophysiology through the American Board of Internal Medicine, as well as in cardiology. HRS? members perform electrophysiology studies and curative catheter ablations to diagnose, treat and prevent cardiac arrhythmias. Electrophysiologists also implant pacemakers, implantable cardioverter defibrillators (ICDs) and cardiac resynchronization devices in patients who are indicated for these life-saving devices. The discipline of electrophysiology has undergone significant change in recent years, crossing clinical frontiers in the treatment of cardiology?s most challenging diseases such as sudden cardiac death, atrial fibrillation and heart failure. As these advances occur, HRS remains committed to improving the quality, safety, and efficiency of patient care.	1) We agree with the reviewer of the importance of clearly stating the inclusion criteria and have done so. 2) In Europe, CRT-P is used in a much broader fashion, even in younger patients who would be ICD candidates. The use of CRT-P is especially important in the very elderly patient population where quality of life concerns, including shocks, are of great concern. A default choice of CRT-D would not be appropriate. 3) We do not believe that further detail is needed about how judgments were discussed We were not developing consensus-statements, such as in guidelines. 4) We changed “widened” to “wider” throughout the text. Our intention was to refer to this in a continuous sense. 5) We note that more information is needed to determine the efficacy of CRT in non-LBBB patients. As the reviewer knows, bundle branch block morphology is confounded by QRS duration. While we acknowledge the subgroup reports from the various trials, we do not believe that these subgroup analyses offer definitive evidence to the effects of

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			HRS appointed three practicing electrophysiologists to review and give feedback on your report. We agree that the AHRQ Technology Assessment Report titled ?Use of Cardiac Resynchronization Therapy in the Medicare Population? provides an excellent, comprehensive, and systemic review of the literature on cardiac resynchronization therapy (CRT). The authors analyze data comparing cardiac resynchronization therapy device (CRT-D) vs. implantable cardioverter defibrillator (ICD), CRT-D vs. CRT pacemakers (CRT-P), and CRT-P vs. optimal medical therapy (OMT). The data are analyzed in terms of a number of specific outcome measures, both beneficial and harmful. HRS is pleased with the recommendations of the report and agrees that there is convincing evidence that CRT-D is effective in improving multiple clinical outcomes compared to a stand-alone ICD in the selected patient cohort. There is convincing evidence that CRT-P is effective in improving multiple clinical endpoints compared to OMT alone in the same population. Although this report is well-written, well-balanced, and fairly inclusive, HRS has some concerns about the methods and evidence. Please see the Society?s comments and recommendations below: General 1) The report should clearly note that this review is limited to: a. Patients with left ventricle ejection fraction (LVEF) ?35% and QRS duration >120 ms undergoing CRT; and b. Randomized controlled trials (RCTs) were included into the review for effectiveness analysis whereas cohort and retrospective studies were allowed for safety endpoints and analysis of predictors. 2) HRS questions some of the conclusions the authors reached regarding reporting safety outcomes and predictors (please see below for specific comments) as well as the clinical utility of performing a comparison between CRT-D and CRT-P in a population already eligible for a primary prevention ICD. 3) Reaching Consensus: The report states that when peer-reviewers did not agree on the available evidence, the matter was resolved by consensus. Additional information is needed	CRT in non-LBBB patients. 6) Our task was to identify and synthesize the evidence. We leave recommendations about clinical practice to guideline panels, who incorporate the evidence, clinical expertise and other issues such as location-specific issues, into developing clinical practice recommendations. 7) We thank the reviewer for these comments. 8) We followed the same process for screening and data abstraction for all studies. We agree that understanding harms is very important and for that, reason expanded our eligibility criteria for studies about harms to include designs other than RCTs. Data inaccuracies: 1) The publication of the study by Goldenberg et al. occurred after the search date for our draft report. This study has been included in the revised version of the report. The study by Goldenberg adds to the evidence in terms of the suggesting the benefit of CRT in LBBB and not in non-LBBB in terms of survival. Multiple issues with this study remain, however. A large number of patients included in the original MADIT-CRT cohort were not followed. This manuscript also does not report the overall mortality rate of the entire population but reports bundle branch (BB) morphology subgroup analyses alone. Also, bundle branch morphology was not a pre-specified subgroup in MADIT-CRT. It was the belief of the group that given these significant limitations, this new report from MADIT-CRT did not change our conclusions in terms of strength of evidence. 2) This statement is based on the meta-analysis we performed, including the studies of minimally symptomatic patients that were included and reported this outcome. 3) We appreciate the reviewer identifying this error. The study cited with paced patients was that by

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			about the process and the number of occurrences. 4) Definition: The report uses the term ?widened QRS?. The report should include a definition of this term. 5) This report and the Guidelines: The findings of this review are supported by the 2012 AHA/ACC/HRS Device Guidelines (focused update) and the 2013 ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR Appropriate Use Criteria. However, a major difference between the current manuscript and 2012 guidelines is that no evidence was noted in this report to conclusively determine utility of CRT in non-LBBB pattern QRS patients. 6) Application to Clinical Practice: While HRS is not concerned with the data as presented; the information would be enhanced if the conclusions would provide some clinical perspective. HRS would appreciate if the authors explain how these conclusions can be translated into clinical practice. 7) Clinical Endpoints: Most of the CRT studies in patients with advanced heart failure were fairly short in duration, so heart failure outcomes were the primary endpoints. If the clinical trials had provided for a longer follow up period, it is likely that mortality would have been an endpoint as well. However, we do understand that extending the randomized clinical trials for longer follow up may be ethically problematic in highly symptomatic patients. 8) Safety endpoints: HRS notices that the rigor shown for data abstraction and selection of studies for efficacy endpoints were not maintained for assessment of safety end-points (e.g. harms). HRS would appreciate if the report explained the rationale behind this decision. HRS believes that safety is equally important as efficacy when physician decide on therapy choices. HRS reviewers found some data inaccuracies: 1) Page vi (Structured Abstract):The abstract (page vi) does not reflect that evidence for mortality benefit that has been described in the rest of the document as well in conclusions and should discuss the survival benefits in the NYHA I-II patients consistent with MADIT-CRT long-term follow-up trial	Shen et al. which was also discussed in that section. This has been corrected. 4) Table 46 was edited and corrected. The section on CRT vs. OMT was similarly corrected. 5) This has been clarified to: “The data are inconclusive as to the effect on this outcome”

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			(Goldenberg I et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014 May 1; 370(18):1694-701) and the RAFT trial. 2) Page 35: 6 Min Walk distance. The conclusion says that ?CRT-D is effective in improving 6MHWD in patients with minimally symptomatic CHF compared to those receiving an ICD alone? but none of the individual data used in the meta-analysis support that. Two of the three studies used in the meta-analysis did not show any significant improvement in 6MHWD and the third study only showed a difference in NYHA III-IV subgroup. The conclusion appears inconsistent with the data and should be corrected. 3) Page 107, Para 2, line 9: ?The study by Mascioli et al. (2012)82 contained one arm that was 100 percent patients with paced RBBB?. The sentence appears incorrect. This study included patients with 2 different varieties of LBBB morphology and compared their response to CRT-D. Paced patients and RBBB patients were excluded. 4) Page 102, Table 46: Column 2. ?There data proffers little corroboration favoring CRT-P versus OMT in mortality? is inconsistent with what is reported in Table 60 ?Studies show statistically significant differences in mortality favoring CRT-P? and in the rest of the document 5) Page 102, Table 46: Column 3: ?No statistically significant differences were found when CRT-P was directly compared to CRT-D?. This statement is inaccurate as the manuscript text clearly mentions that no direct comparisons were made between CRT-D and CRT-P groups	
36.	**Public Reviewer #1** Laura Blum, Heart Rhythm Society	Research Gaps	1) Table 62: The proposed study in Table 62 raises ethical issues with its CRT-P control arm. All these patients qualify for and benefit from an ICD given their LVEF <35% despite adequate medical therapy. To randomize such patients to a non-ICD arm is against standard of care and cannot be endorsed from a guideline perspective. 2) Table 63: HRS proposes a subgroup analysis with QRS duration as a pre-specified criterion of 120-150 msec and >150 msec. This will be very important to assess whether or not the	1) The reviewer raises a controversial point as to whether a trial of CRT-P would be ethical. We believe that such a trial could be justified in an elderly (Medicare) population who may be more concerned about quality, rather than duration, of life, including concerns about shocks. In Europe, CRT-P is much more widely performed, even in ICD-eligible patients. 2) We agree with the reviewer in term of QRS

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			QRS morphology or the duration that plays an important. In addition, another important subgroup would be to separate RBBB and IVCD. 3) Table 64: HRS has come concerns related Table 64 about the lack of CRT benefit in AF patients: The lack of atrioventricular (AV) synchrony and increasing V-rates in AF preventing adequate (>95%) CRT. Combining paroxysmal (especially if episodes are infrequent) and persistent AF would not be ideal as treatment strategies for these vary considerable, given that clear data exists that in AF and congestive heart failure (CHF), pulmonary vein isolation is better than AV node ablation. So using just permanent, rate controlled (v-rates allowing >95% CRT and if not, with plan to perform AV node ablation) AF would be the best comparator for ICD in such a trial. Combining paroxysmal and persistent/permanent AF patients together will confound the findings of the whole study. 4) LV lead location should be included as a predictor for response. Data supporting apical vs. other location of LV epicardial pacing should be considered for discussion	duration and have added that to the table. 3) We appreciate the reviewer's comments. We agree with the reviewer's comments in terms of confounding. As such we have altered the ideal study to include separate arms for PAF and persistent vs. permanent AF. We believe just including permanent AF patients would limit the applicability of such a trial. 4) LV lead location was not examined as an *a priori* predictor. This was added to the limitations section.
37.	**Public Reviewer #1** Laura Blum, Heart Rhythm Society	References	Additional Reference for Consideration: HRS notes that there are new references which should be included in the manuscript. 1) In Goldenberg I et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014 May 1;370(18):1694-701. This study clearly shows that there is significant and persistent long-term survival benefit from early CRT-D in minimally symptomatic patients (NYHA I and II) with LVEF <30% and LBBB, when compared to ICD. There was a 41% relative risk reduction and the number needed to treat (NNT) was 9 to save one life over 7 years. By design, this study should be considered as having the highest strength of evidence and therefore the manuscript content, abstract, and executive summary should be changed to reflect this as this is a ?game-changer? study in terms of mortality benefit in minimally symptomatic patients with the highest level of evidence. This plus evidence from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) offers convincing evidence for the benefit of CRT-D in patients with	1) The study by Goldenberg was published after the first version of this review. It was included in the revised version. We respectfully disagree in terms of this study changing the conclusions of our report. This report from MADIT-CRT did not report on the overall difference in mortality regardless of BB morphology but rather simply reported the BB morphology subgroups. A large number of patients included in the original MADIT-CRT trial were not included in this follow-up. BB was also not a pre-specified subgroup. While we agree that this adds further support to the effect for CRT in LBBB patients, it does not change our conclusions. 2). Sassone B et al. was published after the search date. Also, the trial was/is not registered in clinicatrials.gov and thus not identified via that search. 3) The study by Ruwald was included in our harms

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			LVEF <30% and LBBB and NYHA class I-II. It should also be noted from this MADIT-CRT long-term follow-up study that the mortality benefit observed was independent of sex, type of cardiomyopathy, and QRS duration. Although this benefit was seen in various pre-specified sub-groups, there was no significant treatment-by-subgroup interaction. This study also clearly shows that there was no clinical benefit (and possibly harm) with non-LBBB QRS morphology with a hazard ratio of 1.57 but it should be noted that only ~25% of the MADIT-CRT cohort had non-LBBB morphology. 2) For Sassone B et al. Relation of QRS Duration to Response to Cardiac Resynchronization Therapy. Am J Cardiol. 2014 Oct 30. This retrospective study examined QRS duration as a predictor while using gender and QRS duration in the model. This study identified a ?U? shaped curve for QRS duration impact with LBBB QRS >178 ms showing worse outcomes. 3) Ruwald AC et al. The association between biventricular pacing and cardiac resynchronization therapy-defibrillator efficacy when compared with implantable cardioverter defibrillator on outcomes and reverse remodeling. Eur Heart J. 2014 Aug 11. This is sub study of MADIT-CRT, shows that in patients with LBBB, who were in sinus rhythm at enrolment, BIV pacing exceeding 90% was associated with a benefit of CRT-D in HF/death when compared with ICD patients. Furthermore, BIV pacing ?97% was associated with an even further reduction in HF/death, a significant 52% reduction in death alone, and increased reverse remodeling. 4) Wilton AB et al. Left ventricular lead position and outcomes in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Can J Cardiol. 2014 Apr;30(4):413-9. This is a RAFT sub study, which examines LV lead position and correlating that to CRT outcomes.	section 4) Lead position was not an *a priori* predictor that we examined. This limitation was added to the document.