Project Name: Assessment on Implantable Defibrillators and the Evidence for Primary Prevention of Sudden Cardiac Death

Project ID: CRDT0511

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	I have learned a great amount from reading this thoughtful report. Tremendous effort and analytic work is clearly represented. My major comments relate to the questions asked and the emphasis provided. The overwhelming volume of information has been distilled skillfully into summaries and discussion. However, the relative emphasis is perhaps determined more by the volume of related publications on each aspect rather than the importance of the aspect addressed. There are crucial issues on which we don't have enough information, but these should nonetheless be highlighteled carefully.	Thank you

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	The current challenge facing the medical community is that we hold in one hand the gold standards of randomized trial evidence, the results of which are very robust for the small select population randomized, with the minor limitations of definitions and crossovers as indicated by this review. In the other hand we carry responsibility for the imperfect translation of that data into the large populations that have a greater burden of cardiac and other diseases including frailty, with vast implications for patient decision-making and national resource allocation. If the charge is to weigh the gold standards critically, that has been done responsibly and informatively here. There have been approximately 10,000 ICD inserted monthly in the U.S., most for primary prevention. The challenge remains to summarize what is known, suspected, and unknown about distinguishing the vastly larger real-world patient cohorts in whom those RCT results are likely to align, and where they are likely to diverge. Many therapies designed to reduce a theoretical risk rather than to treat a symptomatic disease are overall neutral if not beneficial. However, the consequences of ICD implantation into patients unlikely to benefit are more often negative than neutral. The gaps in our current knowledge are large with regard to knowing which patients with LVEF < 35% should be offered ICD with expectation of improving meaningful survival. However, there are also large gaps in the knowledge that we should share with patients to help them make informed decisions, including the information most appropriate for them in terms of likelihood and distress from ICD shocks (both appropriate and inappropriate), likelihood of lead complication needing revision, likelihood of needing to consider deactivation of ICD to avoid undesired shocks at the end of life.	Thank you. We added this in Research Gaps.
1	General	This is a commendably thorough and thoughtful review of the randomized trials of implantable defibrillators for primary prevention. The major question addressed is the efficacy of ICD use for primary prevention of sudden cardiac death, which is clearly demonstrated in the randomized trials, with the exception as noted of the early post-infarct period.	Thank you
2	General	I commend AHRQ for taking on this question and the group that developed the report in writing a comprehensive document. It is clearly written.	Thank you.
2	General	I don't have concerns about the overall findings of the report, with the exception of the QOL summary. I do have several concerns about the methodolgy used. In assessing the document, one may want to consider these to ensure a different methodology would not result in different findings.	We have reassessed the QoL data and have changed our conclusion to there being a low strength of evidence for no difference in QoL with ICD use.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
3	General	The report is well done though some may question the need for another review of the benefit of primary prevention. Time may have been better spent on addressing additional sub-populations and other questions such as Do inappropriate shocks worsen outcome or are they a marker of high risk? It is good that the authors discuss the under the excluded studies section. It was not clear why a comparison of CRT-D v. ICD is a measure of ICD effectiveness. While this is an interesting question it seems more appropriate for a CRT review.	Thank you. We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.
4	General	General - The issue of ATP (anti-tachycardia pacing) is not well understood by the authors of the report. Anti-tachycardia pacing is not really an additional feature of an ICD as is cardiac resynchronization. With the exception of the subcutaneous ICD which is not addressed in this report, ATP is available in all ICD currently on the market as is back-up bradycardia pacing. ATP is useful to prevent shocks for patients with monomorphic ventricular tachycardia and just must be programmed on in the device. There is no additional cost of the device with antitachycardia pacing, and it requires on additional hardware or pacing leads. As is the case, a distinction should not be made comparing ICD and ICDs with ATP as they all currently have these features. CRT on the other hand, requires an additional pacing lead be placed into the coronary sinus. The device is more complicated and therefore more costly. It is more difficult to implant. Although there was a mortality benefit in CRT as shown in the CARE-HF study, it was a study of CRT pacemakers and not ICDs as is the scope of this review. Nevertheless, there was additional survival benefit in COMPANION of CRT ICDs over CRT pacemakers and no devices. However, the main reason to implant a CRT device is to reduce the symptoms of congestive heart failure (CHF), to improve ejection fraction, and to decrease hospitalizations from CHF. Almost every major study of CRT in patients with wide QRS durations on electrocardiography and symptomatic heart failure has shown these results. Since reduction in CHF symptoms was specifically noted not to be an approved endpoint for the review, it is almost unfair to review the findings of CRT only on a mortality benefit.	We added to the discussion: “A prior trial compared ICDs with and without ATP for primary and secondary prevention patients and showed benefit for QOL. ATP is now a standard software feature available in all modern transvenous ICD systems.”And reference the PainFree II study by Wathen MS, et al. Prospective randomized multicenter trial of empirical anitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. Circulation. 2004;110:2591-2596 We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.

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5	General	This was a comprehensive review, well organized and followed standard methods for review which were clearly explained in the text. The fact that some key issues and references were omitted leads me to believe that perhaps that none of the lead investigators were cardiologists or have had clinical experience with patients with ICD implants. I have made some suggestions below.	Thank you
4	Abstract	Page vi- the authors note that only one RCT reported performing electrophysiology testing in all patients. That is not true. Both MADIT and MUSTT both performed EP testing in all patients. If MUSTT is not included in this review, it should be. I realized later on reading the section noting that this study was not included due to the initial intention of the study (comparing EP guided therapy to no therapy), but it is truly one of the most powerful studies of prophylactic ICD implantation.	MUSTT did not meet inclusion criteria for KQ1. Because it is a landmark ICD study, it was discussed in detail in the section of supplementary evidence in excluded studies in the discussion. We added a sentence to the introduction where we reference MUSTT as a trial that used EP guided therapy.
1	Executive Summary	Main points are as above. [Refers to comments on KQ 1, Subgroups, KQ 1b and 1c, KQ 2, KQ 3, and General]	Thank you.
3	Executive Summary	The executive summary provides a concise overview of the findings.	Thank you.
4	Executive Summary	Well written and easy to understand	Thank you.
1	Introduction/ Background	The review of the incidence of sudden death is useful background, but as the authors indicate, most sudden deaths are not in patients with previously identified risk, so would not be preventable by ICDs.	Thank you. This is described in introduction and was also added to research gaps.
3	Introduction/ Background	I would have mentioned the ACC/AHA/HRS guidelines in addition to the CMS coverage decision. I realize this is mentioned at the end but this guideline affects how many practice in the community (at least for the non-CMS patients).	We have now reference these guidelines in the introduction.
4	Background- Page 5	Page 5- MADIT II is listed as having a QRS duration of >120 ms an entry criterion. That is untrue, no such ECG criteria were used in MADIT II – it was just ischemic cardiomyopathy, and ejection fraction less than 30%.	You are correct. We have removed the statement regarding QRS. Thank you.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
4	Introduction/ Background	Excellent introduction. Background could be more detailed describing the large public health problem of sudden cardiac death and the effectiveness of the ICD in treating sudden death. The problem arises related to finding the best patients to implant this device – comparing risk to benefit and cost effectiveness.	The problem of risk stratification is highlighted in discussion.
1	Methods	Sudden deaths should be systematically compared to other deaths, particularly heart failure deaths, as has been done for the MADIT trials, which have presented analyses of the trial patients unlikely to benefit from prevention of sudden death due to higher risk of heart failure death.	Our review summarizes all cause mortality which is the most comprehensive measure of mortality. Disease specific mortality may be complementary and competing.
2	Methods	Selections of very small sample size studies and appear to be considered equivalent to larger studies. Does the sample size or the HR/confidence interval increase the weight of the findings?	In meta-analysis, the weight of a study is inversely related to the estimate's variance which is related to precision (both size and events)
2	Methods	Under strength of evidence grading, when comparing clinical trials, little reporting on differences in patient selection or other differences in the trials, which is likely to result in different findings. As an example, SCD-HeFT and COMPANION (lower EF) had different selection criteria. It also relied on different therapies. COMPANION exclusively tested CRT-D and SCD-HeFT exclusively tested (single lead) ICD and may account for the differences seen in subgroup analysis of heart failure class and benefit or lack of benefit from the device.	We assessed the applicability of each study (e.g., based on the eligibility criteria and baseline characteristics) to help determine the generalizability of the conclusions to the population of interest. As part of this, we addressed some of the clinical heterogeneity by sensitivity analysis. We excluded studies that implanted ICDs immediately after MI or after CABG. Excluding more studies would decrease the number of studies summarized in the main analysis. We acknowledge that the review of CRT is not complete Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.We point out in the introduction and the discussion (limitations section) that study populations in ICD and CRT trials have overlapping characteristics, but are not exactly the same.
2	Methods	Selection of clinical trial duration was done not by reviewing the manuscript, but by reviewing the graphs in the manuscript. It is common place to truncate the graph follow-up period so that the follow-up period that has fewer events (later years) are often not on the graph and thus may result in data error.	You have highlighted a limitation, but we are restricted to analyzing the data that are reported (in text or in figures). We consider the duration of followup of the survival curves to be the best indication of the maximal duration of followup analyzed by the authors (unless more explicitly reported).

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Methods	There are several 'layers' of ICD programming. Programming variables that are within the device. There is also the programming parameters that are selected by the physician for a particular patient when the device is implanted and can be changed to allow for anti-tachycardia pacing or not, heart rate for termination of ventricular tachycardia, etc. That is not clear from this document.	There were no trials comparing ATP versus no ATP that met our inclusion criteria. We acknowledged that ATP is an available programming feature in all contemporary devices and thus that particular question is not as relevant. We also describe MADIT – RIT which examine more nuanced programming options. However, this review was not intended to compare different programming algorithms and since this trial did not include a medical therapy arm without ICD, it was not included in our analysis.
2	Methods	SCD-HeFT only had one ICD intervention arm. The arms were: ICD, amiodarone placebo, or amiodarone. The analyses plan was ICD arm vs. placebo arm and amiodarone arm vs. placebo arm. The Table 4 is also incorrect on this topic. Control was amiodarone placebo, not amiodarone). Not clear why these reviewers selected the amiodarone for the control group (instead of protocol defined placebo arm) for this report.	We corrected the table and the corresponding results section to specify for SCD-HeFT, we chose the placebo arm as the comparator. The study found no difference in death rates between the amiodarone and no amiodarone groups.
2	Methods	The title implies these results include all the evidence for the assessment of primary prevention of ICDs. However, if multivariate analyses were not done, then the study was not included. Since one of the aims is to assess subgroup findings, it is important to include those data, but this report does not state what was excluded that may also provide evidence on the overall effectiveness of this therapy and not just on evidence related to subgroup findings. The supporting documents have many papers that were not included, but I am not sure if there were no papers excluded to lack of multivariate analysis. Cannot see any exluded clinical trials in the summary of excluded manuscripts. If no clinical trials were excluded, could drop this point and eliminate the concern. If trials were excluded, should list and make the summary headings clearer to indicate what is excluded.	This restriction applied only to the non-randomized controlled studies. Page 8: "For nRCSs, only those studies that used concurrent controls and reported a multivariate analysis were included." We included all RCTs with at least 10 participants per study group.
2	Methods	If two QOL trials show no difference and one QOL trial show reduced QOL in 'some measures'. The report declares the balance toward worse QOL (although it has low strenght of evidence). Why are the findings not reported as neutral or no difference, as that is consistent with the majority of the results (2 out of 3 trials)? This may show a weakness in the methodology here where the findings can be skewed if few trials are reviewed (3 in this example) and the weight of the findings is in the direction of non-neutral, if most of the findings are neutral and no weight in the opposite direction.	We have reassessed the QoL data and have changed our conclusion to there being a low strength of evidence for no difference in QoL with ICD use.
3	Methods	I agree with the methods used. Inclusion and exclusion criteria were appropriate.	Thank you.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
4	Methods	The usual methods for a study of yours, an immense review of the literature. I will again echo the need to place the MUSTT trial into the analysis.	MUSTT did not meet inclusion criteria for KQ1. Because it is a landmark ICD study, it was discussed in detail in the section of supplementary evidence in excluded studies in the discussion. We added a sentence to the introduction where we reference MUSTT as a trial that used EP guided therapy.
1	Key Question #1	However the broader question of interest for resource allocation and patient decision-making is the effectiveness of the ICD to prolong meaningful survival, which encompasses the risk of mortality from non-sudden cardiac death and non-cardiac death, and the quality of life among survivors. These key considerations are not specifically addressed. As discussed below, there are reasons for concern that the prevention of sudden cardiac death does not translate into the same magnitude of prevention of total mortality.	In the discussion, we highlight the discrepancy of finding a smaller benefit for all cause mortality compared with the larger effect on mortality from SCD, which is likely the result of competing risk.
1	Key Question #1-Subgroups	This thorough review indicates no evidence for subgroup differences in effects. This contrasts directly with the JAMA meta-analysis from a similar collection of trials, indicating absence of benefit in women. This data has gained sufficient public recognition to merit comment. There is biological plausibility for this, as there is recognition of lower sudden death rates in women compared with men with similar severity of heart disease. Ghanbari H, Dalloul G, Hasan R, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:1500-6.	We have added results from meta-analyses for subgroups, including by age and sex, and contrast our findings with those by others in the discussion.
1	Key Question 1b and 1c	The question is asked of CRT-D vs ICD without CRT. The patients are slightly different by virtue of the QRS, so unclear why this is being asked. The recent data from MADIT CRT and REVERSE suggest that all Class II patients with long QRS and LBBB who get ICD should get CRT anyway. Perhaps a more pertinent question is what is the benefit of ICD on top of CRT pacing alone? There is only weak data suggesting that the ICD offers benefit over CRT alone, which improves cardiac and clinical function and provides back-up pacing that may prevent some bradycardiac deaths.	We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.

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5	Key Question 1	In subgroups they seem to miss entirely the lack of data in women, the small number of trials and small number of women. They missed a key meta-analysis of the RCT for PrimaryPrevention of ICD in Women (REF- Arch IM 2009 Ghanbari et al, Effectiveness of Implantable Cardioverter- Defibrillators for the Primary Prevention of Sudden Cardiac Death in Women. With Advanced Heart Failure with editorial by Redberg. They also missed a JAMA article using the NCDR ICD database and CMS data to find that there was NO difference in 1 yr. mortality (the HR was 1) for Medicare beneficiaries who got an ICD compared to matched ones who did not. ref is Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA..JAMA. 2007 Oct 3;298(13):1517-24: Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death, with accompanying editorial. There is also increasing use of ICDs in the pediatric population, often for long QT syndrome. This subgroup should be added. There are many complex issues relating to different risks and benefits in these subgroups – women and children as the etiology, physiology and pathology and competing causes of death are all different in these groups.	We have added results from meta-analyses for subgroups, including by age and sex, and contrast our findings with those by others in the discussion. We rejected the study by Curtis as it included a population not followed from implantation. The population was not followed from the time of implantation, which was a requirement for inclusion. We have inserted this criterion in methods section page 11 "Participants had to be followed from the time of ICD implantation, not only from some arbitrary time before or after ICD implantation." Pediatric populations were not excluded, but there were eligible studies. We added this to research gap in the discussion.

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1	Key Question #2	The low rate of early adverse events and significant risk of inappropriate shocks are addressed well from the robust current registry data and other reports. The higher risks are of adverse events after discharge compared to the initial hospitalization, but this could be better clarified. The abstract and summary include all the adverse events together, but might provide more emphasis on the rate of lead problems, most of which occur after hospital discharge and require repeat procedures. The authors note but again could emphasize that these complications are under-appreciated from the short duration of exposure in most randomized trials. This was not collected from the first years of the NCDR ICD registry but is now being collected in the revised registry format. There is no robust data in any registry on the incidence of post-traumatic stress syndrome following ICD shocks (whether appropriate or inappropriate) in any large registry, but there are multiple small reports. Although these do not allow determination of any denominators for the numerators, this is the major factor compromising quality of life with ICDs and should be discussed, even if only to emphasize that there should be greater efforts to capture this data and address prevention and therapy. Another issue that is crucial although unquantified is the impact of ICD on the quality of death, as addressed in several small studies and position papers on the current deficits in the approach to inactivation of ICDs at the end of life.	We clarified that the distinction between AEs during hospitalization for ICD implantation and late AEs (in abstract, results and discussion). We added the problem of lack of robust data on late adverse events and patient reported outcomes to the research gaps.
5	Key Question 2	They do not include recalls in their Adverse Events. Lead recalls are a big issue for tens of thousands of ICD recipients, as they either have to have a second and risky procedure, or live with knowing they may have a faulty ICD. There have been multiple recalls in the last 5- 10 years of many brands of ICD leads , e.g. Sprint Fidelis, St Jude Riata and the decrement on quality of life and increase in AE and mortality and issues related to recalls must be included in this review.	Recalls were not considered an outcome for this review. However, Appendix Table 18B presents lead related adverse events in patients implanted with leads that were subsequently recalled. Included studies followed patients from the time of implantation and reported events with the number of patients at risk (denominator) clearly specified. These studies are described under Key Question 2 Results, subsection “Late Adverse Events from Cohort Studies”. Studies for the outcomes of mortality and quality of life were limited to comparative studies in the primary prevention population (KQ1).
5	Key Question 2	Inappropriate shocks is an increasingly important issue for ICD recipients, especially in primary prevention and the magnitude of this issue does not come through in this review. They should like (look?) at time trends of rates of inappropriate shock rates. The literature and clinical experience demonstrate that the rate of inappropriate shocks far exceed the rate of appropriate shocks currently. As the bar for implanting ICDs was lowered and more patients at lower risk of SCD are receiving them, the chances of inappropriate shocks/appropriate has exceeded unity.	These issues were included in the Research Gaps section. We clarified that the distinction between AEs during hospitalization for ICD implantation and late AEs (in abstract, results and discussion). We added the problem of lack of robust data on late adverse events and patient reported outcomes to the research gaps.

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1	Key Question #3	The inclusion criteria for the trials is much different than the demographics of the overall heart failure population with LVEF <35%, which could be made more explicit. These demographics are apparent in the NCDR registry population, including much older age and more frequent hospitalization for heart failure, both of which identify patients in whom most mortality results from non-sudden heart failure death or non cardiac causes.	This level of comparison between NCDR and the eligible trials was not part of our Key Questions. However, this is an interesting and relevant issue. Therefore, we have added a paragraph to the Discussion (page 70) that briefly summarizes what Masoudi et al reported in regards to comparing NCDR, MADIT II, and SCD-HeFT.
1	Results-pg. 34-35	The authors allude briefly to the discrepancies between Figure 5 and Figure 7, but it bears emphasis that the mortality curves remain parallel after the first divergence, while the differences in sudden death continue to widen. This is strong support for the concept that prevention of sudden death does not translate directly into prevention of total mortality, as patients who survive appropriate ICD shocks have a high mortality over the next 2 years. Thus some of the deaths "prevented" are not deferred for long. This is true even in the relatively healthy population with mild heart failure burden in the RCTs.	We agree. We have further highlighted this issue in the Discussion (end of the 1st paragraph)
1	Results-pg. 36-38	As above, the question of whether to add CRT to the ICD to improve survival has not been a major focus of decisions, as the major benefit of CRT is to improve symptoms and functional capacity and to decrease hospitalizations, which have been pretty well shown elsewhere.	We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.
1	Results-pg. 53	I am not sure I understand the intended focus of the questions asked in this section. I would have liked to see more comparison of the trial data to the comparative data from the larger registry populations to highlight the similarities and differences.	This level of comparison between NCDR and the eligible trials was not part of our Key Questions. However, this is an interesting and relevant issue. Therefore, we have added a paragraph to the Discussion (page 70) that briefly summarizes what Masoudi et al reported in regards to comparing NCDR, MADIT II, and SCD-HeFT.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	Results	A KEY POINT that should be emphasized in all comparisons is that ICD implantation was done as an elective procedure in the randomized trials, where patients came in from home. In over 10% of US implants is done during a hospitalization for another reason, usually heart failure. The majority of patients receiving ICD in the national registry have had prior heart failure hospitalization, which again describes ~~is~~ a different population, in whom the risk of non-sudden heart failure deaths is higher.	Unfortunately, most trials did not report what percentage of patients were enrolled as inpatients or outpatients. Trial eligibility criteria were not specific regarding prior hospitalizations. We found that only 1 outdated trial (CABG-Patch) specified that the patients were "scheduled" for CABG procedure. Further, 2 nRCs also explicitly reported this information. Chan 2009 enrolled patients from outpatient clinics, and Hernandez (OPTIMIZE-HF and GWTG=HF) included only hospitalized patients, excluding patients admitted electively for ICD therapy. We added this to the applicability section in the discussion "While most trials did not specify that patients were electively admitted for ICD implantation, this is assumed to be the case."
1	Results	The subgroup of the elderly merits greater attention, as it is a major question. Epstein AE, Kay GN, Plumb VJ, et al. Implantable cardioverterdefibrillator prescription in the elderly. Heart Rhythm 2009;6: 1136-43. See attached pdf of article in press regarding the impact of heart failure burden on mortality after ICD implantation.	We have expanded the applicability section in the discussion to address this issue. See page 76.
1	Results	There have been extensive calculations of the relationship between life expectancy after ICD implantation and the benefit of ICD. There is a model from SCD-HeFT (Gillian is author), and a more conservative model from MADIT (I believe Mosaffarian is first author). These have not been highlighted here, but provide perspective regarding the issue of prolonging survival in addition to preventing sudden cardiac death.	We did not include any simulation models but reviewed only primary data on mortality and other outcomes.
2	Results	This document indicates that MADIT was an outlier, but this is likely related to patient selection with a higher risk group selected. Not sure that outlier is the best term to reflect that a different patient population selected to test the device	We agree that the term outlier should not have been used. We have changed the sentence to read that MADIT may differ from other trials. We also added a sentence that this difference may be due to chance, as implied by the meta-analysis of hazard ratios. It is not clear to us that MADIT has a sufficiently different population (especially as compared to MADIT II) to explain the difference.
2	Results	The report may benefit from indicating there is insufficient evidence to support subgroup analysis much of the time, instead of relying only on the statement that the analyses failed to support the findings of difference. This clarification only seems to be noted in the limitations section of the report.	In methods under Strength of Evidence Grading, it is stated that often subgroup analyses are exploratory. This concept has been added to the Discussion also. We do not believe there was insufficient evidence (e.g., consistent results from 7 studies comparing men and women), but the lack of a priori analyses does limit the ability to conclusively say there is no difference between subgroups. (2nd paragraph of Discussion)

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2	Results	A subgroup analysis of inappropriate shock reporting is not clear to me. In shocks between CRT-D and ICD or between dual and single chamber ICDs. This appears to be inconsistent to me. Could benefit from review and clarification.	Thank you. This inconsistency was corrected.
3	Results	The results are clearly displayed.	Thank you.
4	Results	Well written and easy to understand	Thank you.
1	Discussion/ Conclusion	as above… [Refers to comments made in General and Methods, KQs and Results]	No response needed
2	Discussion/ Conclusion	Conclusion that QOL results are negative for ICD use for primary prevention is not supported by my review of the literature and believe the technique used to determine benefit or lack of benefit results in this finding and should be resconsidered. (see #7 above under Methodology section). [Refers to: If two QOL trials show no difference and one QOL trial show reduced QOL in 'some measures'. The report declares the balance toward worse QOL (although it has low strenght of evidence). Why are the findings not reported as neutral or no difference, as that is consistent with the majority of the results (2 out of 3 trials)? This may show a weakness in the methodology here where the findings can be skewed if few trials are reviewed (3 in this example) and the weight of the findings is in the direction of non-neutral, if most of the findings are neutral and no weight in the opposite direction.]	We have reassessed the QoL data and have changed our conclusion to there being a low strength of evidence for no difference in QoL with ICD use.
2	Discussion/ Conclusion	See Methodology comment #3, reporting of Key findings. "3. [Refers to: Selection of clinical trial duration was done not by reviewing the manuscript, but by reviewing the graphs in the manuscript. It is common place to truncate the graph follow-up period so that the follow-up period that has fewer events (later years) are often not on the graph and thus may result in data error"]	You have highlighted a limitation, but we are restricted to analyzing the data that are reported (in text or in figures). We consider the duration of followup of the survival curves to be the best indication of the maximal duration of followup analyzed by the authors (unless more explicitly reported).

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
3	Discussion/ Conclusion	For the NCDR data consider emphasizing that this was hospital reported. Some have argued that hospital have an incentive to under-report complications and a comment in the discussion regarding whether the NCDR data are consistent with other sources would be of interest. It may be too late to add that the appropriateness criteria for ICDs was just released by the American College of Cardiology. Within the areas for research, consider expanding the risk prediction section to suggest evaluation for specific risk factors. For example, where is the best LVEF cutoff? Do published risk scores predict benefit with an ICD (e.g. MADIT risk score)?	This was emphasized throughout the report. We clarified that the distinction between AEs during hospitalization for ICD implantation and late AEs (in abstract, results and discussion). Appropriateness criteria were added in the Introduction. The risk prediction section in Research Gaps was expanded. We added to the introduction: "Attempts have been made to calculate SCD risk score models such as one derived from MADIT-II as well as the Duke risk score in patients with coronary artery disease. The risk scores may be helpful in guiding therapy for a physician but they have not been applied in a prospective manner in clinical trials. An example of an invasive risk stratification tool which has been studied prospectively in MUSTT and MADIT is the electrophysiology study ([158] and MADIT reference). MUSTT provided evidence that electrophysiologically guided antiarrhythmic therapy with ICDs reduces the risk of SCD in high-risk patients with CAD, LVEF ≤40 percent, spontaneous and unsustained VT, or sustained tachyarrhythmia induced by programmed stimulation. Multicenter Automatic Defibrillator Implantation Trial (MADIT)[65]—which included patients with CAD and a prior MI, LVEF <35 percent, and inducible, sustained VT or VF at electrophysiologic study. Thus, the electrophysiology study has a tailored role in risk prediction."
4	Discussion/ Conclusion	Well written and easy to understand	Thank you.
5	Discussion	While it is briefly mentioned under Research Gaps, the issue of the use of ICD in multiple patient populations in which they have not been studies, such as Brugada syndrome, long QT, hypertrophic cardiomyopathy, means that many patients are getting ICD in which we do not know if there is a benefit. The magnitude of this issue – what percentage of implants are for these indications – and possible solutions, such as using the NCDR to track these should be included.	We added the suggestion to study these patients and their outcomes in the NCDR ICD database.(see Discussion under Research Gaps.)
1	Tables	The major tables of trials and registries should include # of patients consistently.	The number of trial participants is shown in the tables of study characteristics for (Table 4. ICD vs. no ICD: Study characteristics, Table 9. ICD vs. CRT-D: Study characteristics), in the forest plots, and in the results tables in the appendix (as denominators).

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	Appendices	These are very complete and detailed.	Thank you.
1	References	The survival in relation to heart failure burden in the Medicare ICD population is highlighted in an article in press in JACC : Chen CY, Stevenson LW, Stewart GC, Seeger JD, Williams L, Jalbert JJ, Setoguchi S, Impact of Baseline Heart Failure Burden on Post-ICD Mortality among Medicare Beneficiaries, Journal of American College of Cardiology; 2013; in press (attached pdf) Masoudi FA, Go AS, Magid DJ, et al. Longitudinal study of implantable cardioverter-defibrillators: methods and clinical characteristics of patients receiving implantable cardioverter-defibrillators for primary prevention in contemporary practice. Circ Cardiovasc Qual Outcomes;5(6):e78-85. Epstein AE, Kay GN, Plumb VJ, et al. Implantable cardioverter-defibrillator prescription in the elderly. Heart Rhythm 2009;6(8):1136-43.	We added detail to our discussion of the Masoudi study. See Pages 72 and 73. And we expanded the applicability section citing these papers.
2	Tables	Check tables and document for labeling. On at least one occasion the reader is referred to Table 14, instead of Table 15.	Thank you. This was fixed on page 55 of the report.
2	Tables	See Methodology section above and comment #5 re: Table 4 [Refers to: SCD-HeFT only had one ICD intervention arm. The arms were: ICD, amiodarone placebo, or amiodarone. The analyses plan was ICD arm vs. placebo arm and amiodarone arm vs. placebo arm. The Table 4 is also incorrect on this topic. Control was amiodarone placebo, not amiodarone). Not clear why these reviewers selected the amiodarone for the control group (instead of protocol defined placebo arm) for this report.]	We corrected the table and the corresponding results section to specify for SCD-HeFT, we chose the placebo arm as the comparator. The study found no difference in death rates between the amiodarone and no amiodarone groups.
3	Tables	The tables are appropriate.	Thank you.
4	Tables	Very comprehensive, well-done	Thank you.
3	Figures	Figures: The figures are appropriate.	Thank you.
4	Figures	Very comprehensive, well-done	Thank you.
2	References	The heading “not of interest” is not informative as it is used here.	The headers are a bit clearer than this. We specify which aspect of the study was not of interest for the review. For example, there are “not of interest” headers for intervention, comparison, outcome, and study design.
2	References	See comment #8 under Methodology.	There is no reviewer comment # 8 under methods.
3	References	The references are appropriate.	Thank you.
4	References	Extensive collection of articles pertaining to the subject. Very comprehensive.	Thank you.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
3	Appendices	The appendices are appropriate.	Thank you.
4	Appendices	as above.	Thank you.

[1] Peer reviewers are not listed in alphabetical order.

[2] If listed, page number, line number, or section refers to the draft report.

[3] If listed, page number, line number, or section refers to the final report.

Project Name: Assessment on Implantable Defibrillators and the Evidence for Primary Prevention of Sudden Cardiac Death

Project ID: CRDT0511

Table 2: Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 1		General	MTWA has a proven negative predictive value of 97-99% for the occurrence of malignant ventricular arrhythmias. Very few medical tests can exclude adverse events with this level of confidence.All candidates for ICD placement should first be sxreened with MTWA to identify those who are at very low risk and may not need an ICD.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
David Bach		General	Microvolt T-Wave Alternans (MTWA) is the first economical test to determine who is susceptible to Sudden Cardiac Death. It's negative results also help determine who needs an implantable cardioverter defibrillator (ICD). MTWA can save billions of dollars in medical costs annually.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
David Bach		General	Medicare must eliminate conflicts of interest in using new medical diagnostic tests. If Medicare is earnest in reducing its medical costs, management would take a more proactive approach to using new technology to solve health problems. That Medicare cannot tell doctors which tests to use is meaningless. Blue Cross-Blue Shield of New York has been telling doctors which tests to use for years. It's time Medicare took the blinders off and its head out of the sand and joined the 21st century.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

David Bach		General	That cardiologists and hospitals refrain from using non-invasive Microvolt T-Wave Alternans (MTWA)to determine susceptibility to Sudden Cardiac Death (SCD) is disgraceful. MTWA has had FDA approval for nearly 14 years and a reimbursement code (#93025) for nearly 7 years and still it isn't used. Will this be another embarrassment for the medical profession like beta blockers that took 17 years to go mainstream? Can the country afford to lose someone to SCD every two minutes (300,000 Americans annually)?	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

David Bach		General	MTWA is a non-invasive test (about a dozen sensors are placed on one's torso) to obtain test results. It takes a half hour to perform on an outpatient basis. Once completed, the sensors are removed and the patient goes home. By contrast, the old technology to determine susceptibility to SCD, electrophysiology (EP), is invasive and far more costly than MTWA. By invasive, I mean an incision is made in one's thigh where an electrical probe is inserted through it and threaded up to the heart. Once there, the probe gives the heart an electrical shock for an average of two hours (it can be up to four hours) to obtain readings. Once the EP test is completed, the probe is removed and the EP patient is put in a hospital for two days to recover from the incision to ensure no infection occurs. Which test would you prefer to take? By far more costly, I mean that the MTWA test may cost about $400 with a reimbursement rate of $180 (average for the U.S. in 2012). By contrast, EP costs nearly $9,000. Of that amount, the hospital collects $6,000 for the two-day patient recovery from the EP test while the cardiologist receives nearly $2,000. So, the hospital's income is reduced by 93% (from $6,000 to $400), and the cardiologists income by 80% (from $2,000 to $400), by using MTWA rather than EP. See the conflict cardiologists and hospitals have using MTWA? Additionally, MTWA's negative results can help determine who needs an ICD. Defibs cost $25,000; to implant them costs an additional $40,000. Columbia University conducted a study of 170,000 ICDs and determined that 30% of them were unnecessary. With about 150,000 defibs implanted annually in Americans, a similar result to the study would indicate that about 45,000 ICDs are unnecessary annually. At $65,000 each (implanted), that works out to a unnecessary annual expenditure for ICDs of $2.925 billion dollars. And that does not include the thousands of dollars spent annually maintaining them. Is Medicare really serious about reducing its medical costs? MTWA is a no-brainer.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

David Bach		General	That cardiologists and hospitals do not use MTWA is evidenced by the sales record for a publicly-held company called Cambridge Heart (symbol: CAMH). It is the exclusive global marketer of MTWA. CAMH's revenue peaked in 2006, just when MTWA received a reimbursement code. It's revenue has declined steadily since then. Source: the SEC's EDGAR system, searching for the company by name or stock symbol and reviewing the company's historical Form 10-Ks. MTWA is also approved for use in Europe and Japan and has a reimbursement code in Japan. Still, it is not used in those locations by ardiologists and hospitals there. Despite having a different pricing system than what is used in the U.S., these medical practitioners also have a conflict of interest in using MTWA. Again, Cambridge Heart's revenue represent worldwide sales of MTWA.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
David Bach		General	MTWA was developed at MIT. NASA uses MTWA on astronauts. Do you think NASA is going to use a two-bit test on people it sends into space? Why isn't MTWA used on other Americans? SCD impacts all types of people: young and old, athletic as well as those not so fit. In early 2012, a popular U.K. soccer player. Fabrice Muamba, nearly succumbed to SCD on the playing field. Only because two cardiologists were in the stands did he survive. He had to retire from the game the following August. A few weeks after Mr. Muamba's SCD occurrence, an Italian soccer player succumbed to SCD on the playing field and a Norwegian swimmer did likewise while attending a swim meet in Flagstaff, AZ. The tragedy is that these deaths were preventable.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
David Bach		General	Cambrige Heart's annual reports, available on the Internet at the Security and Exchange Commission's EDGAR file. Also, view the company's website (www.cambridgeheart.com) for more detailed information about MTWA.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Robert Behnke		General	Hello AHRQ Technology Assessment, I feel compelled to provide the following Information which can save Billions of Dollars and Thousands of Lives as in 850/Day in the USA alone. Please take a look and forward on to anyone you think could help this cause. > Many studies clearly indicate that Cambridge Heart's Microvolt T-Wave Alternans test identifies individuals at high or low risk of sudden cardiac arrest/death. This test does not take long: it is non-invasive, 99% accurate, CMS/Private insurance covered, FDA Approved and relatively inexpensive $200. Unfortunately, for some reason this test is not provided. As a result, about 850 people die every day from sudden cardiac death 1 every 2 minutes in the USA alone. > In addition to add insult to injury, 21% of defibrillators that are implanted are unnecessary, according to a recent JAMA Study. Another study, this one conducted by Columbia University a few years ago, determined that 30% of the 170,000 ICD's were uncalled for. Since each defibrillator costs about $65,000, and there were over 50,000 unnecessarily installed, this amounts to a waste of over $3.2 billion. And this does not include the cost to monitor these unwarranted implants or the often cases of infection that takes place. Yet Cambridge Heart's Microvolt T-Wave Alternans test could have prevented this waste, since it can determine who benefits from the ICD. At 3 years out this test is over 97% accurate. > I hope you become as passionate about this technology as I have and push for it to be the standard and required for ICD Candidates, Pre-Surgery Screening, Physicals over 35 years of age, Athletes, Pilots, Firemen, Policeman and Officials.... Please feel free to contact me at bbehnke@vinzantsoftware.com if I can be of any assistance. For exclusive coverage please contact Cambridge Heart as they love to help at 978-654-7600. > Cambridge Heart http://www.cambridgeheart.com/contact-us > Japans Ministry of Health: http://www.cambridgeheart.com/news/press-releases/135-cambridge-heart-announces-microvolt-t-wave-alternans-receives-reimbursement-coverage-in-japan > Purpose: http://www.cambridgeheart.com/patients > 1 of Many Studies Available: http://www.cambridgeheart.com/news/press-releases/136-	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Robert Behnke		General	Cambridge Heart's Microvolt T-Wave Alternans test should be standard and required for ICD Candidates, Pre-Surgery Screening, Physicals over 35 years of age, Athletes, Pilots, Firemen, Policeman and Officials....	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
Robert Behnke		General	Cambridge Heart's Microvolt T-Wave Alternans test identifies individuals at high or low risk of sudden cardiac arrest/death. This test does not take long: it is non-invasive, 99% accurate, CMS/Private insurance covered, FDA Approved and relatively inexpensive $200.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
Robert Behnke		General	This non-invasive stress test which is way more powerful and accurate then the current standard.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
Robert Behnke		General	Over 99% accurate at identifying people at risk of sudden cardiac arrest / death. People experiencing sudden cardiac arrest have 8% survival rate. Identifying and prevention is the ONLY answer.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
Robert Behnke		General	Cambridge Heart's Microvolt T-Wave Alternans test should be standard and required for ICD Candidates, Pre-Surgery Screening, Physicals over 35 years of age, Athletes, Pilots, Firemen, Policeman and Officials....	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Robert Behnke		General	Clinical Studies: http://www.cambridgeheart.com/mtwa/clinical-data MWTA: http://www.cambridgeheart.com/mtwa/mtwa Fact Sheet: http://www.cambridgeheart.com/about/company-description A Symposium to honor David S. Rosenbaum, MD (strong advocate of microvolt T-wave alternans testing listed under learning objectives below) Co-Sponsored Event Monday, May 06, 2013 Duration: 1 Day Registration Info To learn more about this event, please contact Dr. J. Kevin Donahue at kdonahue@metrohealth.org or visit the MetroHealth website. www.metrohealth.org/rosenbaumsymposium https://www.metrohealth.org/documents/Patient%20Services/Heart%20and%20Vascular/RosenbaumSymposiumBrochure.pdf Course Directors/Faculty: J. Kevin Donahue, MD Learning Objectives: Understanding the connection between repolarization alternans and heart failure-associated ventricular arrhythmias. Be aware of changes in the endo to epicardial gradient in conduction velocity and connexin expression. Know clinical indications and limitations for microvolt T-wave alternans testing and invasive electrophysiology study. Activity Description: We propose a symposium to honor the scientific and academic contributions of Dr. David S. Rosenbaum. Dr. Rosenbaum died in May 2012 of pancreatic cancer. Prior to his death, David was an internationally reknown leader in the field of cardiac arrhythmia research. His specific research focus was understanding mechanisms causing ventricular arrhythmias in heart failure, and his expertise extended from tissue level studies using a technique where voltage sensitive dyes are usedto image the cardiac electrical activity to human studies of outcomes after implantible cardioverter	Thank you.

Robert Behnke		General	I submitted a comment already however new news is available. I wanted to make you aware of the following: MTWA Latest news, Febr 13th, 2013 HRS - 2013 team of reviewers chose to accept the abstract referenced below for Poster Presentation at Heart Rhythm 2013, to be held in Denver, Colorado, May 8 - 11, 2013. Faisal Merchant, MD (1) is the Presenting Author for abstract #9754 titled, Microvolt T-wave Alternans Testing And Risk Of Death In Patients With And Without ICDs. The most important University and Hospital Centres using clinically MicroVolt T Wave Alternans MTWA - Analytic Spectral Method) for ICD Decision Making have participated to the largest Prospective Multi center Clinical Trail where MTWA and Ejection Fraction (EF) results were used in the decision to implant ICD. About 650 patients (EF<40%) have been included in the trial and these patients had follow up of 2 years. 1 Cardiology Division, Emory University School of Medicine, Atlanta, GA	Thank you.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	General	MADIT II [1] and SCD-HeFT [2] are the two major studies supporting ICD usage in primary prevention patients (patients without a history of sustained ventricular arrhythmias). The results of these trials were significant, but the absolute mortality benefit was relatively modest. There is a growing consensus that additional risk stratification is required to increase the efficacy and efficiency of ICD therapy in these patients. Because the results of these studies are relatively modest in terms of absolute mortality benefit, one has to consider carefully the limitations of these studies when applying the results to specific patient groups. The clinical data discussed below demonstrate that primary prevention patients who meet the current Medicare requirements for prophylactic ICD implantation and have a negative microvolt T-wave alternans (MTWA) test measured using the spectral analytic method (the only method approved for reimbursement by Medicare) do not benefit from ICD implantation. Thus approximately 39% [3] of the patients who currently are eligible for ICD therapy, can safely avoid ICD implantation and the morbidity and mortality associated with this treatment [4]. Currently, prophylactic ICD therapy is targeted only to patients with LVEF <= 35%. However, seventy percent of all sudden cardiac deaths (SCDs) occur in patients with LVEF > 35%. [5] Little or no specific therapy is available to reduce SCD in these patients. Patients with a prior myocardial infarction (MI)), a left ventricular ejection fraction > 35% and a positive MTWA test are at substantially elevated risk for sudden cardiac death (SCD) [6]. Among all ICD treatment trials, studies involving EP risk stratification in coronary artery disease (CAD) patients (MADIT [7], MUSTT [8]) demonstrated the greatest mortality benefit for ICD therapy. Therefore, post-MI patients with LVEF > 35% should be considered for MTWA testing and those who test MTWA positive considered for EP testing. Patients then testing EP positive should be considered for ICD implantation. This clinical strategy may serve to reduce the rate of SCD in the LVEF > 35% population.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Executive Summary	? There are significant issues regarding the MADIT II [1] and SCD-HeFT [2] trials which are the basis for coverage of ICD implantation in primary prevention patients. ? The published data demonstrate that primary prevention patients who test negative for MTWA are at extremely low risk of sudden cardiac death and also have a very low rate of all-cause mortality. ? The published data also demonstrate that ICD implantation in such patients with a negative MTWA test provides no mortality benefit. ? MADIT II [1] and SCD-HeFT [2] trial results are not applicable to MTWA negative patients. ? Seventy percent of all sudden cardiac deaths (SCDs) occur in patients with LVEF > 35% [5]. ? Patients with a prior myocardial infarction (MI)), a left ventricular ejection fraction > 35% and a positive MTWA test are at high risk for sudden cardiac death (SCD) [6]. ? Among all ICD treatment trials, studies involving EP risk stratification for CAD patients (MADIT [7], MUSTT [8]) demonstrated the greatest mortality benefit for ICD therapy. ? Thus EP testing should be considered for post-MI, MTWA positive patients with LVEF > 35% with patients testing EP positive being considered for ICD implantation.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Results	MADIT II and SCD-HeFT Trials Current Medicare coverage for ICD implantation in primary prevention patients is mainly based on the MADIT II [1] and SCD-HeFT [2] clinical trials. While these were large and well-run trials, there are a number of issues with regard to the applicability of the results of these studies [9-12] to specific patient groups. ? Referral Bias These trials did not screen consecutive patients for enrollment, rather physicians used their own criteria to decide which of their eligible patients to refer to these trials. Physicians may well have used clinical criteria to refer high risk patients with the result that the patients studied were not representative of the patient population as defined by the enrollment criteria of these trials. ? High All-Cause Mortality Rates Mortality rates in the control arms of these studies were substantially higher than found in other studies involving similar patients. For example, the control arm mortality in MADIT II [1] (all CAD patients) and in the CAD patients in SCD-HeFT [2] (~36% and ~35% at four years, respectively), was substantially higher than in CABG-Patch [13] (all CAD patients, mortality of 24% at four years). Notably, the CABG-Patch [13] trial, which enrolled 1,055 patients similar to those in MADIT II [1] and SCD-HeFT [2] but identified all eligible patients, did not demonstrate a mortality benefit for ICD therapy. Markedly lower annual mortality in comparable patients is also shown in Hohnloser et al [14] (see Table 4 in that publication). These mortality differences could be due to referral bias or other reasons, but in any case raise the issue of the applicability of the results of MADIT II [1] and SCD-HeFT [2] to patients who simply meet the enrollment criteria of these studies. ? Treatment Bias Since neither physicians nor patients were blinded as to which patients received ICD therapy, patients with ICDs may have received more intensive medical attention than the non-ICD patients resulting in better outcomes. ? Analysis and Interpretation Bias Several critical appraisals of the major ICD studies have been published, noting issues with data analysis and result interpretation. Wilson et al [12] reported that ?[m]essage framing, underreporting of ICD complications, and interpretation bias were used to emphasize ICD efficacy in the reporting of ICD primary prevention trials.?	These are all valid concerns about clinical heterogeneity and applicability of many trials. In this regard, it is reassuring that recent studies have shown that individuals matched to those recruited into the trials derive similar benefit. Ref. Al-Khatib SM, Hellkamp A, Bardy GH et al. Survival of patients receiving a primary prevention implantable cardioverter-defibrillator in clinical practice vs clinical trials. JAMA 2013 January 2;309(1):55-62.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Results	Low Event Rates in MTWA Negative Patients Microvolt T-wave alternans has been studied extensively in patient populations similar to those in MADIT II [1] and SCD-HeFT [2]. These studies have shown that, among such patients who have not received an ICD, patients with a negative MTWA test have an extremely low rate of sudden cardiac death (SCD) and all-cause mortality compared to patients with an abnormal test. A 2009 meta-analysis [14] (Table 1 in that publication) showed, among 1,478 patients - few of whom had implanted ICDs - with LVEF < 30% (mean LVEF 27%) the MTWA negative patients had an annual rate of ventricular tachyarrhythmic events of 1.2% compared to an annual rate of 6.3% in the MTWA abnormal patients. A pooled analysis of 2,883 patients without implanted ICDs [3], reported that among patients with LVEF ? 0.35 those patients with a negative MTWA test had an annual SCD rate of 0.9% compared to an annual rate of 4.2% in the patients with an abnormal MTWA test. The above cited meta-analysis [14] (see Table 4) showed that ICD therapy in MADIT II [1] and SCD-HeFT [2] resulted in an average reduction in annual mortality from 9.5% in the control arms to 7.3% in the ICD arms (a relative reduction of 23%). In similar patients (mean LVEF, 27%), overwhelmingly without implanted ICDs, the annual all-cause mortality rate in the entire population was 5.4% compared to an annual mortality rate in the MTWA negative subgroup of 1.7% (a relative reduction of 69%) [14]. In the pooled analysis cited above [3], of patients with LVEF <= 35% none of whom had implanted ICDs, the annual all-cause mortality rate was 2.8% compared to an annual mortality rate in the MTWA negative subgroup of 0.9% (relative reduction of 68%). Thus, in a population of patients similar to those in MADIT II [1] and SCD-HeFT [2], a negative MTWA test in patients without implanted ICDs is associated with a far greater reduction in all-cause mortality than was ICD therapy in MADIT II [1] and SCD-HeFT [2].	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Results	Lack of ICD Efficacy in MTWA Negative Patients There are two published studies which demonstrate that prophylactic ICD therapy is effective in reducing mortality only in MTWA abnormal patients. Chow et al [15], in a prospective cohort of 768 patients with CAD cardiomyopathy (LVEF ? 35%) and no prior sustained ventricular arrhythmia, reported that in patients with a abnormal MTWA test ICD therapy resulted in a significant 55% reduction in all-cause mortality but that no significant change in all-cause mortality resulted from ICD therapy in the MTWA negative patients. In a prospective cohort of 965 patients with CAD and non-CAD cardiomyopathy, Chan et al [16] reported that in patients with an abnormal MTWA test ICD therapy resulted in (Table 4 in that publication) a significant 41% reduction in all cause mortality (annual mortality reduced from 12.1% to 7.1%), but that no significant change in all-cause mortality resulted from ICD therapy in the MTWA negative patients.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.
Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Results	Lack of Applicability of MADIT II and SCD-HeFT Trials to MTWA Negative Patients In translating the results of prospective interventional health outcomes study into clinical guidelines and coverage policies, there is an implicit assumption that all of the patients who met the enrollment criteria had a fairly similar level of risk. If a subgroup of the patients in the study is found to have a very different risk profile than the rest of the population, even if an average benefit from therapy is found for the entire population, it cannot be assumed that this benefit accrues to the subgroup. As shown above, among patients with characteristics similar to those in MADIT II [1] and SCD-HeFT [2], MTWA negative patients have dramatically lower rates of SCD and all cause mortality compared to the remainder of the population. Thus the MADIT II [1] and SCD-HeFT [2] trials do not provide evidence that MTWA negative patients benefit from ICD implantation.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Results	Use of MTWA to Risk Stratify Post-MI Patients with LVEF > 35% Seventy percent of all sudden cardiac deaths (SCDs) occur in patients with LVEF > 35%. [5] Yet, currently little specific therapy is available to reduce SCD in these patients. Patients with a prior myocardial infarction (MI)), a left ventricular ejection fraction > 35% and a positive MTWA test are at substantially elevated risk for sudden cardiac death (SCD). Ikeda et al [6] in a study of 1,041 post-MI patients with preserved ejection fraction (LVEF >= 40%, mean LVEF 55%) showed that at 24 months follow-up the event rate (SCD, cardiac arrest or resuscitated ventricular fibrillation) was 10% among the MTWA positive patients and 0.4% among the MTWA negative patients (p < 0.0001). Of all ICD treatment studies, studies involving EP risk stratification in CAD patients (MADIT [7], MUSTT [8]) demonstrated the greatest mortality benefit for ICD therapy. The annual absolute reduction in mortality in MADIT was approximately 9% (as measured at 4 years of follow-up). In MUSTT the annual absolute reduction in mortality was approximately 8% (as measured at 5 years of follow-up). In comparison, as noted above the average ICD mediated absolute reduction in mortality in MADIT II and SCD-HeFT (both of which did not involve EP risk stratification) was only 2.2%. The evidence thus shows that ICD therapy in CAD patients who are inducible at EP is highly effective. Two studies have shown that there is a 40% rate of EP inducibility in MTWA positive patients (36% [17] and 43% [18]) indicating that there would be a high yield of positive EP tests following a positive MTWA in post-MI LVEF > 35% patients. Furthermore, in the ABCD trial the redictive values for arrhythmic events associated with a positive MTWA test and a positive EP study were essentially additive when both tests were positive [18]. Therefore, post-MI patients with LVEF > 35% should be considered for MTWA testing and those who test MTWA positive considered for EP testing. Patients then testing EP positive should be considered for ICD implantation. This clinical strategy may serve to reduce the rate of SCD in the LVEF > 35% population.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	Discussion/Conclusion	There is a lack of evidence to demonstrate that ICD therapy benefits primary prevention patients with a negative MTWA test. Indeed, no study has ever demonstrated a benefit for ICD implantation either in an MTWA negative population or in any other population with a SCD or all-cause mortality rate anywhere remotely as low as has been found in MTWA negative patients with depressed LVEF. An MTWA-guided strategy would reduce the number of ICD implants in the primary prevention population currently meeting CMS indications for ICD therapy by approximately 39% [3] without impacting the mortality benefit of ICD therapy. Currently prophylactic ICD therapy is targeted only to patients with LVEF <= 35%. However, seventy percent of SCDs occur in patients with LVEF > 35%. There is currently little or no specific therapy to prevent SCD in LVEF > 35% who have not previously experienced a sustained ventricular tachyarrhythmia. Post-MI patients with LVEF > 35% who have a positive MTWA test are at high risk of sudden cardiac death. ICD therapy has been demonstrated be highly effective in CAD patients risk stratified by means of EP. Thus post-MI patients with LVEF > 35% should be considered for evaluation by means of MTWA testing. Those patients who test MTWA positive should be considered for EP testing and those who test EP positive considered for ICD therapy. This clinical strategy may substantially reduce SCD in the LVEF > 35% population.	A technology assessment of MTWA was not within the scope of this review. The challenge to better risk stratify and identify individuals who may benefit from ICD implantation is highlighted in the discussion under the future research needs section.

Richard J. Cohen	Whitaker Professor in Biomedical Engineering, MIT; Head Scientific Advisory Board and Consultant Cambridge Heart, Inc.	References	[1] A. J. Moss, et al., "Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction," N Engl J Med, vol. 346, pp. 877-83, Mar 21 2002. [2] G. H. Bardy, et al., "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure," N Engl J Med, vol. 352, pp. 225-37, Jan 20 2005. [3] F. M. Merchant, et al., "Clinical utility of microvolt T-wave alternans testing in identifying patients at high or low risk of sudden cardiac death," Heart Rhythm, vol. 9, pp. 1256-64 e2, Aug 2012. [4] M. R. Reynolds, et al., "The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators," J Am Coll Cardiol, vol. 47, pp. 2493-7, Jun 20 2006. [5] E. C. Stecker, et al., "Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study," J Am Coll Cardiol, vol. 47, pp. 1161-6, Mar 21 2006. [6] T. Ikeda, et al., "Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study," J Am Coll Cardiol, vol. 48, pp. 2268-74, Dec 5 2006. [7] A. J. Moss, et al., "Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators," N Engl J Med, vol. 335, pp. 1933-40, Dec 26 1996. [8] A. E. Buxton, et al., "A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators," N Engl J Med, vol. 341, pp. 1882-90, Dec 16 1999. [9] A. E. Buxton, et al., "Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study," J Am Coll Cardiol, vol. 50, pp. 1150-7, Sep 18 2007. [10] C. Cevik, et al., "Prophylactic implantation of cardioverter defibrillators in idiopathic nonischemic cardiomyopathy for the primary prevention of death: a narrative review," Clin Cardiol, vol. 33, pp. 254-60,	Thank you.

Del M. Conyers	Heart Rhythm Society	General	The Heart Rhythm Society (HRS) appreciates the opportunity to provide comments on the draft report regarding the assessment on implantable defibrillators and the evidence for primary prevention of sudden cardiac death (SCD). 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 more than 5,300 specialists in cardiac pacing and electrophysiology, consisting of physicians, scientists and their support personnel. Electrophysiology is a distinct specialty of cardiology, and lectrophysiologists are board certified in clinical cardiac electrophysiology through the American Board of Internal Medicine, as well as in cardiology. HRS? members perform lectrophysiology 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, SCD, atrial fibrillation, (AF) and heart failure (HF). As these advancements occur, HRS is committed to improving the quality, safety, and efficiency of patient care. The Society recognizes that this report is rigorous and the methodology of evidence collection and synthesis is strong. We hope that these comments are useful and look forward to working with AHRQ staff on these issues. Additionally, we encourage AHRQ staff to share HRS?s comments with its colleagues at the Centers for Medicare and Medicaid Services responsible for coverage determination. If you have questions about these public comments or would like additional information about HRS activities, please contact HRS?s Director of Quality Improvement, Del Conyers at dconyers@hrsonline.org. Below, the Society offers comments on specific aspects of the draft report.	Thank you

Del M. Conyers	Heart Rhythm Society	Executive Summery	The report contains a summary of scientific evidence pertaining to the primary prevention of SCD through the use of ICDs. By reviewing a number of relevant publications, the report asks three primary questions regarding: 1) the efficacy of primary prevention ICD implantation in the candidate patient population; 2) the nature of adverse events associated with device implantation; and 3) the types of patients evaluated in these studies. The report is based on evidence obtained through a comprehensive examination of randomized and non-randomized studies, many considered landmark and contemporary, in the realm of primary prevention ICD implantation. Findings from studies germane to the particular question being assessed (as outlined above) are summed and recapitulated, with a ?Strength of Evidence? rating assigned to the resulting conclusion. The authors conclude that ICD implantation in appropriately selected candidates reduces the risk of all-cause mortality and SCD, without apparent difference in effect whether standard ICD or one capable of cardiac resynchronization therapy defibrillator (CRT-D) is utilized. This finding is congruent with current treatment guidelines and present clinical practice.	Thank you
Del M. Conyers	Heart Rhythm Society	Key Question 2	Early adverse events (AEs) related to ICD implantation are relatively infrequent with serious AEs occurring less commonly. Possible risk factors associated with the occurrence of early AEs have been established including specific patient-related features and details of physician training/background and operative center. The findings reported by the authors also are well accepted by the electrophysiology community, and such items often are considered in the clinical decision-making process when ICD implantation is anticipated. Additional commentary is provided below regarding late AEs as part of the discussion/conclusion.	Thank you

Del M. Conyers	Heart Rhythm Society	Key Question 2	The report recognizes the predominant risk identifier resulting in primary prevention ICD implantation is reduced left ventricle ejection fraction (LVEF), most often measured via echocardiogram. Several studies used additional criteria such as non-sustained ventricular tachycardia, HF symptom class, and electrocardiographic QRS duration. Only one study included in the report used electrophysiologic (EP) testing as a risk stratifier. A small number of analyses studied ICD implantation soon (generally <40 days) following myocardial infarction, which is now felt to be a relative contraindication to primary prevention ICD implantation. These conclusions align with current treatment guidelines and clinical practice.	Thank you
Del M. Conyers	Heart Rhythm Society	Introduction/Background	The Society appreciates the recognition of the existing 2008 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. HRS encourages AHRQ to review the following documents, 2013 Appropriate Use Criteria (AUC) for ICD/CRT Therapy; 2012 Focused Update for Device-Based Therapy of Cardiac Rhythm Abnormalities; ACC/AHA Guidelines for the Management of Patients with Heart Failure; and ICD Indications: 2013 HRS-ACC-AHA Expert Consensus on ICD Indications Outside of Current Guidelines . These documents are meant to provide additional guidance concerning the decision to implant ICDs and CRT devices in a variety of clinical scenarios that may or may not be represented in the guidelines, often providing additional guidance in areas where there are gaps in guidelines.	We have referenced these documents in the introduction under current guidelines:

Del M. Conyers	Heart Rhythm Society	Methods	HRS remains concerned about the summary comparisons of the benefits of ICD and ICD plus Cardiac Resynchronization Therapy (CRT) because such comparisons are somewhat simplistic and potentially misguided. Importantly, the patient populations for primary prevention ICD overlap somewhat with those who are eligible for CRT-D, but they are not exactly the same. The intention of ICD therapy is restoration of normal sinus rhythm in the setting of life-threatening arrhythmias, and the intention of CRT is improvement of functional status and symptoms of HF. While both of these can affect mortality, they are different intended therapies and attempts to make overarching comparisons fail to recognize the fundamental differences in the underlying populations and the goals of therapy for ICD and CRT. Therefore, we remain concerned that the authors do not go far enough to make these distinctions clear enough. Without further clarification, those who are not as familiar with these key nuances may potentially draw sweeping conclusions from these summary estimates. Therefore, we urge the authors to include information in the limitations section about how such different populations may affect the overall estimates.	We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed. We have made these distinctions clearer and highlight that the comparison of CRT-D vs ICD does not provide a complete summary of the effects of CRT to avoid readers drawing sweeping conclusions on the effectiveness of CRT therapy. See Introduction and discussion.

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	BENEFITS Efforts to determine a differential effect of anti-tachycardia pacing (ATP) is not sought further as the report accurately recognizes that no studies specifically measuring additive mortality of devices with this feature have been published. Given that appropriate exclusion, the authors may want to alter the title on page 37 indicating that devices with and without ATP will be discussed. Additionally, ATP is an available programming option on all modern transvenous ICD systems and can be readily activated by a clinician if deemed appropriate for any given patient. Several recent studies have, however, identified adverse effects (including increased mortality) with ICD shock therapy for relatively slower ventricular arrhythmias, with the observation of favorable outcomes in separate studies where more aggressive ATP programming strategies were employed. It must be remembered that ATP must only be used in carefully selected individuals at the discretion of the caregiver/physician as it carries its own set of benefits and consequences beyond mortality effects. The development of appropriate ICD shock underscores the lifesaving potential of primary ICD implantation. While nearly all studies measured the effect of ICD implantation on overall mortality, arrhythmic mortality, and sudden death, only a fraction evaluated the occurrence of ICD shock/therapy. Delivery of single appropriate ICD shock/therapy in many situations may be considered a life-sparing event; however, the significance of multiple lifesaving ICD shocks/therapies over time in a single patient is perhaps under-recognized, despite such intervention?s effect of saving an individual?s life ?multiple times over.?	This was explained. Refer to pages in Results KQ1. We added this to the discussion. Comparison of different programming algorithms was beyond the scope of this report. Nevertheless, we have featured the findings of MADIT-RIT in the discussion under supplementary evidence from excluded studies. “We have also added this comment under research gaps: Evolution in programming algorithms may also alter the benefits harms balance. As discussed above, MADIT-RIT showed mortality benefit for programming algorithms which may be additive to the benefit of an ICD alone “ This is an issue that relates to the variability of the number of appropriate shock(s) per person. In our review, the outcome of interest was mortality rather than appropriate shocks since the two are not always directly correlated. Methodologically, it is unclear how to better assess for the significance of multiple lifesaving therapies and the possible positive or negative effects of multiple shock interventions.

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	RISKS Quality of life (QOL) is found to possibly have a negative impact following ICD implantation, with appropriately low strength of evidence assigned to this finding. Despite assigning a low strength of evidence for this finding (as outlined in Table 3), on page 22, the authors summarize that both the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and the Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated ardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVERT) trial did not demonstrate any reduction in quality of life, and the Coronary Artery Bypass Graft Patch Trial (CABG-PATCH) was the only one that showed reduction in some of the domains of the Short Form (36) Health Survey (SF-36 form). However, we encourage the authors to further acknowledge that CABG-PATCH implanted epicardial ICD systems which are much more invasive and large compared to the transvenous systems implanted in MADIT-II. Such older technologies are almost never employed currently. Furthermore, that generation of devices was ?committed? in that they delivered a shock once charging began regardless of whether the arrhythmia was still persisting. Given this evolving technology, we strongly urge the authors to acknowledge the very different nature of the systems used in CABG-PATCH before placing such weight on the QOL findings. The paucity of health status data in the era of Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PAINFREE-Rx II), Primary Prevention Parameters Evaluation (PREPARE) trial, and Multicenter Automatic Defibrillator Implantation Trial: Reduce Inappropriate Therapy (MADIT-RIT) means that, in the modern era, the QOL effect of ICD therapy is unknown, in addition to the current finding that there is a low grade of evidence due to the lack of clinical trial data. As already noted, relatively few studies have examined this variable, which is of relatively complex nature given multiple associated (and contributing) issues such as occurrence of ICD shock, progressive cardiovascular illness, and other comorbid conditions. Attempting to draw conclusions in today's patients with modern programming strategies based on outdated strategies has the potential to be misleading for patients, physicians, and olicymakers.	Given the feedback on QoL, we have reassessed the QoL data and have changed our conclusion to there being a low strength of evidence for no difference in QoL with ICD use.

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	While the report acknowledges fast-paced technological advances for ICDs, HRS further highlights two areas of technological innovation ? programming advances, as well as new lead options ? which can dramatically affect the risk-benefit calculation. The report further notes the recent Food and Drug Administration (FDA) approval of the first subcutaneous ICD, which incorporates a generator and a lead that is implanted below the skin along the bottom of the rib cage and breast bone, removing the need for fluoroscopic guidance and direct vascular or cardiac access, and thus reducing the potential risk profile of the procedure. In addition, programming advances have dramatically reduced the instances of inappropriate shock, as highlighted in the PREPARE trial, the MADIT-RIT, Dual Chamber and VVI Implantable Defibrillator (DAVID) Trials I and II, INTRINSIC-RV, and PainFREE Rx II. Importantly, these studies provide clear evidence that ICDs in patients with HF with at least moderately-reduced left ventricular (LV) systolic function are associated with striking mortality benefits. Therefore, we strongly urge the authors to further examine the effects of various programming strategies in these populations that clearly modify the benefits of ICDs. In doing so, the authors would likely note that right ventricular (RV) pacing without CRT in patients with ICD therapy is clearly associated with worse outcomes (as evidenced in DAVID), so strategies to minimize RV pacing in these patients are critically important. Similarly, in patients with an ICD, several studies (both observational and randomized) have examined the approaches of modern detection algorithms and therapy strategies (more aggressive use of ATP prior to ICD shocks) that have clearly demonstrated fewer therapies in general, fewer inappropriate therapies, and a high likelihood of restoring sinus rhythm without shocks. Importantly, not only do these approaches have these benefits, they do not increase mortality. MADIT-RIT clearly demonstrated an incremental mortality benefit from the use of these approaches in addition to the benefits of ICD therapy without these advanced strategies, such as those seen in trials like the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). A failure to recognize these incremental benefits of novel programming strategies and the goal of minimization of RV pacing is a weakness of the document. Given the evolving technology of ICDs and CRT devices (including its programming), current benefits of both technologies are likely under-estimated in the current literature. Thus, as these technological advances are	A review of programming algorithms was not within the scope of this report. Further, the PainFree and DAVID trials included a mix of patients who required an implanted defibrillator for primary or secondary prevention. We acknowledge in the discussion that novel programming strategies may change the benefit harms assessment and that MADIT-RIT showed mortality benefit for programming algorithms which may be additive to the benefit of an ICD alone.

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	The document does mention the higher risk of complications with dual chamber (as opposed to single chamber) ICDs. At present, there appears to be a paucity of data supporting dual chamber ICD implantation in all patients who meet primary prevention ICD indications. The variation in usage of dual chamber ICDs (as previously reported in the National Cardiovascular Data Registry or NCDR ICD Registry) highlights this controversy or paucity of data on this topic, which has implications related to costs. Perhaps a section regarding recommendations for ICD implantation (in the absence of CRT indications) might be considered.	The introduction now includes a section on current guidelines and appropriate use criteria for ICD or CRT.
Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	Late adverse events following ICD implantation are documented within the report, with appreciation for the difficulty in recording such events owing to variability in definitions and parameters studied. Early adverse events are generally captured within the NCDR ICD Registry. However, the authors note a key limitation that only inpatient complications are included in the NCDR data, which is likely a gross underestimation of real-life complications that are often noted after hospital discharge. In particular, lead or mechanical complications may be underestimated. In addition, the elderly have higher complication rates from device implantation. Finally, the impact of lead advisories and recalls also will impact complications, which may be underestimated in this report. Therefore, the authors may want to consider mentioning this in the section related to future study or limitations. Despite these limitations, the continued application of the NCDR ICD Registry, particularly in its most recent rendition, may offer further opportunity to allow systematic self-reporting of late adverse events (especially those involving ICD system failure) given its inclusion of generator replacement procedures and recent incorporation of lead-related procedures. Improved post-market surveillance by industry and non-industry entities also is expected to augment this process.	We clarified that the distinction between AEs during hospitalization for ICD implantation and late AEs (in abstract, results and discussion). We added the problem of lack of robust data on late adverse events and patient reported outcomes to the research gaps.

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	Although the NCDR ICD Registry has answered many of the initial questions regarding ?real life? efficacy of ICDs for primary prevention indications, it still has value related to clinical practice trends. Although it is somewhat time-consuming to complete these registry forms, it does allow each center the ability to track and benchmark with other centers. With the addition of new information in the executive summary of the NCDR ICD Registry reports, centers can identify if their physicians are appropriately implanting devices for class I or class II guideline indications. In addition, it allows a ?real life? look at which types of patients are receiving ICDs outside of those patients enrolled in prior clinical trials. For example, patients with chronic kidney disease (CKD) on dialysis were excluded from clinical trials, but do receive ICDs and may not necessarily derive the same benefit. The very elderly may have been excluded from some clinical trials, and it will be important to continue to track ICD usage and benefit in these patients. The impact of changing and newer ICD technology also may impact the benefit of ICD therapy (such as, the now approved totally subcutaneous ICD system). Although the questions addressed by the Medicare Coverage with Evidence Development (CED) may be answered, there remain newer questions and ongoing issues for exploration. Thus, the NCDR ICD Registry continues to have a meaningful benefit by tracking ?real life? usage of this life-saving technology	Thank you

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	SUBPOPULATIONS Reduced LVEF is the primary means of risk stratification for SCD detailed within the report. To a lesser degree, other identifiers also are considered, such as HF symptom (i.e. New York Heart Association class) and results of EP testing. Though imperfect, reduced LVEF offers a non-invasive, readily available and relatively straightforward assessment of arrhythmic risk, associated with a range of numbers-needed-to-treat (NNT) values for ICD benefit. The importance of better risk stratification should be emphasized. While it is beyond the scope of the current report, additional risk stratification tools are continually being examined, including measures of autonomic function and most notably, T-wave alternans. This latter modality has been formally studied in a comparative analysis with EP testing in the ABCD (Alternans Before Cardioverter Defibrillator) Trial (J Am Coll Cardiol. 2009;53(6):471-479). In addition, advances in magnetic resonance imaging (MRI) or genetic testing may be useful in the future. Additional trials also should focus on women, who have been traditionally under-represented in clinical ICD trials, and on patients with CKD, as well as the elderly. Newer technology, such as the totally subcutaneous ICD, and future technology (with ?leadless pacing?), also may impact on the benefit of primary prevention ICDs. While seemingly elusive, it is hoped that the discovery of improved risk stratifiers, either alone or in combination, will yield greater estimates of arrhythmic risk, possibly reducing the rate of unnecessary ICD implantation.	The importance of better risk stratification has been emphasized in the Research Gaps section in the discussion. We have added the following to the discussion: “While it is beyond the scope of the current report, additional risk stratification tools are continually being examined, including measures of autonomic function such as, T-wave alternans. This latter modality has been formally studied in a comparative analysis with EP testing in the ABCD (Alternans Before Cardioverter Defibrillator) Trial (J Am Coll Cardiol. 2009;53(6):471-479). In addition, advances in magnetic resonance imaging (MRI) or genetic testing may be useful in the future.”

Del M. Conyers	Heart Rhythm Society	Discussion/Conclusion	Although the lack of benefit of ICD therapy in the early post-myocardial infarction (MI) period has been adequately addressed in randomized trials (particularly the Defibrillator in Acute Myocardial Infarction Trial or DINAMIT and Immediate Risk Stratification Improves Survival or IRIS trial), the optimal timing post-revascularization has not been completely answered. Most of the post-revascularization data has been extrapolated from other studies examining the benefit of ICD therapy for primary prevention, not specifically aimed at determining the optimal timing post-revascularization (as patients were excluded from trial enrollment early post-revascularization). Although the CABG-Patch did directly address this issue, this was an older study that did not utilize modern technology. Further, as outlined in the review, the primary meta-analyses of the randomized controlled trials (RCTs) excluded these three trials because they included patients who ?would also fall outside of the current clinical guidelines for implantation as well as guidelines for Medicare coverage.? The exclusion of patients from prior studies does not necessarily indicate ?lack of benefit? for all patients during this early revascularization time period. In addition, there are some subgroups of patients who will likely never be studied prospectively. For example, a patient with reduced left ventricle function who develops complete heart block following valve replacement surgery with incidental bypass surgery or the patient with Sick Sinus Syndrome who needs a pacemaker post-operatively may be appropriate for ICD therapy to avoid a ?second surgery? three months post-operatively (if LV function does not improve). In addition, a patient with a long-standing nonischemic cardiomyopathy (CM) who develops one vessel coronary artery disease (CAD) and requires percutaneous coronary revascularization (PCI) might also be appropriate for ?early? ICD therapy. The 2013 Appropriate Use Criteria (AUC) for ICD/CRT Therapy ~~provides~~ assessed levels of appropriateness for implanting ICDs and CRTs in 369 real-life case scenarios, with the goal of enhancing physician and patient decision making and improving care and health outcomes. The AUC document should be used in conjunction with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and the 2012 Focused Update.	The 2013 Appropriate Use Criteria (AUC) for ICD/CRT Therapy are now referenced in the introduction to be used in conjunction with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and the 2012 Focused Update.

Del M. Conyers	Heart Rhythm Society	Methods	HRS is further concerned with the conclusion on page 38-39 that ?overall, there is low strength of evidence that all-cause mortality is similar for patients with NYHA Class I or II heart disease who receive cardiac resynchronization therapy defibrillator (CRT-D) or ICD alone for primary prevention (Table 7).? The authors have excluded analysis of a key clinical trial in this area: the Resynchronization?Defibrillation for Ambulatory Heart Failure Trial (RAFT) (Tang et al, NEJM 2010). The authors noted that they did not include the RAFT and other studies examining similar issues because the trials were ?not exclusively primary prevention trials?. However, unlike the other cited trials, the RAFT trial looked at the hard outcome of total mortality and congestive heart failure (CHF) hospitalization. In addition, the trial highlighted that in patients with NYHA II CHF or above, with wide QRS, there was definitely a mortality benefit of CRT-D compared to ICD alone. Therefore, we strongly encourage the authors to include this trial in their analysis before making conclusions that there is little evidence to support use of CRT-D versus ICD in patients with NYHA II symptoms of CHF and not to simply exclude its evidence due to the overall focus of the trial, given the information it provides. In addition to potential revisions to Table 7, Table 9 also would need to be revised to include the RAFT trial.	We have added the RAFT trial, including a description of the different NYHA Classes across the studies of CRT-D.

Del M. Conyers	Heart Rhythm Society	Methods	While the rates of complications appear to be well represented, HRS is concerned with the lack of definition in Table 12 of a ?serious adverse event.? Given that not all adverse events are equal post-ICD implant, it is important that the authors define such events appropriately. For instance, HRS would suggest that sepsis/infection requiring extraction of the device should be considered a ?serious adverse event? because it is potentially fatal, whereas a post-implant hematoma or superficial phlebitis can be quite minor and should not be considered a ?serious adverse event.? Therefore, HRS encourages the authors to include a discussion in the complications section of this paper about the relative importance of various complications on patient morbidity and mortality and more specificity in what defines a ?serious adverse event? versus ?any adverse event? (whether a ?late? or ?early? event).	For early (in-hospital) events in the NCDR ICD database, we tabulated serious adverse events as categorized by study authors: cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, hemothorax, pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, pericardial tamponade, and arteriovenous fistula. One study (Tsai, 2011 PMID 21878667) also included lead dislodgement. For the summary of late (out of hospital) AEs we did not include as separate category of "serious adverse events"
Del M. Conyers	Heart Rhythm Society	Methods	Although it is clear that the Multicenter Unsustained Tachycardia Trial (MUSTT) was excluded from this analysis because it was not designed with the specific intention to test ICD therapy versus no ICD therapy for primary prevention of SCD, it is only one of two studies (along with MADIT I), which examined the utility of EP testing in risk stratification, resulting in a lower number to treat. Also, it included patients who were earlier post-revascularization. The authors may consider including some of the MUSTT data in the revascularization discussion. However, this was a small study and perhaps this data may not have an impact on the previously described findings. CABG-Patch also included patients immediately post-revascularization, but this utilized epicardial systems, which are now outdated technology.	The reasons for excluding MUSTT are correctly stated by the reviewer. We have summarized MUSTT in the discussion.

Del M. Conyers	Heart Rhythm Society	Methods	Given the critical clinical evidence provided by the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trials I and II, HRS would encourage the authors to provide additional information on why these randomized controlled trials were not directly included within the discussion. We strongly encourage this data to be included in future examinations of this topic. The DAVID trials examined the impacts of the programming of ICDs and CRT on survival benefit and heart failure hospitalization. Given the evolving technology of ICDs and CRT devices (including its programming), current benefits of both technologies are likely under-estimated in the current literature.	A review of programming algorithms was not within the scope of this report.
John Gordon Harold	American College of Cardiology	General	The American College of Cardiology (ACC) is pleased to offer comments on the draft report assessing the use of implantable defibrillators for primary prevention of sudden cardiac death. The ACC is transforming cardiovascular care and improving heart health through continuous quality improvement, patient-centered care, payment innovation and professionalism. The College is a 43,000-member nonprofit medical society comprised of physicians, nurses, nurse practitioners, physician assistants, pharmacists and practice managers, and bestows credentials upon cardiovascular specialists who meet its stringent qualifications. The College is a leader in the formulation of health policy, standards and guidelines, and is a staunch supporter of cardiovascular research. The ACC provides professional education and operates national registries for the measurement and improvement of quality care. More information about the association is available online at http://www.cardiosource.org/ACC.	Thank you

John Gordon Harold	American College of Cardiology	General	This draft report is an extensive analysis of existing data. The conclusions from this report are consistent with outcomes from a large number of randomized clinical trials and clinical registries. The findings from this report are also consistent with the ACC/AHA ICD guidelines published in 2008 and a Focused Update in 2012. These clinical recommendations from the guidelines correlate with the coverage criteria established by CMS. The authors indicated other meta-analyses have been conducted on similar questions and topics from similar clinical data sets in the past. Findings and conclusions from the current report are consistent with what practitioners have known for some time. Nothing appears to be new or different from what has been recommended from the guidelines and established CMS coverage on ICD for primary SCD prevention. In this sense, the draft report is not controversial because of its alignment with ACC documents and current literature. ACC reviewers were puzzled as to why the authors undertook such an extensive analysis and review of existing?but relatively old?trials, registries, and literature to affirm the current state of affairs without attempting to add anything new to our understanding of the field.	Thank you
John Gordon Harold	American College of Cardiology	General	A more interesting and potentially useful report might strive to address knowledge gaps that would identify areas for new research topics that could advance medical science and improve patient care. ICD and SCD prevention data are insufficient or less robust from elderly populations (75-80 years old), women, and minority groups.	We have now added detailed subgroup analyses, including for women and elderly.
			Special clinical circumstances may warrant ICD implantation in patients who had a recent myocardial infarction within 30-40 days (IRIS and DYNAMIT trials), coronary artery bypass graft or percutaneous coronary intervention within 90 days, or newly diagnosed non-ischemic cardiomyopathy within 90 days. A critical analysis of the existing data on these topics would bring new information to this field to assist health care providers and policymakers in making educated patient care decisions.	Aggregate data in clinical trials have limited ability to address special clinical circumstances. We have included detailed subgroup analyses, which are exploratory for most comparisons. We have added a reference to the Appropriate Use criteria in the introduction.

John Gordon Harold	American College of Cardiology	General	Collection and analysis of registry data is one of the most reasonable ways to address knowledge gaps and improve patient care outside of clinical trials. The ICD Registry continues to be a powerful quality benchmarking tool for any facility involved in implantable cardioverter defibrillator (ICD) implantation, upgrade, or replacement. It establishes national standards for understanding treatment patterns, clinical outcomes, device, safety, and the overall quality of care provided to ICD implantation patients. The ACC anticipates that data collection tools such as the ICD Registry and other NCDR registries will continue to provide evidence-based quality improvement solutions for cardiologists and other medical professionals who are committed to measurement, improvement, and excellence in cardiovascular care. Finally, in addition to these general comments on the nature and value of the document, addressing several specific errors or omissions below would improve the document.	We agree.
John Gordon Harold	American College of Cardiology	General	Thank you for your consideration. We hope these comments will prove helpful and will be shared with appropriate staff at CMS should any future coverage issues arise. Please contact James Vavricek, Senior Specialist for Regulatory Affairs, at jvavricek@acc.org or 202-375-6421 to coordinate activities or seek additional information.	Thank you.
John Gordon Harold	American College of Cardiology	Key Question 1a & 1c	Page 19, line 2: It seems possible the mean age of 86 is an error.	This is not an error. The Mezu study only enrolled patients ≥80 years old. The mean age in the control arm was 86 ± 4 years.
John Gordon Harold	American College of Cardiology	Table	Page 26, Table 5A: In the NYHA Class section, MADIT II did not include class IV patients. Class II-III should be listed in the comparison column.	The Moss 2002 study reports enrolling patients with NYHA class IV: 5% in the defibrillator arm and 4% in the conventional-therapy arm.
John Gordon Harold	American College of Cardiology	Table	Table 5A on pages 26-27 is complex and difficult to understand. The data on women who receive ICDs is not completely clear. Some data would indicate that women benefit more from CRTDs and less from ICDs. However, that does not appear to be clear from these data. Furthermore, subgroup analyses of post-hoc analyses of these studies are highly problematic.	Table 5A has been modified to improve clarify, to include meta-analyses, and to highlight the subgroup pairs that have been compared by 2 or more studies. Note that Table 5A (and 5B) are restricted to studies of ICD vs no ICD, not CRT-D.

John Gordon Harold	American College of Cardiology	Table	Data on Table 5B are similarly confusing. These data do not show that this is similarity in benefit of an ICD under all circumstances and does not include all the data in this regard. Consider the data on kidney disease; it is likely that the information is underpowered to determine which group will necessarily benefit the most or the least.	The nonsignificant P values for the interactions indicate that the studies failed to find differences between subgroups that are not likely due to random chance. Underpowered subgroups increase the likelihood of the apparent differences being due to chance alone. We do not say there is evidence of a similarity of benefit, but instead that the evidence fails to support a difference.
John Gordon Harold	American College of Cardiology	Table	In table 7, number needed to treat data may or may not be accurate but do not include the long-term follow-up data from some of the studies.	We have revised the NNT analyses to include data from all reported years.
John Gordon Harold	American College of Cardiology	Table	Page 58, Table 12: It would be helpful for ?death alone? should be included in the table.	We considered death alone to be an efficacy outcome. We included the composite outcome of "Any adverse event or death" as there were reports of some subgroups that only used this outcome for their analyses.
John Gordon Harold	American College of Cardiology	Table	Page 62, section Studies of Patients with Ischemic Cardiomyopathy and Remote MI: Authors should consider noting that an electrophysiology study was required for the MADIT I trial. This is an important difference from the later trials. The study design and patient inclusion explain the higher mortality in this trial.	This feature of MADIT I is described on page 57 in the section entitled "Diagnostic Tests and Algorithms Used to Select Patients", where it states "Only MADIT reported using electrophysiology testing."

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	Boston Scientific Corporation (Boston Scientific) appreciates the opportunity to provide comments on the Agency for Healthcare Research and Quality (AHRQ) Technology Assessment draft report on Implantable Defibrillators. Boston Scientific is dedicated to transforming lives through innovative medical solutions that improve health of patients around the world, Boston Scientific supplies medical devices and technologies used by the following medical specialty areas, all of which provide beneficiary care in the hospital inpatient setting: ? Cardiac Rhythm Management; ? Gastroenterology; ? Interventional Bronchoscopy; ? Interventional Cardiology; ? Interventional Radiology; ? Oncology; ? Neuromodulation; ? Urology; and ? Women?s Health. We share AHRQ?s commitment to developing and disseminating evidence reports and technology assessments to help patients, physicians, payers, and other stakeholders improve patient outcomes, reduce costs, and increase patient access.	Thank you

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	Implantable defibrillator (ICD) technology is a long-established and recognized therapy that has been proven clinically beneficial for primary prevention of sudden cardiac death (SCD). We concur with the main conclusions generated from the draft technology assessment that the long-standing available evidence supports the clinical value of ICD for primary prevention of SCD: ? ICD therapy shows benefit with regard to all-cause mortality and SCD in patients with reduced left ventricular ejection fraction (LVEF) and ischemic or nonischemic cardiomyopathy beyond immediate post-MI. ? High strength of evidence exists that in-hospital adverse events are infrequent and though patients may receive inappropriate shocks from ICDs, that these events are minimized with improved programming algorithms. ? Eligibility requirement for those indicated for ICD shows that the findings are applicable to individuals with nonischemic or ischemic cardiomyopathy and reduced LVEF and correlate with the coverage criteria set by CMS.	Thank you
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Introduction	We believe that the assessment could be further strengthened with the inclusion of all available ICD technology in the introductory section of the assessment. Absent from this introductory discussion of ICD technology is the subcutaneous ICD (the S-ICD? System) which was approved by the FDA on September 28, 2012. The S-ICD System is the world?s first and only ICD that provides defibrillation therapy without touching the heart, leaving the vasculature untouched. The S-ICD System is indicated to provide defibrillation therapy for the treatment of life-threatening ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing. We recommend that AHRQ add to page 3 of the introduction, following the last sentence to the first paragraph of the ?ICD Technology? section; ?New technology offers a totally subcutaneous ICD system. The subcutaneous ICD is similar to transvenous ICDs with the exception that the subcutaneous ICD electrode (lead) is placed subcutaneously and does not touch the heart or vascular system.?	The subcutaneous ICD system was approved in September, 2012, after the bulk of the evidence review for this report had been completed. The device is described in the discussion as an example of a technological advance that makes it imperative to critically reevaluate the incremental net benefit and cost of evolving medical and device therapies.

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Key Question 1	In the summary findings (Table 3, page 18) for ICD vs. no ICD for the outcome of all-cause mortality, the NNT (number needed to treat) was reported at one year which is too short of a follow-up interval to adequately measure the life-saving ability of the ICD. Because ICDs are measured by mortality, it would be more meaningful if the analysis or measurement was extended to at least three to five years to permit the accumulation of enough events to truly discern ICD benefit. Most ICDs last 5 years but given the lack of follow-up beyond three years in most studies, the minimum should be three years for a more accurate measure of benefit with the NNT metric.	The NNT analyses have been revised to included data from all reported years.
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Key Question 1	In Table 4, COMPANION is included as an ICD versus non-ICD study when in fact it was CRT therapy with or without defibrillation (CRT-D versus CRT-P). The influence of two therapies on mortality may overstate the results. We recommend that AHRQ either reconsider the use of COMPANION or add a statement that acknowledges the limitation that the two simultaneous treatments were given. Furthermore, the devices used were described as single-chambered ICDs, when in fact, they were multi-chambered devices (RA, RV, and LV). (Table 4, page 24)	In Companion, we contrasted CRT-D versus medical therapy (without CRT-P). While this may slightly overstate the benefit of combined therapy, the study showed only a borderline statistically significant finding for mortality in favor of CRT-P vs. medical therapy suggesting that the difference for the primary composite outcome was driven by heart failure admissions. The description of the control arm for Companion has been specified in Table 4 to be “No ICD, medical therapy.”

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Table	As referenced in Table 4, there is inconsistency in the studies that are included in this table [Table8] as primary prevention studies. For example, MADIT-CRT was not composed exclusively of patients for primary prevention but also included secondary prevention patients as well. RAFT was another study that included secondary prevention patients and this was excluded from inclusion in the table. If the purpose is to include only primary prevention patients, our recommendation is to either remove MADIT-CRT from the table or retain it and also include the reference to the RAFT study in the evaluation. Both studies demonstrated mortality benefit in the labeled population. Given the addition of both of these studies, we believe Table 8 would have a much stronger result and would also include secondary prevention patients. (page 37).	Thank you. Our criterion was to include studies that included predominantly patients undergoing ICD implantation for primary prevention. The RAFT study has now been added.
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Key Question 1	If MADIT-CRT is retained in the analysis, it is important to point out the reviewers of this draft document used an older New England Journal of Medicine publication and did not reference the FDA?s Summary of Safety and Effectiveness guidance that reported the influence of the left bundle branch population where a significant reduction in mortality was seen (HR=0.65, 95% CI =0.42, 1.00, p=0.044). In 2010, these results were updated by the FDA Panel and should be used to ensure the document is consistent with current indications and guidelines. (pages 37-38)	We were unable to include grey literature in our review.
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	Key Question 2	In regards to the second key question, a more comprehensive review of the Adverse Events could be made more robust by the inclusion of the Adverse Event data from the Summaries of Safety and Effectiveness report found on the FDA website. The reporting and enumeration of Adverse Events is more extensive than the NCDR registry.	We were unable to include grey literature in our review.

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	The report mentioned the need to evaluate the incremental net benefits and cost of emerging medical and device therapies such as the S-ICD System which was approved by the FDA on September 28, 2012. Boston Scientific believes that the S-ICD System offers a clinical solution in advancing the next generation of implantable defibrillation therapy without leads that go into the heart or vasculature system. The S-ICD System is indicated to provide defibrillation therapy for the treatment of life-threatening ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing. The S-ICD System is able to treat a broad subset of patients eligible for defibrillation including, but not limited to: patients with venous access problems and younger patients who will require defibrillation therapy for an extended period of their lives. We believe that the AHRQ assessment can be further strengthened by noting the clinical studies to date that show the safety and clinical effectiveness of the SICD system. Recent studies by Kobe et al. (2012) compared and matched S-ICD patients to a single chamber ICD cohort group and the results indicate similar device performance with respect to ventricular fibrillation conversion, adverse event rates, and inappropriate shock rates. In addition, Gold et al. (2012) evaluated the algorithm performance in the multicenter trial (START) to measure the accuracy of initial arrhythmia detection. Both single-chamber transvenous ICD and dual-chamber transvenous ICD configurations were studied. The results indicated that the S-ICD arrhythmia detection is as good if not better than that of transvenous ICD systems.	As discussed, technological advances emerging during the conduct of the systematic review, such as the S-ICD could not be considered and will require evaluation in a future review.
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	In closing, Boston Scientific applauds AHRQ?s efforts to be open and transparent in this process. We support AHRQ?s efforts to use evidence reports and technology assessments to ensure patients receive the most appropriate and promising treatments to improve health outcomes, while at the same time collecting sufficient information to make and update coverage decisions.	Thank you

Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	We believe that the overall conclusions and recommendations discussed further support the clinical value of ICDs for the treatment of SCD in primary prevention patients. The draft technology assessment strengthens the evidence review process in providing a high level summary of the key issues in defining the continued adoption and support of life saving technologies such as ICDs.	Thank you
Kristen Hedstrom and Parashar B. Patel	Boston Scientific	General	We appreciate the opportunity to comment on this important topic, and your consideration of our overall perspectives. If you or your staff has questions, please do not hesitate to contact Michael Ferguson, PhD (Director Health Economics, 508-652-5234; michael.ferguson@bsci.com) or Kristen Hedstrom, MPH (Director Healthcare Policy, 202-637-8021; kristen.hedstrom@bsci.com).	Thank you
Barbara K. Veath	Medtronic, Inc.	General	Medtronic appreciates this opportunity to comment on AHRQ?s technology assessment, and we look forward to continuing to collaborate with AHRQ. We further appreciate AHRQ?s commitment to the transparency of its review process. On this note, Medtronic recommends that the AHRQ Technology Assessment Program post its draft key questions for stakeholder comment to ensure that stakeholders have the opportunity to comment on key methodological concerns as well as submit significant pieces of evidence to support AHRQ?s review before AHRQ conducts the research. The Effective Health Care Program at AHRQ has a similar process to ensure the transparency of its research projects, and we have found that the process facilitates timely and important stakeholder feedback to be incorporated throughout the assessment process. We have included the full citations in the Reference comment box.	Thank you. We will pass on this suggestion to AHRQ.

Barbara K. Veath	Medtronic, Inc.	Introduction/Background	On page 4, Medtronic recommends modifications to its definition of cardiac resynchronization therapy (CRT) to ensure an accurate description of the therapy. Specifically, we propose the first paragraph on page 4 read as follows: ?Currently, device-based therapy also includes the ability to deliver cardiac resynchronization therapy (CRT) via the addition of a left ventricular lead. CRT may be delivered in the form of a standalone biventricular pacemaker (CRT-P) or in addition to an implantable cardioverter defibrillator (CRT-D). CRT implantation involves the placement of right atrial, right ventricular, and left ventricular leads. The difference between CRT-P and CRT-D relates to the type of right ventricular lead (with or without coils) and the type of generator. The goal of CRT is to improve quality of life and prolong survival in patients who manifest electrical dyssynchrony and cardiac dysfunction via atrial-synchronized biventricular pacing.?	This section was edited accordingly.
Barbara K. Veath	Medtronic, Inc.	Introduction/Background	On page 5, Medtronic also recommends revisions to accurately reflect the MADIT II study inclusion criteria. Medtronic suggests, "...and from MADIT II?which included patients with prior MI, LVEF <30 percent, and a QRS duration of >120 milliseconds," be changed to, "...and from MADIT II?which included patients with prior MI, and a LVEF < 30 percent".(1)	Thank you. We have removed the statement regarding QRS.
Barbara K. Veath	Medtronic, Inc.	Methods	Key question 1 specifies outcomes of interest were limited to clinical outcomes including death from sudden cardiac death (SCD), all-cause mortality, sustained ventricular tachyarrhythmia, quality of life (QoL), and other patient-reported outcomes. Medtronic suggests AHRQ broaden the clinical outcomes assessed to include outcomes other than mortality that heavily impact quality of life. According to the Heart Failure Society of America guidelines, improving symptoms and quality of life, slowing the progression of heart failure (HF), and reducing mortality are three primary issues that must be considered when treating HF patients with reduced left ventricular ejection fraction (LVEF).(2) Since all primary prevention patients for sudden cardiac death have HF with reduced LVEF, Medtronic suggests AHRQ include outcomes related to HF hospitalizations as well as patient quality of life outcomes such as well-accepted HF quality of life measures, exercise performance, and symptom or functional capacity improvement. We provide studies that address these outcomes in the Results section.	We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.

Barbara K. Veath	Medtronic, Inc.	Results	Key questions 1b and 1c assess the effects of ICD with CRT or anti-tachycardia pacing (ATP) versus ICD alone on clinical outcomes and patient-reported outcomes. The AHRQ report concludes there is a low strength of evidence finding no difference between CRT-D and ICD for patients with New York Heart Association (NYHA) I or II cardiomyopathy. This conclusion was drawn from three studies, the MADIT-CRT, Diab 2011, and MENDMI. Medtronic suggests AHRQ include the significant study, Resynchronization?Defibrillation for Ambulatory Heart Failure Trial (RAFT), which addresses the effect of ICD with CRT versus ICD without CRT on clinical outcomes, specifically all-cause mortality. AHRQ excluded RAFT along with other trials since it was not a primary prevention trial. While the main paper for RAFT did not specify the proportions of patients with a primary or secondary ICD indication,(3) a later publication showed that 1546 of 1787 patients, or 86.5% of patients, who received a right ventricular defibrillation lead as having a primary prevention indication.(4) Since the proportion of secondary prevention patients was less than the 20% threshold required in the AHRQ study selection criteria, Medtronic recommends including results from RAFT in its evidence assessment.	Thank you. The RAFT study has now been added.

Barbara K. Veath	Medtronic, Inc.	Results	Key questions 1b and 1c also conclude that there is insufficient evidence evaluating differential effects on outcomes of interest between ICD with versus ICD without anti-tachycardia pacing (ATP). Medtronic believes that the results of the Pacing Fast Ventricular Tachychardia Reduces Shock Therapies (PainFREE Rx II) Trial provides evidence to answer key questions 1b and 1c and should be included in this assessment based on AHRQ?s study selection criteria. PainFREE Rx II was a randomized controlled trial that compared ICDs with and without ATP for primary and secondary prevention patients who were all newly implanted with ICDs.(5) The study examined quality of life using the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), a well-accepted and widely-used instrument. The PainFREE Rx II trial found that patients in both the primary and secondary prevention groups experienced a significant improvement in quality of life between baseline and 12 months.(6) Based on AHRQ?s study selection criteria, we recommend that AHRQ include the results of the study in its final assessment of the evidence on differences in outcomes between ICD with ATP and ICD alone.	Key questions 1b and 1c are limited to studies predominantly in the primary prevention population. PainFREE Rx II is 57% secondary prevention. Inappropriate shock data from this study was included in Key Question 2. The study has been referenced in the discussion.
Barbara K. Veath	Medtronic, Inc.	Results	Key question 1b also assesses the effects of ICD with CRT versus ICD on quality of life and reported no studies were available that address this question. Key question 1b also does not include outcomes on HF hospitalizations. Based on our comments in the Methods section above, Medtronic believes that AHRQ should incorporate studies that assess HF hospitalizations and quality of life outcomes including widely-used HF quality of life measures, exercise performance, and symptom or functional capacity improvement. Specifically, the COMPANION study showed that primary prevention patients with a CRT-D had a statistically significant increase in the distance walked in 6-minutes, an improvement in quality of life using the Minnesota Living with Heart Failure questionnaire, and improved NYHA symptoms compared with optimal medical therapy alone and no ICD.(7) Additionally, compared with ICD alone, CRT-D patients in the MADIT-CRT study had improved quality of life as measured by the Kansas City Cardiomyopathy Questionnaire.(8) Furthermore, HF related events including hospitalizations were significantly reduced with CRT-D.(9)	We agree that the review of CRT is not complete in this report. Our report only addressed the question of the effect of CRT in addition to ICD for prevention of SCD and mortality. We added text to highlight this in abstract, discussion and limitations section. We believe that a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included. Such a review would potentially address the question posed.

Barbara K. Veath	Medtronic, Inc.	Results	Finally, to clarify AHRQ?s description of the COMPANION and SCD-HeFT studies, we suggest changing on page 19 the second paragraph under ?All-Cause Mortality? to read: ?It should be noted that two studies?COMPANION85 and SCD-HeFT46?were three-arm studies that each included an ICD intervention that could be construed as the ICD intervention of interest. COMPANION compared an ICD with CRT (CRT-D) versus optimal medical therapy alone, and CRT without ICD (CRT-P) versus optimal medical therapy alone. A direct comparison between CRT-D and CRT-P was neither pre-specified nor calculated. However, we determined that the comparison of CRT-D versus no ICD (or CRT) was most similar to the comparison in other studies. SCD-HeFT compared ICD versus conventional therapy without an ICD or amiodarone, and amiodarone versus conventional therapy without an ICD. The study found no difference in death rates between the amiodarone and no amiodarone groups. We chose the comparison of ICD versus conventional therapy without an ICD or amiodarone as the most relevant.?	We have edited this section to clarify that: In Companion, we contrasted CRT-D versus medical therapy (without CRT-P). In SCD-Heft, we contrasted ICD versus medical management without amiodarone.
Barbara K. Veath	Medtronic, Inc.	Results	Medtronic believes that incorporating these studies and modifications will allow AHRQ to more comprehensively evaluate the state of evidence for impact of ICDs with or without ATP or CRT, on the prevention of sudden cardiac death and changes in patient reported outcomes in the primary prevention patient population.	We have edited this section to clarify that: In Companion, we contrasted CRT-D versus medical therapy (without CRT-P). In SCD-Heft, we contrasted ICD versus medical management without amiodarone.

Barbara K. Veath	Medtronic, Inc.	Discussion/Conclusion	The Discussion section provides supporting information as to why certain studies were excluded from the assessment. Specifically, it notes that the RAFT study was not included since it was not an exclusively primary prevention trial. Medtronic disagrees with AHRQ's decision to exclude RAFT and encourages AHRQ to include RAFT in its analysis as it finalizes the report. Of the 1787 patients who received a right ventricular defibrillation lead in the RAFT study, 1546, or 86.5%, were classified as primary prevention patients,(10) meeting AHRQ?s patient selection criteria. Given the predominance of a primary prevention indication in RAFT patients, the size and duration of this important study, and the alignment of inclusion criteria with AHRQ?s definition for a primary prevention indication, we encourage AHRQ to include the overall results from RAFT in its analysis.	RAFT has been included

Barbara K. Veath	Medtronic, Inc.	References	1. Noyes K, Corona E, Zwanziger J, et al. Health-related quality of life consequences of implantable cardioverter defibrillators: results from MADIT II. Med Care 2007 May;45(5):377-85. 2. Heart Failure Society of America. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6): 475-539. 3. Tang ASL, Wells, GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363(25):2385-2395. 4. Parrkash R, Thibault B, Sterns L, et al. Sprint Fidelis lead fractures in patients with cardiac resynchronization therapy devices: Insight from the Resynchronization/Defibrillation for Ambulatory Heart Failure (RAFT) Study. Circulation. 2012;126(25):2928-2934. 5. Wathen MS, et al. Prospective randomized multicenter trial of empirical anitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. Circulation. 2004;110:2591-2596. 6. Sweeney, MO, et al. Appropriate and inappropriate ventricular therapies, quality of life, and mortality among primary and secondary prevention implantable cardioverter defibrillator patients: results from the Pacing Fast VT REduces ShockThErapies (PainFREE Rx II) trial. Circulation. 2005 Jun 7;111(22):2898-905. 7. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140 ?2150. 8. Veazie PJ, Noyes K, Li Q, et al. Cardiac resynchronization and quality of life in patients with minimally symptomatic heart failure. J Am Coll Cardiol. 2012;60(19):1940-1944. 9. Moss AJ, Hall WJ, Cannon DS, et al. Cardiac-resynchronization therapy for the prevention of heart failure events. N Engl J Med. 2009;361:1329-38.	Thank you.

[071] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.
[2] Affiliation is labeled "NA" for those who did not disclose affiliation.
[3] If listed, page number, line number, or section refers to the draft report.
[4] If listed, page number, line number, or section refers to the final report.