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Comparative effectiveness of cardiac implantable electrical devices

Daniel B Kramer^{1,2}, Laura A Hatfield³, and Sharon-Lise T Normand^{3,4}

¹Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

²HSL-IFAR, Hebrew SeniorLife Institute for Aging Research, Boston, Massachusetts, USA

³Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts, USA

⁴Department of Biostatistics, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA

Selecting the right cardiac implantable electrical device for the right patient at the right time remains a critical public health problem. Consensus guidelines generally conform to the inclusion criteria for the pivotal clinical studies, but several important considerations remain distressingly murky for patients considering implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or pacemaker (CRT-P) function.¹ How effective are these therapies in subgroups that are relatively uncommon in clinical studies, but common in practice, particularly older patients and those with substantial comorbidities?² How effective are these therapies compared with one another in patients eligible for either based on current criteria? Can subgroups be identified that clearly do not benefit from or may even be harmed by these therapies? What are the best estimates of *individual* outcomes with or without therapy that might improve informed consent and shared decision-making?³

Into this fray step Woods and colleagues, whose network meta-analysis of nearly 13 000 patients with heart failure and reduced EF is published in *Heart*.⁴ Assembling data from 13 separate randomised trials, representing 95% of all such randomised patients, Woods *et al* compared the survival advantage of CRT-D, CRT-P and ICD versus medical therapy alone and each other with the goal of providing tailored survival benefits according to key covariate combinations such as age and sex. The network meta-analytical approach uses direct treatment comparisons (such as studies examining CRT vs medical therapy) to learn about comparative effectiveness and also indirect treatment comparisons (eg, CRT vs medical therapy in one study, ICD vs medical therapy in another) to supplement or even replace direct evidence. All three devices achieved substantial relative risk reductions for mortality compared with medical therapy alone (42%, 29% and 28%, respectively) in

Correspondence to Dr Daniel B Kramer, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Boston, MA 02215, USA; dkramer@bidmc.harvard.edu.

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unadjusted analyses. The authors detail the results of their final adjusted model that included QRS width, left bundle branch block (LBBB), age and sex, walking through different combinations of characteristics to demonstrate the more precise outcome estimates (see figure 1). For example, on examining subgroups of patients with reduced EF and QRS ≥ 120 ms, CRT-D was associated with a statistically significant mortality reduction in 15 out of 16 subgroups, with estimated relative risk reductions in mortality ranging from 28% (HR 0.72 (0.51 to 1.01)) to 53% (HR 0.47 (0.34 to 0.66)). The greatest reduction in mortality was seen in women ≥ 60 years old with QRS duration ≥ 150 ms and LBBB, whereas men aged <60 with non-LBBB QRS duration ≥ 120 to <150 ms was the only group for which the CIs include the null value (1.0). For patients with narrow (<120) QRS complexes, the adjusted analyses considered only ICDs versus medical therapy—their analytical approach did not aim to reinterrogate the effectiveness of CRT in patients with narrow QRS complexes.

From these results, the authors conclude that their adjusted model builds on the primary clinical trial outcomes to provide estimates of greater robustness than simply extrapolating from the many subgroups published with each study, or aggregating these across studies in a simple meta-analysis. These estimates may, in theory, provide more precise inputs into individualised decision-support tools for patients according to their characteristics, but do not, as the authors themselves note, generally argue for changes to the guidelines. Notably, Woods *et al* suggest that their findings may support modest refinement of the guidelines with respect to the differential impact of ICDs on patients with and without prior infarction as the aetiology of their systolic dysfunction, with the latter given a less robust recommendation (class IB) in the European guidelines. Less clear is whether a class IA versus IB characterisation carries enough weight to sustain the debate, as the individual clinical trial data illustrate consistently lower annual event rates of arrhythmic death in non-infarct populations.

Several limitations to the present study merit comment. One of the most important limitations of the trials themselves, and subsequently a network meta-analytical approach to them, is the very limited time horizon available. Mean patient follow-up across all 13 studies was only 2.5 years (range 0–7.5). Though some of these studies have subsequently published findings with longer follow-up, these data were excluded by Woods *et al* due to reportedly high numbers of crossover patients blurring the analyses. In addition, as noted by the authors themselves, the adjusted model did not include atrial fibrillation or chronic kidney disease as these were not reliably reported in the aggregated studies. This is a critical shortcoming that directly blunts the attempts to leverage their model for real-world patients. Both atrial fibrillation and chronic kidney disease are common comorbidities that have consistently been shown to attenuate the benefit of ICD therapy or increase mortality in device recipients.⁵⁶ In addition, programming of the devices themselves has evolved over time, with a significant impact on outcomes,⁷ and this also may blunt the precision of the estimates provided.

The suggestion that ischaemic aetiology is not an important factor in treatment choice is based on the failure of that variable to improve model fit in the presence of multiple other covariates, but these results are not shown. Similarly, including EF as a potential modifier of the effects of CRT led to ‘biologically implausible’ interaction terms, so this was also

dropped. With so many clinical factors available as predictors of survival and possibly response to treatment, it is useful to understand the full space of interactions among these factors and build models rigorously, without ad hoc modelling choices and selective inference. Multivariable results are a strength of this paper relative to other meta-analyses emphasising treatment effect heterogeneity,⁸ but the authors might have been even more comprehensive. Differences in follow-up time across studies is a key challenge in network meta-analysis and one the authors do not address.⁹ Comparing effects from an arm in a trial with particularly long follow-up with an arm in a trial with shorter follow-up requires assuming a constant HR, which is hard to justify, or accommodating time-varying hazards. Similarly, more detail regarding the authors' assessment of the consistency of device effectiveness in their network (ie, the expectation that the device 'effect' is the same, regardless of comparison group) would strengthen further our interpretation of the study findings. Assessment of the consistency of the various pairwise comparisons could lead to different conclusions if this source of variation is ignored in calculations.

In sum, the contribution from Woods and colleagues may be useful in guiding clinicians and patients through the decision-making process with more comprehensive estimates of benefits. Forthcoming quality of life data from the same group, and perhaps pooled data on the survival outcomes and also procedural and other complications, may further strengthen the knowledge base around CRT and ICD use. The pivotal clinical trials clearly show that CRT and ICDs can save lives. Ultimately, however, given the heterogeneity of effect across patient groups and the extraordinary costs of these therapies, the real test of progress in this field will be whether clinicians can move towards these more elusive, but essential, estimates of what *this* device will mean for *this* patient at *this* time.

Efficiently integrating evolving estimates of risks and benefits into a patient-centred process of shared decision-making—even as new prospective studies hopefully refine outcomes more clearly—will require sustained effort from clinicians, policy makers and the public. Following the guidelines is easy. Building upon the clinical trial data to make device-based therapies more effective will not be.

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References

1. Kusumoto FM, Calkins H, Boehmer J, et al. HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *Circulation*. 2014; 130:94–125. [PubMed: 24815500]
2. Kramer DB, Matlock DD, Buxton AE, et al. Implantable cardioverter-defibrillator use in older adults: proceedings of a Hartford change AGENTS symposium. *Circ Cardiovasc Qual Outcomes*. 2015; 8:437–46. [PubMed: 26038525]

3. Lewis KB, Stacey D, Matlock DD. Making decisions about implantable cardioverter-defibrillators from implantation to end of life: an integrative review of patients' perspectives. *Patient*. 2014; 7:243–60. [PubMed: 24668214]
4. Woods B, Hawkins N, Mealing S, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart*. Published Online First: 12 Aug 2015. 10.1136/heartjnl-2015-307634
5. Pun PH, Al-Khatib SM, Han JY, et al. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: a meta-analysis of patient-level data from 3 randomized trials. *Am J Kidney Dis*. 2014; 64:32–9. [PubMed: 24518128]
6. Alba AC, Braga J, Gewarges M, et al. Predictors of mortality in patients with an implantable cardiac defibrillator: a systematic review and meta-analysis. *Can J Cardiol*. 2013; 29:1729–40. [PubMed: 24267811]
7. Ruwald AC, Schuger C, Moss AJ, et al. Mortality reduction in relation to implantable cardioverter defibrillator programming in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT). *Circ Arrhythm Electrophysiol*. 2014; 7:785–92. [PubMed: 25136077]
8. Zusterzeel R, Spatz ES, Curtis JP, et al. Cardiac resynchronization therapy in women versus men: observational comparative effectiveness study from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2015; 8:S4–11. [PubMed: 25714821]
9. Kunz LM, Normand SL, Sedrakyan A. Meta-analysis of rate ratios with differential follow-up by treatment arm: inferring comparative effectiveness of medical devices. *Stat Med*. 2015; 34:2913–25. [PubMed: 26011521]

Figure 1.

Estimated HRs and 95% CIs for each treatment (row) versus each contrast treatment (column). The subgroups on each panel's x axis are defined by gender, age (<60 years, 60+ years), QRS duration (<120 ms, 120–149 ms, 150+ ms) and LBBB (Y=yes, N=no). The colours indicate results from two different samples: the full sample and the reduced sample that omits patients with QRS <120 ms and NYHA class I. This figure reproduces the main results from table 2 and the sensitivity results from table S5 of the Woods *et al* article. CRT-D, cardiac resynchronisation therapy-defibrillator; CRT-P, CRT-pacemaker; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; MT, medical therapy; NYHA, New York Heart Association.