Complications from prophylactic replacement of cardiac implantable electronic device generators in response to United States Food and Drug Administration recall: A systematic review and meta-analysis

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BACKGROUND The number of cardiac implantable electronic device (CIED) recalls and advisories has increased over the past 3 decades, yet no consensus exists on how to best manage patients with these CIEDs, partially because rates of complications from prophylactic replacement are unknown.

OBJECTIVE The purpose of this study was to establish rates of complications when recalled CIED generators are replaced prophylactically.

METHODS We searched MEDLINE and the Cochrane Controlled Trials Register for reports of prophylactic replacement of recalled CIED generators. Studies with <20 subjects were excluded. We then conducted a meta-analysis of qualifying studies to determine the rates of combined major complications, mortality, and reoperation.

RESULTS We identified 7 citations that met our inclusion criteria and reported ≥ 1 end-points of interest. Four were single center, and 3 were multicenter. Six studies collected data retrospectively (n = 1213) and 1 prospectively (n = 222). Using a random effects model to combine data from all included studies, the rate of major complications was 2.5% (95% confidence interval [CI] 1.0%-4.5%). Combining data from 6 studies reporting mortality and reoperation, the rates were 0.5% (95% CI 0.1%–0.9%) and 2.5% (95% CI 0.8%–4.5%), respectively.

CONCLUSION Prophylactic replacement of recalled CIED generators is associated with a low mortality rate but nontrivial rates of other major complications similar to those reported when CIED generators are replaced for other reasons. Thus, when considering replacing a recalled CIED generator, known risks of elective generator replacement likely apply and can be weighed against risks associated with device failure.

KEYWORDS Recall; Cardiac implantable electronic devices; Complications; Mortality

ABBREVIATIONS **CI** = confidence interval; **CIED** = cardiac implantable electronic device; **CRT** = cardiac resynchronization therapy; **FDA** = United States Food and Drug Administration; **ICD** = implantable cardioverter-defibrillator

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Introduction

Cardiac implantable electronic devices (CIEDs), including pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices, all have an inherent rate of failure. When an unforeseen failure mechanism or rate of failure is identified after a device has been approved, the United States Food and Drug Administration (FDA) may issue an advisory or recall, typically in cooperation with the device manufacturer. During the past 3 decades, partly because of the increasing complexity of CIEDs, there has been an increase in the number and rate of pacemaker and ICD advisories and recalls.[1,2]

When these device problems cannot be addressed through noninvasive software updates, providers must consider how to best manage patients with advisory or recalled CIEDs *in situ.* Options include intensified monitoring with intervention only if and when there is evidence of generator malfunction or failure vs prophylactic generator replacement. This consideration depends on the suspected failure rate and mechanism and potential outcomes of failure along with patient characteristics and preferences. To date, there is no consensus on how to best manage patients with recalled generators *in situ,* due in part to a paucity of information about the risk of prophylactic replacement of these generators.

Therefore, we sought to perform a systematic review and meta-analysis of observational studies to more accurately

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estimate the risk of complications associated with prophylactic replacement of CIED generators under FDA advisory or recall.

Methods

Search strategy

An expert reference librarian designed and conducted an electronic search strategy with input from the primary investigator. The initial search was implemented in PubMed (September 2014) using a combination of medical subject headings (MeSH) and keywords to combine the subjects of CIEDs, FDA recall or advisory, and complications from CIED replacement procedures. After this initial search, terms were translated and a similar search was used in the Cochrane Database (Appendix 1). The search was limited to the English language. The bibliographies of selected full-length manuscripts were reviewed manually to identify any additional relevant references not captured in our search.

Eligibility

Any study that systematically reported complications from the prophylactic replacement of advisory or recalled CIEDs were eligible for inclusion. Studies were excluded if they had <20 subjects.

Extraction

All screening decisions were made and tracked in a DistillerSR database (Evidence Partners Inc, Manotick, Ontario, Canada) by 2 investigators (EPZ, DP). Extracted data included patient characteristics, combined major complications, mortality, and reoperation/pocket revision. Disagreements were resolved by consensus. We evaluated the strength of evidence using approaches described by the Agency for Healthcare Research and Quality (AHRQ)[3] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[4]

End-points

The primary end-point of interest was combined major complications. Other end-points included mortality and reoperation/pocket revision.

Overall combined major complications

The end-point of combined major complications was defined variably among included studies (Table 1). In some cases, this represented complications detailed in the manuscript, which for the purpose of this study were combined by the primary investigator for an overall rate.

Mortality

Death as a complication of generator replacement was defined as occurring during the operation or in the immediate postoperative period (<30 days postprocedure).

Table 1 Definition of combined major complications by study

Author, year	Definition
Moore,[14] 2009	Death + any complication requiring reoperation (infection, bleeding/hematoma, system malfunction)
Amin,[9] 2008	Death + any complication associated with device replacement
Mahajan,[13] 2008	Death + any complication associated with reoperation
Costea,[15] 2008	Death + any complication requiring reoperation (bleeding/hematoma, lead damage, device "protrusion") + stroke
Kapa,[12] 2007	Any complication requiring intervention or reoperation up to 60 days postprocedure
Hauser,[11] 2006	Death
Gould,[10] 2006	Death + any complication requiring reoperation (infection, bleeding, system malfunction, pain)

Reoperation/pocket revision

Reoperation and/or pocket revision as a complication of CIED generator change was defined as any complication leading to an unexpected reoperation or pocket revision. In some cases, a definition was not explicitly provided. In other cases, this end-point represented complications that clearly resulted in reoperation and/or pocket revision, which for the purpose of this analysis were combined by the investigators. These included, but were not limited to, bleeding into the CIED header requiring revision, hematoma, system malfunction, pocket infection requiring extraction, lead damage requiring revision, and site pain requiring reoperation.

Data analysis

Most meta-analyses are calculated using standard meta-analysis software such as the Comprehensive Meta Analysis program (Biostat, Englewood, NJ).[5] However, these programs use normal approximations, which are not appropriate for very small counts. Many of the counts in the studies included in our analyses are either 0 or 1. This problem was discussed by Hasselblad et al.[6] For the particular end-points in this study, it is important to base the calculations on the binomial distribution because that is the distribution of the individual study rates.

The calculation of a fixed effects estimate for a series of independent binomial distributions is estimated from the pooled numerators and denominators. The logical random effects model is the beta-binomial distribution.[7] This distribution can be fitted to the observed counts using FAST*-PRO software (Academic Press, Boston, MA).[8]

Results

Search results

Our search identified 142 abstracts, which were reviewed for inclusion and exclusion criteria (Figure 1). Among this group of abstracts, 91 were excluded because of irrelevance to our topic of interest. The full manuscripts for the remaining 51