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Future Research Prioritization in Cardiac Resynchronization Therapy

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ABSTRACT

Background: Although cardiac resynchronization therapy (CRT) is effective for some patients with heart failure and a reduced left ventricular ejection fraction (HFrEF), evidence gaps remain for key clinical and policy areas.

Objective: Review the data on the effects of CRT for patients with HFrEF receiving pharmacological therapy alone or pharmacological therapy and an ICD and then, informed by a diverse group of stakeholders, to identify evidence-gaps, prioritize them and develop a research plan.

Method: Relevant studies were identified using PubMed and EMBASE and ongoing trials using clinicaltrials.gov. Forced-ranking prioritization method was applied by stakeholders to reach a consensus on the most important questions.

Participants: Twenty-six stakeholders contributed to the expanded list of evidence gaps, including key investigators from existing RCTs and others representing different perspectives, including patients, the public, device manufacturers, and policymakers.

Results: Of the 18 top-tier evidence gaps, 8 were related to specific populations or subgroups of interest. Seven were related to the comparative effectiveness and safety of CRT interventions or comparators, and three were related to the association of CRT treatment with specific outcomes. The association of comorbidities with CRT effectiveness ranked highest, followed by questions about the effectiveness of CRT among patients with atrial fibrillation and the relationship between gender, QRS morphology and duration, and outcomes for patients with either CRT-D or ICD.

Conclusion: Evidence gaps presented in this paper highlight numerous, important clinical and policy questions for which there is inconclusive evidence on the role of CRT and provide a framework for future collaborative research.

Key words: Cardiac resynchronization therapy, evidence gaps, future research prioritization

Abbreviation list:

AF = atrial fibrillation

AHRQ = Agency for Healthcare Research and Quality

AV = atrioventricular

CRT = Cardiac resynchronization therapy

ECG = Electrocardiogram

EPC = Evidence-based Practice Center

ESG = Evidence Synthesis Group

HFrEF = Heart failue with reduced ejection fraction

HF = Heart failure

ICD = Implantable crdioverter defibrillator

LBBB = Left bundle branch block

LVEF = Left ventricualr ejection fraction

PILG = Principal Investigator Leadership Group

RCT = Randomized controlled trial

INTRODUCTION

Cardiac resynchronization therapy (CRT), with or without an implantable cardioverter defibrillator device (ICD), is an important advance in the care of a selected group of patients

with heart failure (HF). Several landmark randomized clinical trials (RCTs) have demonstrated that CRT is an effective therapy for patients with symptomatic HF who have a reduced left ventricular ejection fraction (<35%; HFrEF), a prolonged QRS duration (≥130ms) and in sinus rhythm (1-4) in addition to pharmacological therapy alone or pharmacological therapy and an implantable cardioverter defibrillator (ICD) (5). CRT improves cardiac function, symptoms, quality of life and exercise capacity and reduces HF hospitalizations, ventricular arrhythmias, and mortality and is cost-effective (6-10). Although up to 14% of patients with HF meet the eligibility criteria for CRT, it appears generally underused, with great heterogeneity in its implementation in North America and Europe and elsewhere (11-13).

Despite the clear benefits of CRT and strong endorsement in clinical guidelines for selected patients, many clinical and policy questions remain (14). Indeed, in 2009 the Institute of Medicine recommended that evaluating the effectiveness of CRT should be a top priority for future research (15). For patients, clinicians, payers, policymakers, and device manufacturers it remains important to identify and answer key questions about patient selection for CRT as well as device therapy optimization.

The National Heart, Lung, and Blood Institute (NHLBI; R01 HL131754-03) funded the Duke University Evidence Synthesis Group (ESG) to synthesize the evidence related to CRT with the ultimate goal of developing decision support tools for patients, clinicians, and policymakers. An initial step in this process was to work with diverse stakeholders to identify and prioritize timely clinical and policy evidence gaps. Subsequent efforts will use decision modeling and Bayesian statistics to explore the high-priority gaps that we have identified using pooled patient-level data from existing RCTs and registries. This article summarizes the results of the topic prioritization process by this group of stakeholders.

METHODS

Prioritization Approach

Our approach to prioritizing the evidence gaps involved several steps that were initially developed by the Agency for Healthcare Research and Quality (AHRQ)'s Evidence-based Practice Center (EPC) Program (16) and followed our previous prioritization process (17) (**Figure 1**). These steps broadly involved seeking input from clinical experts and evaluating recent systematic reviews to identify a preliminary list of evidence gaps; transforming these gaps into research questions; selecting and engaging stakeholders to identify additional gaps and prioritize them; and reviewing recently published and ongoing studies that were relevant to the stakeholders' list of priorities. Our team has used this process for similar work with AHRQ(18-20) and with the Patient-Centered Outcomes Research Institute (PCORI)(17,21-23) which has informed their future research needs portfolio and targeted funding announcements.

Identification of Evidence Gaps

We applied an iterative process to identify evidence gaps for CRT use in patients with HF. First, the ESG team sought input from clinical experts at Duke University (SMA, DF, MF) and identified and evaluated recently published clinical practice guidelines, consensus statements, and systematic reviews in order to create an initial list of evidence gaps. This list was neither complete nor prioritized. Next, the evidence gaps were organized into broad topics within CRT and transformed into research questions.

Selection and Engagement of Stakeholders

Our aim was to establish a diverse panel of participants including clinicians, researchers, representatives from patient advocacy groups, federal and non-governmental funding agencies, cardiovascular professional societies, health care decision-makers and policymakers, and industry. The stakeholder group was developed using previously described taxonomy, and the

group included representatives of the following stakeholders groups identified in the 7P framework: patients and public, providers, purchasers, payers, policymakers, principal investigators, and product makers (16,24). Within each of these groups, we solicited participation of at least one person with content expertise and a unique viewpoint on the clinical area of CRT and its current uncertainties. We received stakeholder input at various points in the process through individual conference calls, group web-based conferences, and emails outlining the process and proposed list of evidence gaps.

The stakeholder group (**Supplemental Table 1**) was asked to review and propose additional questions for prioritization and, through a series of four conference calls, the evidence gaps were discussed and expanded. Suggestions were reviewed by the ESG team, and a revised document with unique gaps in evidence across a broad range of topics was developed. The final document was shared with the stakeholders for review to ensure appropriate implementation of their suggestions. The final list included 40 identified research priorities (**Supplemental Table 2**).

Prioritization of Future Research

Stakeholders were invited to rank the expanded list of research priorities. They used a Likert scale to indicate how critical the gap was to decision making, followed by a forced-ranking prioritization method previously described by the AHRQ EPC's Future Research Needs projects (16) and also used in the ICD prioritization project (17) by the ESG team. In this exercise, participants were allocated 15 votes that could be applied to any of the 40 identified research gaps, with a maximum of 3 votes per item. No set criteria were prescribed for the prioritization process; instead stakeholders were asked to determine the most important unanswered research questions on CRT. Stakeholders were also asked to self-report their perceived perspective as that of a patient, clinician, public, purchaser, payer, policymaker, device manufacturer, or principal investigator, with the understanding that individual stakeholders could embody more than one

perspective. Following these exercises, the evidence gaps were separated into three prioritization tiers (top, middle, lower). Only priorities in the top tier that were ranked as highest priority by at least one-third of stakeholders moved on to the horizon scan stage.

Horizon Scan of Studies Potentially Relevant to Top-Tier Evidence Gaps

The final step in the prioritization process included a scan of the current evidence pertinent to the identified top-tier research questions. To identify published research and ongoing studies, the ESG team searched the published literature using PubMed and EMBASE to identify relevant RCTs and prospective observational studies published since 2008 and applicable to the identified research gaps. **Supplemental Table 3** provides the exact search strategies. Two independent ESG members reviewed the identified titles and abstracts for inclusion/exclusion. We included articles if they met the following criteria: (1) presented original data or secondary analysis of data from an RCT or prospective observational study and (2) included data related to CRT use with a stated objective that could be categorized according to our identified list of research priorities. Articles included by either reviewer underwent abstraction of their applicability to identified evidence gaps. One team member abstracted the data, and a second (SMA or MF) over-read the accompanying abstraction to check for accuracy and completeness. All results were tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

We also searched clinicaltrials.gov (October 5, 2018) using the term "cardiac resynchronization therapy" and searched for ongoing and recently completed but unpublished studies. ESG team members reviewed all study summaries identified by the search and marked them as potentially pertinent to one or more of the identified research priorities. We then abstracted the study type (observational or RCT), recruitment status, and sample size.

RESULTS

A total of 26 stakeholders were included in different steps of our prioritization process, of whom 22 (84.6%) provided input on the evidence gaps list. The stakeholders represented an array of different expertise and perspectives and self-identified as clinician (N=14), clinical researcher (N=18), patient/public (N=3), policymaker (N=1), device manufacturer (N=2), or other (health technology assessor, N=1). We included principal or key investigators from each of the existing RCTs of CRT who also served on our PI Leadership Group (PILG), and therefore the perspective of clinical researchers was strongly represented in our stakeholder group (69% of stakeholders).

We consolidated the questions into four broad categories of CRT evidence gaps: (1) specific population or subgroup of interest; (2) comparative safety and effectiveness of available interventions or comparators; (3) association of treatment with specific outcomes of interest; and (4) optimal timing or setting for treatment.

Ranked Future Research

After the expanded list of evidence gaps was identified, a total of 21 stakeholders contributed to the online prioritization process. The initial prioritization rankings from the stakeholders ranging from "of critical importance" (rank=9) to "of limited importance" (rank=0) are presented in **Supplemental Table 4**. Next, the forced ranking prioritization process produced the final score of prioritizations ranking for each evidence gap **(Table 1)**. The ranked gaps are accompanied by the number of voting stakeholders, the total score, and the perspective represented by these votes. The evidence gaps considered as top-tier priority are shaded in gray and represent those in the top third through forced ranking (top 14 of the original 40 evidence gaps) or that were rated as critical to decision making by greater than 40% of the stakeholders

(**Supplemental Table 4**). Note that the evidence gaps prioritized with the Likert scale process overlapped well with the forced-ranking prioritization method.

Of the 18 top-tier evidence gaps, 8 questions were related to the topic of specific populations or subgroup of interest, with the questions of effectiveness of CRT among patients with comorbidities (gap #6) and the effectiveness of CRT among patients with atrial fibrillation (AF) (gap #5) ranking highest. A total of seven evidence gaps were related to the topic of comparative effectiveness and safety of CRT interventions or comparators, and three gaps were related to the association of CRT treatment with specific outcomes (**Table 1**). All of the top-tier questions included stakeholders from diverse perspectives. Overall the top-tier evidence gaps ranked by the complete stakeholder group remained within the top tier for the various stakeholder groups – although the order of these gaps changed (**Supplemental Table 5**). Exceptions to this consistency included evidence gaps that focused on prediction of early death (evidence gap 37), reduction in cost (evidence gap 34), and reduction in sudden cardiac death (evidence gap 33) which were prioritized by our patient/public stakeholders but were considered second-tier priority by the complete group of stakeholders.

Horizon Scan of Potential Studies Relevant to Top-Tier Evidence Gaps

Our literature search identified 2,617 potentially relevant articles. Of these, 306 met our inclusion criteria, consisting of 44 RCTs of unique original trials or secondary analyses of original trials and 262 prospective cohort studies. The sample size of the included studies ranged from 10 to more than 10,000 patients.

On clinicaltrials.gov we found 236 ongoing or completed studies related to CRT research. A total of 89 (76 completed, 13 ongoing) studies met our inclusion criteria and were applicable to one of the 18 top-tier research priorities. All 18 top-tier research gaps were covered by at least one pending or completed clinical study.

Supplemental Table 6 describes the included studies, number of patients, and objectives. **Table 2** summarizes the number of published RCT and observational studies as well as ongoing/completed clinical trials for each evidence gap. These results show a paucity of trials examining the top 8 priority questions, with one notable exception: the association between comorbidities and CRT effectiveness. However, there was significant heterogeneity across the trials in relation to sample size and definitions of factors and outcomes. For example, completed trials (in clinicaltrials.gov) related to comorbidities and CRT effectiveness had sample sizes ranging from 6 to 2,200 patients, and the comorbidities included diabetes, kidney disease, and pulmonary hypertension.

DISCUSSION

Of the 18 top-tier evidence gaps, the association of comorbidities with CRT effectiveness ranked highest. The evidence that led to the approval and initial adoption of CRT in clinical practice stemmed from RCTs that either excluded patients with certain comorbid clinical conditions or were underpowered to establish the efficacy of CRT in important patient subgroups. However, patients with a substantial burden of comorbidities are frequently encountered by clinicians who, in the absence of data, often struggle with how to present the potential benefits of CRT. Thus, it is not surprising that the question about CRT effectiveness among patients with commonly encountered comorbid conditions (gap #6) was the top-tier evidence gap. The importance of this gap is further highlighted by the lower implantation rates of CRT among patients with common comorbid conditions. While lower rates could be due to the perceived higher procedural complications and concerns over competing risks of non-cardiac death, the paucity of data and conflicting data on outcomes of CRT in these patients also likely play a role (25). A total of 36 findings for gap #6 demonstrated variable results, mostly

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suggesting that CRT was beneficial for patients with commonly encountered comorbid conditions such as diabetes mellitus or chronic kidney disease. Some studies, however, suggested a lack of benefit, warranting further investigation. Several comorbid conditions such as end-stage renal disease, right ventricular dysfunction, pulmonary hypertension, and other lung diseases had little evidence evaluating CRT effectiveness.

Two of the top-tier gaps relate to patients with AF, gap #5 (effectiveness of CRT among patients with paroxysmal, persistent, and permanent AF) and gap #16 (association between AV node ablation and CRT effectiveness among patients with AF). About one in four CRT patients has AF (26), yet evidence on the effectiveness of CRT for such patients is limited mainly to secondary analyses of RCTs and national registries (27,28). Whereas analyses of RCTs suggest less benefit from CRT in patients with AF and atrial flutter (26,29), a retrospective analysis of the U.S. National Cardiovascular Data Registry indicated lower rates of mortality, all-cause readmission, and HF readmission among eligible patients with CRT-D (CRT plus ICD) when compared with ICD alone; however, this analysis may have suffered from residual confounding and selection bias (30). Our literature search identified 5 RCTs (with 71 to 229 patients included in these RCTs), 17 prospective observational studies (with 22 to 9,122 patients), and 3 ongoing trials that are potentially applicable to evidence gaps in the treatment of patients with AF. Published literature mostly suggests less benefit from CRT in patients with AF, with insufficient evidence on AF subtypes and the effect of device-specific pacing modes on outcomes. Current clinical guidelines provide a class IIa (level of evidence B) recommendation for atrioventricular (AV) node ablation with CRT in patients with AF (31). However, the role of AV node ablation for the management of AF in the setting of CRT requires additional exploration, especially in relation to selecting appropriate patients and the timing of CRT (32,33). The apparent benefit of CRT in these trials may reflect the deleterious effects of RV pacing in the control group in some

of these studies (34). The atrio-ventricular component of resynchronisation that optimizes ventricular filling and reduces diastolic mitral regurgitation may be a key effect of CRT for many patients with HFrEF that bi-ventricular pacing alone cannot deliver.

Another top-tier evidence gap relates to the relationship between sex, QRS morphology and duration, and outcomes for patients with either CRT-P (CRT plus pacemaker) or CRT-D (gap #4). While it has been suggested that women derive greater benefit from CRT (35,36), some reports suggest they are less likely to receive one (37). Some have suggested that sex disparities in CRT-use is because women are less likely to meet the selection criteria such as typical left bundle branch block (LBBB), but the reported sex disparities are likely to be multifactorial (38). Our horizon scan found 23 RCT-based analyses or prospective observational studies that explored this question, and an ongoing medium-sized clinical trial (clinicaltrials.gov NCT02344420). More dedicated research is needed to address this possible health care inequality.

Important clinical topics are covered by gap #22 (is upgrade from a dual chamber pacemaker or defibrillator to a CRT device associated with HF-free survival among patients with a high burden of right ventricular pacing?) and gap #24 (left ventricular ejection fraction [LVEF] threshold at which CRT is superior to dual chamber pacing in high grade or complete AV block). It is well established that a large percentage of pacing in the right ventricle can impair cardiac function and induce HF in about 30% of patients (39). Current guidelines recommend biventricular pacing in patients with an LVEF of ≤50% and concomitant requirement for ventricular pacing of >40% (40). While small trials have suggested no benefit of preventive biventricular pacing for patients with a normal LVEF (>50%) on mortality and HF hospitalizations (41,42), the BLOCK-HF (biventricular versus right ventricular pacing in heart failure patients with atrioventricular block) trial showed benefit from biventricular pacing in

patients with HF and a left ventricular EF (LVEF) of <50% (43). However, the BIOPACE (biventricular pacing for atrioventricular block to prevent cardia desynchronization) trial failed to show a significant improvement in outcomes with CRT compared with right ventricular pacing in patients with AV block (44). Because the full trial results have not been published, it is difficult to interpret these findings. Our horizon scan uncovered 24 published articles on these 2 related questions, with a limited number of dedicated RCTs. Clinicians and patients often struggle to make the important decision of what device type to implant, and professional societies and as well as policymakers are unable to make evidence-guided recommendations and coverage choices. Therefore, there is a need for more research in this area especially around early identification of patients with a deterioration in left ventricular function following chronic right ventricular pacing, and the level of ventricular pacing that should trigger the need for CRT.

Limitations

Despite our efforts to be comprehensive, other research needs will be identified in the future in the light of new technology and understanding. Further, the number of stakeholders we engaged was limited, and a different group of stakeholders could have potentially ranked the future research needs differently. However, our stakeholder group was comprised of a diverse panel of experts representing a range of perspectives, with a specific focus on patient-centered research. It is possible that as part of our systematic review we either missed or misclassified studies and the related knowledge gaps; however, our team has extensive experience with systematic reviews and attempts to institute standardized measures to assure reproducibility and completeness.

Next Steps

The prioritized evidence gaps presented in this paper highlight numerous, highly relevant unanswered clinical and policy questions on the role of CRT. Following this prioritization process, the ESG team will continue to collaborate with principal investigators from existing trials of CRT to harness the power of patient-level data from more than 10 years of clinical trials representing nearly 10,000 patients. As part of an ongoing collaboration funded by NHLBI (1R01HL131754), we are creating combined data set of the individual patient data from each of the trials, and using Bayesian statistics and decision modeling we are exploring the top three prioritized key uncertainties identified in this manuscript. This collaboration among our team, the PIs of the key trials, and the different companies – and inclusion of patient level data -- is unprecedented. Initial analyses will focus on the highest prioritized topics including: the association between comorbid diseases and the effectiveness of CRT therapies, the effectiveness of CRT among patients with atrial fibrillation, and the relationship between sex, QRS duration and morphology and outcomes for patients with CRT-D compared to CRT-P or ICD.

Perspectives

Competency in Medical Knowledge: Of the 18 top-tier evidence gaps we identified, 8 were related to specific populations or subgroups of interest. Seven gaps were related to the comparative effectiveness and safety of CRT interventions or comparators, and three gaps were related to the association of CRT treatment with specific outcomes. The association of comorbidities with CRT effectiveness ranked highest, followed by questions about the effectiveness of CRT among patients with atrial fibrillation and the relationship between gender, QRS morphology and duration, and outcomes for patients with either CRT-D or ICD.

Translational Outlook: The prioritized evidence gaps presented in this paper highlight numerous highly relevant unanswered clinical and policy questions on the role of CRT, which need to be addressed with dedicated analyses and clinical studies.

REFERENCES

1.   Bristow MR, Saxon LA, Boehmer J et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. New England Journal of Medicine 2004;350:2140-2150.

2.   Cleland JGF, Daubert J-C, Erdmann E et al. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. New England Journal of Medicine 2005;352:1539-1549.

3.   Gold MR, Thebault C, Linde C et al. Effect of QRS Duration and Morphology on Cardiac Resynchronization Therapy Outcomes in Mild Heart Failure: Results From the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Study. Circulation 2012;126:822-829.

4.   Tang ASL, Wells GA, Talajic M et al. Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure. New England Journal of Medicine 2010;363:2385-2395.

5.   Woods B, Hawkins N, Mealing S et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. Heart 2015;101:1800-6.

6.   Colquitt JL, Mendes D, Clegg AJ et al. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. Health Technology Assessment 2014;18:1-560.

7.   Feldman AM, de Lissovoy G, Bristow MR et al. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. J Am Coll Cardiol 2005;46:2311-21.

8.   Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. Eur Heart J 2007;28:42-51.

9.   Bogale N, Priori S, Cleland JG et al. The European CRT Survey: 1 year (9-15 months) follow-up results. European journal of heart failure 2012;14:61-73.

10.   Dickstein K, Normand C, Auricchio A et al. CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients-who is doing what to whom and how? European journal of heart failure 2018;20:1039-1051.

11.   Bank AJ, Gage RM, Olshansky B. On the underutilization of cardiac resynchronization therapy. J Card Fail 2014;20:696-705.

12.   Hawkins NM, Bennett MT, Andrade JG et al. Review of eligibility for cardiac resynchronization therapy. The American journal of cardiology 2015;116:318-24.

13.   Osmanska J, Hawkins NM, Toma M, Ignaszewski A, Virani SA. Eligibility for cardiac resynchronization therapy in patients hospitalized with heart failure. ESC Heart Fail 2018;5:668-674.

14.   Tracy CM, Epstein AE, Darbar D et al. 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm S. Circulation 2012;126:1784-1800.

15.   Initial National Priorities for Comparative Effectiveness Research : Health and Medicine Division.

16.   Chang SM, Carey TS, Kato EU, Guise JM, Sanders GD. Identifying research needs for improving health care. Annals of internal medicine 2012;157:439-45.

17.   Al-Khatib SM, Gierisch JM, Crowley MJ et al. Future Research Prioritization: Implantable Cardioverter-Defibrillator Therapy in Older Patients. J Gen Intern Med 2015;30:1812-20.

18.   Eapen ZJ, McBroom AJ, Gray R et al. Priorities for comparative effectiveness reviews in cardiovascular disease. Circ Cardiovasc Qual Outcomes 2013;6:139-47.

19.   Crowley MJ, Powers BJ, Myers ER, McBroom AJ, Sanders GD. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treatment of ischemic heart disease: Future research needs prioritization. American heart journal 2012;163:777-782 e8.

20.   Dolor RJ, Patel MR, Melloni C et al. Treatment Strategies for Women With Coronary Artery Disease: Future Research Needs: Identification of Future Research Needs From Comparative Effectiveness Review No 66. Rockville (MD), 2013.

21.   Gierisch JM, Myers ER, Schmit KM et al. Prioritization of patient-centered comparative effectiveness research for osteoarthritis. Annals of internal medicine 2014;160:836-41.

22.   Gierisch JM, Myers ER, Schmit KM et al. Prioritization of research addressing management strategies for ductal carcinoma in situ. Annals of internal medicine 2014;160:484-91.

23.   Crowley MJ, McCrory DC, Chatterjee R et al. Prioritization of research addressing antipsychotics for adolescents and young adults with bipolar disorder. Annals of internal medicine 2014;160:492-8.

24.   Concannon TW, Meissner P, Grunbaum JA et al. A new taxonomy for stakeholder engagement in patient-centered outcomes research. J Gen Intern Med 2012;27:985-91.

25.   Pun PH, Sheng S, Sanders G et al. Prescription of Guideline-Recommended Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy Among Patients

Hospitalized With Heart Failure and Varying Degrees of Renal Function. The American journal of cardiology 2017;119:886-892.

26.   Kalscheur MM, Saxon LA, Lee BK et al. Outcomes of cardiac resynchronization therapy in patients with intermittent atrial fibrillation or atrial flutter in the COMPANION trial. Heart Rhythm 2017;14:858-865.

27.   Brignole M, Botto G, Mont L et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420-9.

28.   Doshi RN, Daoud EG, Fellows C et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). Journal of cardiovascular electrophysiology 2005;16:1160-5.

29.   Healey JS, Hohnloser SH, Exner DV et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2012;5:566-70.

30.   Khazanie P, Greiner MA, Al-Khatib SM et al. Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation: Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry. Circ Heart Fail 2016;9.

31.   Epstein AE, DiMarco JP, Ellenbogen KA et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6-75.

32. Brignole M, Pokushalov E, Pentimalli F et al. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. Eur Heart J 2018;39:3999-4008.

33. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. J Am Coll Cardiol 2012;59:719-26.

34. Cleland JG, Keshavarzi F, Pellicori P, Dicken B. Case selection for cardiac resynchronization in atrial fibrillation. Heart Fail Clin 2013;9:461-74, ix.

35. Zabarovskaja S, Gadler F, Braunschweig F et al. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace 2012;14:1148-55.

36. Arshad A, Moss AJ, Foster E et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011;57:813-20.

37. Chatterjee NA, Borgquist R, Chang Y et al. Increasing sex differences in the use of cardiac resynchronization therapy with or without implantable cardioverter-defibrillator. Eur Heart J 2017;38:1485-1494.

38. Zusterzeel R, Curtis JP, Canos DA et al. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: results from the NCDR. J Am Coll Cardiol 2014;64:887-94.

39. Fang F, Sanderson JE, Yu CM. Should all patients with heart block receive biventricular pacing? All heart block patients with a pacemaker indication should receive biventricular pacing: one move, double the gains? Circ Arrhythm Electrophysiol 2015;8:722-9.

40. Kusumoto FM, Schoenfeld MH, Barrett C et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction

Delay: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol 2018.

41.   Albertsen AE, Nielsen JC, Poulsen SH et al. Biventricular pacing preserves left ventricular performance in patients with high-grade atrio-ventricular block: a randomized comparison with DDD(R) pacing in 50 consecutive patients. Europace 2008;10:314-20.

42.   Stockburger M, Gomez-Doblas JJ, Lamas G et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). European journal of heart failure 2011;13:633-41.

43.   Curtis AB, Worley SJ, Adamson PB et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368:1585-93.

44.   BIOPACE Trial Investigators and Coordinators. Study presentation [slides]. Available at: http://clinicaltrialresults.org/Slides/TCT 2014/Blanc_Biopace.pdf. Accessed January 23, 2019.

Table 1. Ranked CRT Evidence Gaps

Top-tier evidence gaps are shaded gray. These gaps correspond to those in the top third (i.e., top 14 evidence gaps) as indicated by forced ranking or that were rated as being critical to decision making by more than 40% of stakeholders (adding in an additional 4 gaps).

Evidence Gap	Score	Stakeholders N	Perspectives
6. What is the association between comorbid diseases (e.g., chronic kidney disease, chronic lung disease, atrial fibrillation, diabetes mellitus, arterial and pulmonary hypertension, right ventricular dysfunction, and patients on dialysis) as well as the burden of comorbidities and the effectiveness of CRT-P and CRT-D?	19	13	9 healthcare providers, 9 researchers/investigators, 1 device manufacturer, 2 patients/public, 1 Other, 1 policymaker
5. What is the effectiveness of CRT among patients with paroxysmal, persistent, and permanent AF?	18	12	7 healthcare providers, 8 researchers/investigators, 1 device manufacturer, 1 patient/public, 1 Other, 1 policymaker
4. What is the relationship between gender, QRS morphology and duration, and outcomes for patients with either CRT-D or ICD?	17	11	7 healthcare providers, 9 researchers/investigators, 1 device manufacturer, 1 patient/public, 1 Other, 1 policymaker
24. What is the EF threshold at which CRT is superior to dual chamber pacing in high grade or complete AV block?	17	11	7 healthcare providers, 9 researchers/investigators, 1 patient/public, 1 Other, 1 device manufacturer, 1 policymaker
11. What is the comparative safety and effectiveness of CRT compared with no CRT among patients with a LBBB and EF >35%?	16	7	6 healthcare providers, 4 researchers/investigators, 1 patient/public, 1 policymaker
16. What is the association between AV node ablation (vs. no AV node ablation) and CRT effectiveness among patients with AF and history of AF with rapid ventricular response?	15	9	6 healthcare providers, 6 researchers/investigators, 1 patient/public, 2 device manufacturers
1. What is the comparative safety and effectiveness of CRT (vs. no CRT) among patients ≥75 years old? ≥80 years old?	14	9	8 healthcare providers, 6 researchers/investigators, 1 patient/public, 1 Other
17. What is the minimum percentage of biventricular pacing required for CRT-D to be superior to ICD?	13	10	6 healthcare providers, 8 researchers/investigators, 1 patient/public, 1 policymaker
32. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with improvement in overall survival in patients with CRT?	13	8	4 healthcare providers, 6 researchers/investigators, 1 patient/public

Evidence Gap	Score	Stakeholders N	Perspectives
22. Is upgrade from a dual chamber pacemaker or defibrillator to a CRT device (vs. no upgrade) associated with HF free survival among patients with a high burden of RV pacing?	12	8	4 healthcare providers, 7 researchers/investigators, 1 patient/public, 1 Other, 1 device manufacturer
8. Does CRT benefit (compared to no CRT) vary based on QRS duration (<150ms vs ≥ 150ms)?	11	6	2 healthcare providers, 5 researchers/investigators, 1 patient/public, 2 device manufacturers, 1 policymaker
26. Does CRT (compared to ICD) improve survival in very advanced HF as demonstrated by NYHA class and/or LV size/function?	11	6	4 healthcare providers, 4 researchers/investigators, 1 patient/public, 1 Other
13. What is the comparative safety and effectiveness of CRT-D versus CRT-P overall and among subgroups defined by cardiomyopathy etiology and QRS morphology?	10	5	4 healthcare providers, 3 researchers/investigators, 1 patient/public, 1 device manufacturer
18. What is the optimal percentage of biventricular pacing required to optimize outcomes among CRT recipients?	10	7	4 healthcare providers, 6 researchers/investigators, 1 patient/public
29. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with improvement in quality of life and functional status in patients with CRT?	10	5	3 healthcare providers, 3 researchers/investigators, 1 patient/public
19. What is the association of PVC burden prior and post CRT-D implantation on outcomes? Any data on associations of PVC ablation and outcomes?	8	7	3 healthcare providers, 6 researchers/investigators, 2 patients/public, 1 Other, 1 policymaker
3. Do CRT outcomes differ based on patient race and ethnicity?	7	6	4 healthcare providers, 5 researchers/investigators, 1 device manufacturer
20. Is the PR interval associated with the effectiveness of CRT (vs. no CRT)?	7	5	4 healthcare providers, 4 researchers/investigators
31. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with reductions in heart failure (HF) hospitalizations in patients with CRT?	7	4	2 healthcare providers, 3 researchers/investigators
28. What is the role of endocardial CRT especially in "non-responders" and with the advent of novel oral anticoagulants (NOACs)?	6	4	2 healthcare providers, 4 researchers/investigators, 1 patient/public, 1 Other
14. In looking at the control arms of the available CRT trials, which patients are at the highest risk of heart failure or death?	5	3	3 healthcare providers, 2 researchers/investigators, 1 device manufacturer
21. Is AV delay programming and/or CRT optimization associated with any	5	4	3 healthcare providers, 3 researchers/investigators

Evidence Gap	Score	Stakeholders N	Perspectives
observed relationship between PR interval and outcomes among CRT patients?			
25. Does RV lead location predict outcomes among CRT patients?	5	3	3 healthcare providers, 3 researchers/investigators
33. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with reduction in the risk of sudden cardiac death in patients with CRT?	5	4	2 healthcare providers, 2 researchers/investigators, 1 patient/public
34. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with reduction of cost in patients with CRT?	5	3	1 healthcare provider, 3 researchers/investigators, 1 patient/public
37. What are the echocardiographic predictors of early death (within 30 days) after CRT implantation (i.e. are there echocardiographic predictors of CRT futility)?	5	3	1 healthcare provider, 3 researcher/investigator, 2 patients/public, 1 Other, 1 policymaker
39. Do outcomes and complications vary based on timing relative to prior heart failure hospital admission?	5	4	1 healthcare provider, 3 researchers/investigators, 2 patients/public, 1 Other, 1 device manufacturer
40. Are the CRT outcomes observed in the community predicted by the available clinical trial evidence?	5	5	3 healthcare providers, 4 researchers/investigators, 1 patient/public, 1 Other, 1 policymaker
2. What is the association between heart failure duration and history of heart failure hospitalizations prior to implantation of CRT (vs. no CRT) with outcomes?	4	3	3 healthcare providers, 2 researchers/investigators
9. Do the location and extent of left ventricular dyssynchrony predict outcomes among CRT patients?	4	3	2 healthcare providers, 2 researchers/investigators, 1 device manufacturer
10. What is the relationship between height, weight, BMI, diabetes, and outcomes of CRT-D vs. ICD (i.e. does the obesity paradox apply to CRT patients and does diabetes modify this relationship)?	4	4	3 healthcare providers, 2 researchers/investigators
12. Is CRT more effective than an ICD at halting progressive remodeling in the subset of HF patients who do not demonstrate classic echocardiographic response (defined as 15% improvement in LV end systolic volume)?	4	4	2 healthcare providers, 4 researchers/investigators
15. In looking at the control arms of the available CRT, what are the predictors of worsening LVEF?	4	3	3 healthcare providers, 2 researchers/investigators, 1 device manufacturer

Evidence Gap	Score	Stakeholders N	Perspectives
7. What is the relationship between chronic lung disease, receipt of CRT vs. no CRT, and outcomes, particularly symptom burden and quality of life?	3	3	3 healthcare providers, 1 researcher/investigator
23. Is there an association between time since MI/revascularization and CRT outcomes?	3	2	1 healthcare provider, 2 researchers/investigators, 1 patient/public, 1 Other
27. Is LV end systolic volume superior to EF at predicting whether CRT is superior to dual chamber pacing in high grade or complete AV block?	3	3	3 healthcare providers, 2 researchers/investigators
30. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with a short term and durable improvement in LVEF and other echocardiographic parameters in patients with CRT?	3	3	2 healthcare providers, 2 researchers/investigators
36. What are the rates and predictors of appropriate and inappropriate ICD therapy events (shocks and/or ATP) among patients with CRT-D vs. ICD only?	1	1	1 researcher/investigator, 1 patient/public, 1 Other
38. What is the distribution of modes of death in responders vs. non-responders to CRT?	1	1	1 researcher/investigator, 1 patient/public, 1 Other
35. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with reduction in atrial and ventricular arrhythmias in patients with CRT?	0	0	NA

Abbreviations: AF=atrial fibrillation; ATP=antitachycardia pacing; AV=atrioventricular; CRT=cardiac resynchronization therapy; CRT-D=CRT with ICD; CRT-P=CRT with pacemaker; ECG=electrocardiogram; EF=ejection fraction; HF=heart failure; ICD=implantable cardiac device; LBBB=left bundle branch block; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; PVC=premature ventricular contraction; RCT=randomized controlled trial; RV=right ventricular

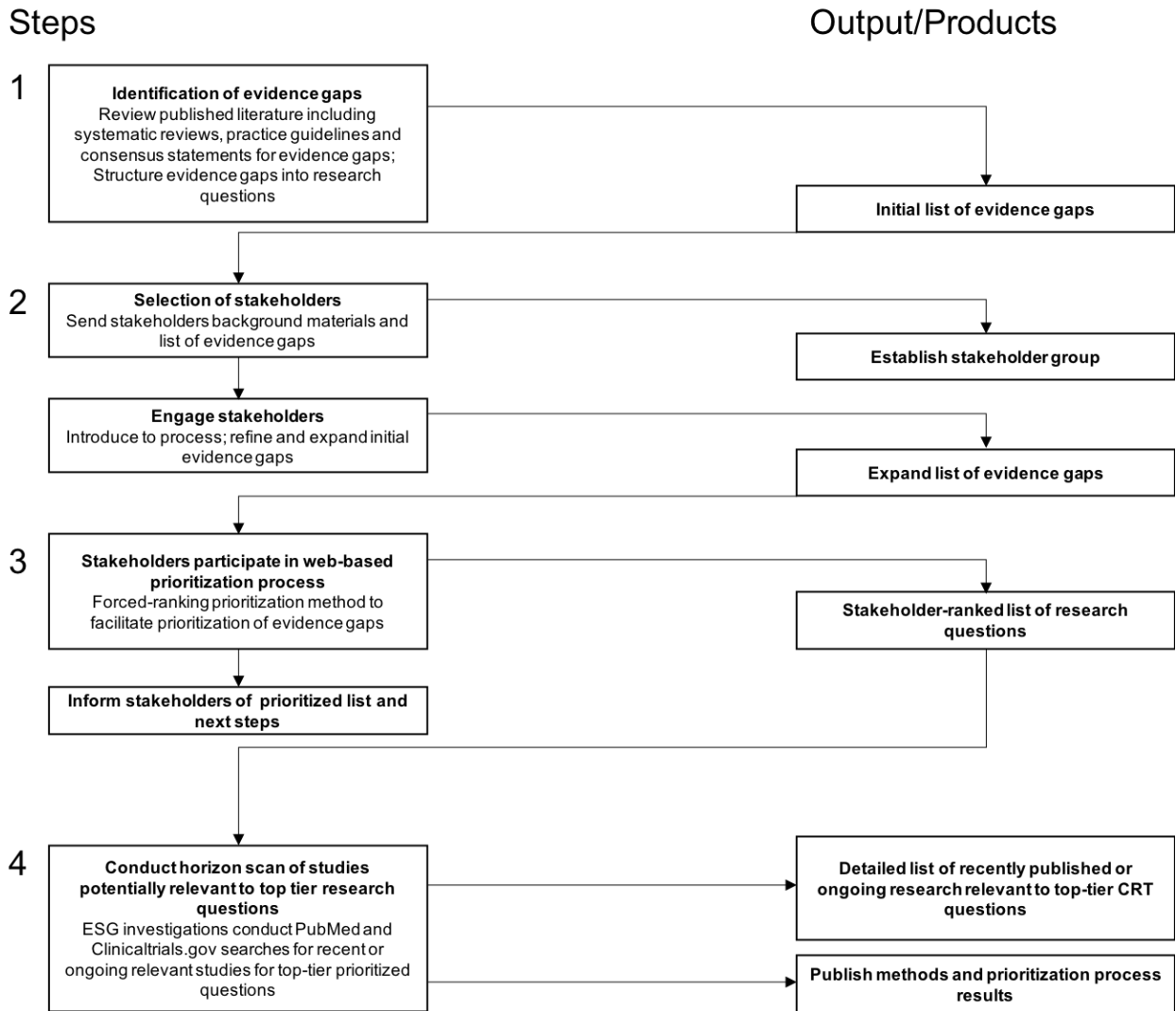**Table 2. Number of Potentially Relevant Studies for Top Tier Evidence Gaps**

Evidence Gap Topic (in Ranked Order)	Number of Studies			
	RCTs*	Prospective Observational Studies	Clinical Trials (Completed)	Clinical Trials (Ongoing)
6. What is the association between comorbid diseases (e.g., chronic kidney disease, chronic lung disease, atrial fibrillation, diabetes mellitus, arterial and pulmonary hypertension, right ventricular dysfunction, and patients on dialysis) as well as the burden of comorbidities and the effectiveness of CRT-P and CRT-D?	3	33	10	2
5. What is the effectiveness of CRT among patients with paroxysmal, persistent, and permanent AF?	4	12	3	1
4. What is the relationship between gender, QRS morphology and duration, and outcomes for patients with either CRT-D or ICD?	5	18	6	2
24. What is the EF threshold at which CRT is superior to dual chamber pacing in high grade or complete AV block?	3	3	2	0
11. What is the comparative safety and effectiveness of CRT compared with no CRT among patients with a LBBB and EF >35%?	0	6	1	2
16. What is the association between AV node ablation (vs. no AV node ablation) and CRT effectiveness among patients with AF and history of AF with rapid ventricular response?	3	8	3	2
1. What is the comparative safety and effectiveness of CRT (vs. no CRT) among patients ≥75 years old? ≥80 years old?	1	17	8	1
17. What is the minimum percentage of biventricular pacing required for CRT-D to be superior to ICD?	2	1	3	0
32. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with improvement in overall survival in patients with CRT?	13	103	24	2
22. Is upgrade from a dual chamber pacemaker or defibrillator to a CRT device (vs. no upgrade) associated with HF free survival among patients with a high burden of RV pacing?	4	9	5	0
8. Does CRT benefit (compared to no CRT) vary based on QRS duration (<150ms vs ≥ 150ms)?	1	13	9	0
26. Does CRT (compared to ICD) improve survival in very advanced HF as demonstrated by NYHA class and/or LV size/function?	2	16	4	0

Evidence Gap Topic (in Ranked Order)	Number of Studies			
	RCTs*	Prospective Observational Studies	Clinical Trials (Completed)	Clinical Trials (Ongoing)
13. What is the comparative safety and effectiveness of CRT-D versus CRT-P overall and among subgroups defined by cardiomyopathy etiology and QRS morphology?	2	20	3	0
18. What is the optimal percentage of biventricular pacing required to optimize outcomes among CRT recipients?	2	4	3	0
29. What is the predictive accuracy of a model that includes available clinical, ECG, echocardiography, and device parameters associated with improvement in quality of life and functional status in patients with CRT?	12	55	48	3
19. What is the association of PVC burden prior and post CRT-D implantation on outcomes? Any data on associations of PVC ablation and outcomes?	2	1	1	0
20. Is the PR interval associated with the effectiveness of CRT (vs. no CRT)?	1	7	5	0
40. Are the CRT outcomes observed in the community predicted by the available clinical trial evidence?	2	14	3	0

* Unique original RCTs or secondary analyses of original RCTs

Abbreviations: AF=atrial fibrillation; AV=atrioventricular; CRT=cardiac resynchronization therapy; ECG=electrocardiogram; EF=ejection fraction; HF=heart failure; ICD=implantable cardiac device; LBBB=left bundle branch block; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; PVC=premature ventricular contraction; RCT=randomized controlled trial; RV=right ventricular

(Central Illustration) Figure 1. Overview of Prioritization Process

Steps   Output/Products

1 | **Identification of evidence gaps**
Review published literature including systematic reviews, practice guidelines and consensus statements for evidence gaps; Structure evidence gaps into research questions

Initial list of evidence gaps

2 | **Selection of stakeholders**
Send stakeholders background materials and list of evidence gaps

Establish stakeholder group

Engage stakeholders
Introduce to process; refine and expand initial evidence gaps

Expand list of evidence gaps

3 | **Stakeholders participate in web-based prioritization process**
Forced-ranking prioritization method to facilitate prioritization of evidence gaps

Stakeholder-ranked list of research questions

Inform stakeholders of prioritized list and next steps

4 | **Conduct horizon scan of studies potentially relevant to top tier research questions**
ESG investigations conduct PubMed and Clinicaltrials.gov searches for recent or ongoing relevant studies for top-tier prioritized questions

Detailed list of recently published or ongoing research relevant to top-tier CRT questions

Publish methods and prioritization process results

Abbreviations: CRT=cardiac resynchronization therapy; ESG=Evidence Synthesis Group