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Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Initial management of cardiac implantable electronic device (CIED) infection requires removal of the infected CIED system and treatment with systemic antibiotics. However, the optimal timing to device re-implantation is unknown. The aim of this study was to quantify the incidence of re-infection after initial management of CIED infection, and to assess the effect of timing to re-implantation on re-infection rates.

Design: Systematic review and meta-analysis

Interventions: A systematic review and meta-analysis was performed of studies published up to February 2018. Inclusion criteria were: (a) documented CIED infection, (b) studies that reported the timing to device re-implantation and (c) studies that reported the proportion of participants with device re-infection. A meta-analysis of proportions using a random effects model was performed to estimate the pooled device re-infection rate.

Primary and secondary outcome measures: The primary outcome measure was the rate of CIED re-infection. The secondary outcome was all-cause mortality.

Results: Of the 280 screened studies, 8 met inclusion criteria with an average of 96 participants per study (range 15 to 220 participants). The pooled incidence rate of device re-infection was 0.45% (95% confidence interval, 0.02 to 1.23%) per person year. Time to device re-implantation may affect rates of re-infection when device re-implantation occurs at ≤ 72 hours compared to >72 hours. There did not appear to be a difference in re-infection rates when time to re-implantation was stratified at 1 week. Heterogeneity was moderate (I^2 = 61%).

Conclusions: The incident rate of re-infection following initial management of CIED infection is not insignificant. Our findings suggest a trend that time to re-implantation affects rates of re-infection when device re-implantation occurs at ≤ 72 hours compared to >72 hours.

PROSERO Registration Number: CRD4201810960

STRENGTHS AND LIMITATIONS

- To our knowledge, this is the first systematic review and meta-analysis to assess the rate of re-infection following initial cardiac implantable device infection, and the impact of timing to device re-implantation.
- Studies identified from the systematic review were mainly retrospective studies that varied in patient population, study quality, and follow-up, which contributed to the heterogeneity in the pooled results of the meta-analysis.
- The results of our systematic review and meta-analysis highlight the need for additional well-designed studies in this area.

INTRODUCTION

Cardiac implantable electronic device (CIED) infections are a major cause of morbidity and mortality,[1,2] and are associated with substantial healthcare costs.[3,4] In the United States (US), one admission for an infected CIED can range from $14 360 to $53 349 USD.[3] As the number of CIED implantations increase worldwide, the rate of infectious complications is also rising.[5,6] More concerningly, the rate of CIED infections is outpacing the increase in implantations.[7] This is the likely result of the expanding indications for cardiac resynchronization therapy (CRT) and prophylactic implantable cardioverter defibrillators (ICDs) and the increasing need for permanent pacing in an aging patient population; CIEDs are being implanted in increasingly complex patients with multiple comorbidities who are at an increased risk of infectious complications.[2]

Treatment of CIED infections typically requires complete extraction of the infected CIED systems (including generator and leads), debridement and administration of antibiotics to eradicate infection.[8] Delays in device extraction have been associated with significant increase in mortality.[9] Furthermore, failure to remove an infected CIED has been associated with a 7-fold increase in 30-day mortality.[10] There is also an increase in relapse of infection when hardware is not removed,[11] which is postulated to be attributable to biofilm formation.[12]

Following CIED removal, it is critical to evaluate whether or not the CIED requires re-implantation, as over time the indication for CIED may no longer be present.[8] In the majority of patients that require device replacement for infection, the optimal timing to re-implantation is unknown. The ideal re-implantation strategy would minimize the number of procedures and the duration of risk that patients may experience without a CIED (i.e. ventricular arrhythmias, or worsening heart failure without resynchronization). Notably, the optimal timing to re-implantation should not increase the risk of device re-infection.

The evidence regarding timing to re-implantation following CIED infection is relatively sparse and based primarily on consensus opinion.[11] A recent prospective study assessed the relationship between timing of re-implantation to relapse of CIED infection within a six-month time period.[11] Their findings suggested that once the infected hardware was removed timing to re-implantation had little impact on recurrent infection.[11]

Current expert recommendations from the Heart Rhythm Society suggest that blood cultures should be negative for at least 72 hours prior to device re-implantation.[8] A longer duration may be required depending on the clinical scenario (i.e. if there is another untreated source of infection). In the presence of valvular vegetations, it is proposed that device re-implantation be delayed to a minimum of 14 days.

Given the relative paucity of evidence supporting the optimal timing to device re-implantation following CIED infection, our study aims to systematically review the available literature, to summarize the pooled re-infection rates after initial CIED infection, and to assess if there is a potential association of re-infection with time to device re-implantation.

METHODS

The study protocol and report is based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[13] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE).[14] The study protocol was designed *a priori* and registered with PROSPERO, CRD4201810960.

Eligibility Criteria

Publications were selected based on the following inclusion criteria: (a) cohort studies or randomized control trials that included patients with documented CIED infection with complete hardware removal as part of the management, (b) studies that reported the timing to device-re-implantation following management of initial CIED infection, and (c) studies that reported the outcome of device re-infection following re-implantation. All publications were limited to those involving adult (age 18 years or older) human participants.

Search Strategy

A systematic electronic search was performed in consultation with a librarian scientist, using MEDLINE (1946-), EMBASE (Excerpta Medica Database 1974-) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Abstracts of Review Effects, Cochrane Central Registry of Controlled Trials, and Health Technology Assessment) databases for observational studies and randomized controlled trials that met inclusion criteria. This was followed with a hand search of the reference lists of relevant articles. The search strategy included both controlled vocabulary (MeSH terms) as well as key words that were identified during the scoping review. The main search concepts included (a) cardiac implantable devices, (b) device infection, and (c) timing to device re-implantation. All searches were conducted without date limitations, and included manuscripts published up to February 22, 2018. The detailed search strategy is included in ***Appendix A***.

Study Selection and Data Extraction

Two reviewers (DC and ERM) independently screened the study titles and abstracts to exclude irrelevant studies. The same reviewers then independently reviewed the full manuscripts for eligible studies and recorded the main reason for exclusion. Disagreements were resolved through consensus, and consultation of a third reviewer (RS) if necessary. Interrater agreement was quantified using Cohen's kappa coefficient. Data extraction was performed in duplicate by the same two reviewers into a standardized electronic spreadsheet. Data elements for extraction were pre-specified, and included the age and sex of participants, type of CIED infection (i.e. endocarditis or pocket infection), device type (i.e. pacemaker, implantable cardioverter defibrillator or cardiac synchronization therapy), number of leads,

microbiology, timing to re-implantation, rate of device re-infection, mortality rate and study follow up time.

Assessment of Study Quality

The risk of bias was assessed using the Newcastle-Ottawa scale[15] and updated Cochrane Risk of Bias Tool[16] for non-randomized and randomized controlled trials respectively. Risk of bias was assessed independently by two reviewers (DC and ER) and discrepancies resolved by consensus.

Patient and Public Involvement

Patients or members of the public were not involved in the study design or analysis.

Statistical Analysis

The pooled incidence rate and 95% confidence interval (CI) for outcomes of interest were obtained. The primary outcome of the meta-analysis was the rate of CIED re-infection. The secondary outcome was all-cause mortality. Data were pooled using a random-effects meta-analysis of proportions model using the Dersimonian and Laird method[17] incorporating a Freeman-Tukey double arcsine transformation.[18] A random-effects model was chosen *a priori* on the basis of the anticipated heterogeneity among study baseline characteristics and the impact on device re-infection rates. The Metaprop package in Stata 15.1 (Stata Corp., College Station, TX, USA) was used to obtain the pooled estimate.[19] All analyses were performed using Stata IC 15.1. Rates of CIED re-infection were standardized across studies by the duration of follow up and reported as the incident rate per person-year.

Due to the potential for significant variation in follow up time and the possibility of zero count data in the included studies, we performed a secondary analysis using a mixed-effects Poisson-distribution model to estimate the pooled incidence rate of re-infection.[20] To assess if re-infection rates were affected by time to device re-implantation, a meta-regression of the incidence rates and time to re-implantation was performed. Pre-specified subgroup analyses included stratification of the primary outcome by median time to device re-implantation of greater than 72 hours and those with a median re-implantation time of 72 hours or less. Re-infection rates stratified by re-implantation prior to one week versus at one week or greater were also assessed. The stratification of timing to re-implantation was chosen based on current expert recommendations for CIED infections without or with lead endocarditis, respectively.[8,21] As meta-regression is an underpowered analysis, a p-value < 0.10 was considered significant.

Heterogeneity across the studies was tested with the Cochran Q and I^2 statistics.[22,23] We considered an I^2 statistic of >25% as a low degree of heterogeneity, >50% as moderate heterogeneity, and >75% as high heterogeneity.[24]

RESULTS

Study Selection and Characteristics of Included Studies

Among 280 unique citations identified in the literature search, 18 studies were retrieved for full text review (***Figure 1***). The interrater agreement during the initial screening was substantial (Kappa = 0.61). Following the full text review, a total of eight studies met inclusion criteria.[11,25-31] There were no randomized controlled trials (RCTs) identified in the systematic review that met the inclusion criteria. All eight included studies were observational in design; three were prospective[11,25,27] and five were retrospective.[26,28-31] Of the ten studies that were excluded: four assessed the wrong study population,[32-35] five did not report device re-infection rates,[36-40] and one had the wrong study design.[41]

The characteristics of the included studies are summarized in ***Table 1***. The observation cohorts had a range of 15 to 220 participants, for a total of 744 participants who underwent complete explantation of an infected CIED with subsequent re-implantation of a new device. The range of the mean age was 50 to 71 years and the proportion of women included in the studies was 19 to 32%. The majority of studies reported on device infections related to pacemakers and ICDs,[25,26,29,31] and two studies included CRT infections.[27,30] The microbiology of the CIED infections was not consistently reported among the studies. The most common reported etiology of CIED infection was coagulase negative staphylococci (range 40 to 70%), followed by *Staphylococcus aureus* (range 9 to 30%) and Gram-negative bacilli (range 11 to 20%). The duration of follow up after device re-implantation varied substantially from 6 to 312 months.

Study Quality

As there were no RCTs identified in the systematic review, the Newcastle-Ottawa scale was used to assess risk of bias in each of the included studies. Two measures within the scale were not applicable given the design of the included studies; the six measures that were graded were: (a) cohort representativeness, (b) exposure ascertainment, (c) outcome absence at baseline, (d) assessment of outcome, (e) adequacy of observation duration, and (f) completeness of cohort-follow up. The majority of studies had the highest quality-level indicators in all six measures. Two studies selected populations that may not be representative of the overall CIED population: Mountantonakis *et al.* focused on the patients with localized pocket infection for assessing the safety of same day device re-implantation following extraction.[29] The cohort described by Molina did not represent the contemporary population of CIED patients, as a significant proportion of devices in the study cohort underwent CIED implantation by sternotomy or thoracotomy with placement of epicardial patches.[28] Two studies did not clearly detail if all patients had been accounted for by the end of the study and there were concerns of bias with regards to their completeness of follow up.[28,31]

Re-infection following Management of Infection CIED Infection

In our primary analysis, the incidence rate of first device re-infection for the pooled cohort was 0.45% (95% confidence interval (CI), 0.02 to 1.23%) per person-year (***Figure 2***). There was a moderate degree of heterogeneity (I^2 = 61%). In our secondary analysis using a mixed-effects Poisson regression model, the incidence rate of re-infection was similar to our primary analysis at 0.58% (95% CI, 0.21 to 1.55%) per person year.

Effect of Time to Re-implantation

Time to re-implantation >72 hours was associated with a trend toward a higher incidence of CIED re-infection (unadjusted incident rate ratio (IRR) 4.8; 95% CI 0.9 to 24.3, p=0.06 mixed-effects Poisson regression). Given the smaller number of included studies identified by the systematic review, we were unable to adjust for additional variables. When stratifying time to device re-implantation by one week or less, there did not appear to be a significant difference in incidence rate (p=0.7 mixed-effects Poisson regression).

Mortality following CIED Infection

Only five of the included studies reported all-cause mortality.[11,25-28] Among the 508 patients included in these studies, 42 deaths (8.3%) were observed over a median follow up of 14 months. In the random effects analysis, the incidence rate of death was 5.0% (95% CI, 0.1 to 15.5%) per person-year of follow up (***Figure 3***). There was a high degree of heterogeneity (I^2 = 96%).

DISCUSSION

Principle Findings

We found that the pooled re-infection rate following initial management of CIED infection was approximately 0.5% per person-year. To our knowledge, this is the first systematic review and meta-analysis reporting the pooled re-infection rates following original management of CIED infection. The substantial heterogeneity seen in the pooled analysis suggests the presence of several variables that can affect the incidence rate of re-infection. Factors may include the presence of bacteremia, response to treatment, or patient factors, such as the presence of immunosuppression.[1]

When we examined infection risk based on timing of re-implantation, a time of greater than 72 hours was associated with a 4-fold higher incidence rate compared to re-implantation at 72 hours or less. Using a one week cut-point for time to device re-implantation, there was no difference in re-infection rates. We consider these results exploratory, as meta-regression is considered an underpowered analysis. Specifically, given the small number of studies included in the pooled analysis, we were unable to adjust for potentially important confounders. For example, the higher re-infection rate associated with time to re-implantation >72 hours may be

due to an increased number of comorbid conditions in the corresponding study populations, or a high proportion of systemic infections requiring additional time to clear the bloodstream of bacteremia. Important covariates, which we were unable to adjust for at the meta-regression level, were the proportions of documented endocarditis, lead vegetations or bacteremia compared to localized pocket infection.

Management of Cardiac Device Infections

Treatment of CIED infections requires complete extraction of the infected CIED systems (including generator and leads) and administration of systemic antibiotics to eradicate infection.[8] In the majority of patients that require device replacement, the optimal timing to re-implantation is unknown. Conceptually, re-implanting a device too early during the treatment course may result in a higher infection relapse rate if the infection has only been partially eradicated by systemic antibiotics. However, the longer hospital stays while awaiting device re-implantation are associated with increased health care costs, decreased patient quality of life, and the potential for acquiring non-device related nosocomial infections. Furthermore, there is the potential for adverse events related to the absence of ICD or CRT therapies, such as worsening heart failure or delay to treatment of malignant ventricular arrhythmias.

Time to Device Re-implantation

There is a paucity in the literature exploring the timing of CIED replacement and risk of re-infection. Our systematic review only identified eight studies that reported the time to re-implantation and the rate of device re-infection.[11,25-31] The majority of these studies are limited by their retrospective study design[26,28-31] and small sample sizes. Furthermore, the primary study designs did not focus on assessing the effect of time to re-implantation on subsequent CIED re-infections. Consistent with the relatively paucity in the literature guiding time to device re-implantation, we noted a wide range in the median time to device re-implantation (i.e. same day re-implantation to over two weeks).

One of the largest contemporary prospective cohorts tracking CIED infections found a repeat infection risk of 1.8% among patients who were re-implanted.[11] This study found a high variation in physician practice when determining the time to device re-implantation, yet timing to re-implantation did not seem to affect re-infection rates. With the caveat of a relatively small sample size and limited follow up, the authors suggested that an array of other risk factors may have a larger role in determining infection relapse rates compared to decisions regarding timing to re-implantation.[11] Consistent with this notion, some studies suggest that factors, such as the presence of hemodialysis for renal failure, pocket hematomas, malignancy, or *Staphylococcus aureus* bacteremia are the leading risk factors in estimating the risk of re-infection.[42,43] In fact, small single-center studies suggested that same-day re-implantation is feasible for patients with isolated CIED pocket infections and is not associated with adverse outcomes.[29,44]

Current expert consensus recommendations from the Heart Rhythm Society and American Heart Association suggest a 72 hour and 14 day waiting period for re-implantation based on blood culture negativity and the presence of valvular vegetations, respectively.[8,21] However, the quality of evidence supporting these recommendations are weak (Grade IIaC), and based mainly on a single retrospective study of 127 patients.[40] Our findings do not support this conclusion as re-implantation at greater than 72 hours was associated with increased infection rates. However, there are significant limitations to our findings, which should be considered exploratory and reinforces the need for additional research to guide recommendations regarding timing to re-implantation.

Study Limitations

Our study requires interpretation in the context of a number of limitations. Firstly, time to re-implantation and device re-infection rates were inconsistently reported in the literature. Five studies were excluded at the level of the full text screen as they did not report device re-infection rates. Additionally, the adopted diagnostic criteria for device infection were inconsistently reported among the included studies, which may contribute to the heterogeneity in the pooled estimate of incidence rate of CIED re-infection. Secondly, the meta-analyses included mainly retrospective studies that varied in patient population, study quality, and follow-up, contributing to the clinical variability and heterogeneity in our pooled analysis. Thirdly, we attempted to explore the relationship between time to re-implantation and re-infection rates. An important limitation is the unavailability of patient level data and times to follow up. To explore the potential association, we performed a Poisson-distribution meta-regression. However, given the small number of studies that met inclusion criteria, the meta-regression was underpowered, and we were unable to properly adjust for other confounders with the potential to affect re-infection rates.

Implications for Future Research

Additional prospective, well-designed studies are required to explore the effect of timing to re-implantation on re-infection rates, with adequate adjustment for patient comorbidities, extent of infection (i.e. localized pocket infection, vegetation or bacteremia) and the causative pathogen. Based on the several small studies reporting on the safety of same day re-implantation and in light of our findings, larger studies are necessary to validate the safety of the one-stage contralateral device replacement approach compared with delayed device replacement. Given the potential impact on hospital length of stay, an economic evaluation comparing these strategies will also be an important component.

Finally, the advent of new technology such as leadless pacemakers and subcutaneous ICDs may obviate the need to delay device re-implantation following extraction of infected CIED systems. The current assumption is that these newer devices are associated with a lower risk of

infection: leadless pacemakers have significantly less surface area for bacterial seeding, and subcutaneous ICDs do not contain any components exposed to the bloodstream. Nevertheless, the use of these novel devices to replace infected conventional CIEDs following antimicrobial therapy, or the rates of infection associated with these devices have yet to be assessed.

CONCLUSION

The incident rate of re-infection following initial management of CIED infection is not insignificant. Our findings suggest a trend that time to re-implantation affects rates of re-infection when device re-implantation occurs at ≤ 72 hours compared to >72 hours. The findings of this study need to be interpreted with circumspection due to the moderate heterogeneity among included studies.

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AUTHOR CONTRIBUTIONS

JC, DVE, ER and DC were responsible for conception of this research study and methodology. DS and ER wrote the manuscript. DS, ER and RS were responsible for data collection and analysis. All authors reviewed the manuscript and analyses.

DATA AVAILABILITY STATEMENT

The data used to compile the meta-analysis is available upon request.

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COMPETING INTERESTS

DVE has received research grants from Medtronic Inc, GE Healthcare, and St Jude Medical outside of the submitted work. The remaining authors have no conflicts of interest to disclose.

REFERENCES

1 Polyzos, K. A., Konstantelias, A. A. & Falagas, M. E. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace* **17**, 767-777, doi:10.1093/europace/euv053 (2015).

2 Greenspon, A. J. *et al.* 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* **58**, 1001-1006, doi:10.1016/j.jacc.2011.04.033 (2011).

3 Sohail, M. R., Henrikson, C. A., Braid-Forbes, M. J., Forbes, K. F. & Lerner, D. J. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* **171**, 1821-1828, doi:10.1001/archinternmed.2011.441 (2011).

4 Tarakji, K. G. *et al.* Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* **7**, 1043-1047, doi:10.1016/j.hrthm.2010.05.016 (2010).

5 Mond, H. G. & Proclemer, A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* **34**, 1013-1027, doi:10.1111/j.1540-8159.2011.03150.x (2011).

6 Valzania, C., Torbica, A., Tarricone, R., Leyva, F. & Boriani, G. Implant rates of cardiac implantable electrical devices in Europe: A systematic literature review. *Health Policy* **120**, 1-15, doi:10.1016/j.healthpol.2015.11.001 (2016).

7 Voigt, A., Shalaby, A. & Saba, S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol* **33**, 414-419, doi:10.1111/j.1540-8159.2009.02569.x (2010).

8 Kusumoto, F. M. *et al.* 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm* **14**, e503-e551, doi:10.1016/j.hrthm.2017.09.001 (2017).

9 Viganego, F. *et al.* Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol* **109**, 1466-1471, doi:10.1016/j.amjcard.2012.01.360 (2012).

10 Le, K. Y. *et al.* Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm* **8**, 1678-1685, doi:10.1016/j.hrthm.2011.05.015 (2011).

11 Boyle, T. A. *et al.* Reimplantation and Repeat Infection After Cardiac-Implantable Electronic Device Infections: Experience From the MEDIC (Multicenter Electrophysiologic Device Infection Cohort) Database. *Circulation. Arrhythmia and electrophysiology* **10**, doi:10.1161/CIRCEP.116.004822 (2017).

12 Gaynor, S. L. *et al.* Laser assistance for extraction of chronically implanted endocardial leads: infectious versus noninfectious indications. *Pacing Clin Electrophysiol* **29**, 1352-1358, doi:10.1111/j.1540-8159.2006.00547.x (2006).

13 Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **339**, b2535, doi:10.1136/bmj.b2535 (2009).

14 Stroup, D. F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* **283**, 2008-2012 (2000).

15 Wells GA *et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* , <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]> (2000).

16 Higgins, J. P. *et al.* in *Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.* Vol. 10 (Issue 1) (eds J. Chandler, J. McKenzie, I. Boutron, & B. Welch) (2016).

17 DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177-188 (1986).

18 Freeman, M. & Turkey, J. Transformations related to the angular and the square root. *Ann Math Stats* **21**, 607-611 (1950).

19 Nyaga, V. N., Arbyn, M. & Aerts, M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* **72**, 39, doi:10.1186/2049-3258-72-39 (2014).

20 Spittal, M. J., Pirkis, J. & Gurrin, L. C. Meta-analysis of incidence rate data in the presence of zero events. *BMC Med Res Methodol* **15**, 42, doi:10.1186/s12874-015-0031-0 (2015).

21 Baddour, L. M. *et al.* Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* **121**, 458-477, doi:10.1161/CIRCULATIONAHA.109.192665 (2010).

22 Cochran, W. G. The comparison of percentages in matched samples. *Biometrika* **37**, 256-266 (1950).

23 Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539-1558, doi:10.1002/sim.1186 (2002).

24 Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560, doi:10.1136/bmj.327.7414.557 (2003).

25 Amraoui, S. *et al.* Comparison of delayed transvenous reimplantation and immediate surgical epicardial approach in pacing-dependent patients undergoing extraction of infected permanent pacemakers. *Heart Rhythm* **12**, 1209-1215, doi:10.1016/j.hrthm.2015.02.023 (2015).

26 Chua, J. D. *et al.* Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* **133**, 604-608 (2000).

27 Deharo, J. C. *et al.* Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study. *Heart* **98**, 724-731, doi:10.1136/heartjnl-2012-301627 (2012).

28 Molina, J. E. Undertreatment and overtreatment of patients with infected antiarrhythmic implantable devices. *Ann Thorac Surg* **63**, 504-509 (1997).

29 Mountantonakis, S. E., Tschabrunn, C. M., Deyell, M. W. & Cooper, J. M. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. *Europace* **16**, 252-257, doi:10.1093/europace/eut220 (2014).

30 Saeed, O., Gupta, A., Gross, J. N. & Palma, E. C. Rate of cardiovascular implantable electronic device (CIED) re-extraction after recurrent infection. *Pacing Clin Electrophysiol* **37**, 963-968, doi:10.1111/pace.12407 (2014).

31 Tascini, C. *et al.* Management of cardiac device infections: A retrospective survey of a non-surgical approach combining antibiotic therapy with transvenous removal. *J Chemother* **18**, 157-163, doi:10.1179/joc.2006.18.2.157 (2006).

32 Amraoui, S. *et al.* Single surgical procedure combining epicardial pacemaker implantation and subsequent extraction of the infected pacing system for pacemaker-dependent patients. *J Thorac Cardiovasc Surg* **146**, 302-305, doi:10.1016/j.jtcvs.2012.07.026 (2013).

33 Le Franc, P. *et al.* Extraction of endocardial implantable cardioverter-defibrillator leads. *The American journal of cardiology* **84**, 187-191 (1999).

34 O'Nunain, S. *et al.* The treatment of patients with infected implantable cardioverter-defibrillator systems. *J Thorac Cardiovasc Surg* **113**, 121-129, doi:10.1016/S0022-5223(97)70407-0 (1997).

35 Rickard, J. *et al.* Cardiac venous left ventricular lead removal and reimplantation following device infection: a large single-center experience. *J Cardiovasc Electrophysiol* **23**, 1213-1216, doi:10.1111/j.1540-8167.2012.02392.x (2012).

36 Cassagneau, R. *et al.* Long-term outcomes after pocket or scar revision and reimplantation of pacemakers with preerosion. *Pacing Clin Electrophysiol* **34**, 150-154, doi:10.1111/j.1540-8159.2010.02950.x (2011).

37 Kennelly, B. M. & Piller, L. W. Management of infected transvenous permanent pacemakers. *Br Heart J* **36**, 1133-1140 (1974).

38 Margey, R. *et al.* Contemporary management of and outcomes from cardiac device related infections. *Europace* **12**, 64-70, doi:10.1093/europace/eup362 (2010).

39 Rickard, J. *et al.* Survival of patients with biventricular devices after device infection, extraction, and reimplantation. *JACC Heart Fail* **1**, 508-513, doi:10.1016/j.jchf.2013.05.009 (2013).

40 Sohail, M. R. *et al.* Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* **49**, 1851-1859, doi:10.1016/j.jacc.2007.01.072 (2007).

41 Vogt, P. R. *et al.* Surgical management of infected permanent transvenous pacemaker systems: ten year experience. *J Card Surg* **11**, 180-186 (1996).

42 Essebag, V. *et al.* Clinically Significant Pocket Hematoma Increases Long-Term Risk of Device Infection: BRUISE CONTROL INFECTION Study. *J Am Coll Cardiol* **67**, 1300-1308, doi:10.1016/j.jacc.2016.01.009 (2016).

43 Leung, S. & Danik, S. Prevention, Diagnosis, and Treatment of Cardiac Implantable Electronic Device Infections. *Curr Cardiol Rep* **18**, 58, doi:10.1007/s11886-016-0733-x (2016).

44 Nandyala, R. & Parsonnet, V. One stage side-to-side replacement of infected pulse generators and leads. *Pacing Clin Electrophysiol* **29**, 393-396, doi:10.1111/j.1540-8159.2006.00359.x (2006).

FIGURE LEGENDS

Figure 1. Flow Diagram of Study Selection for Systematic Review

Figure 2. Pooled Incidence Rate of Device Re-Infection

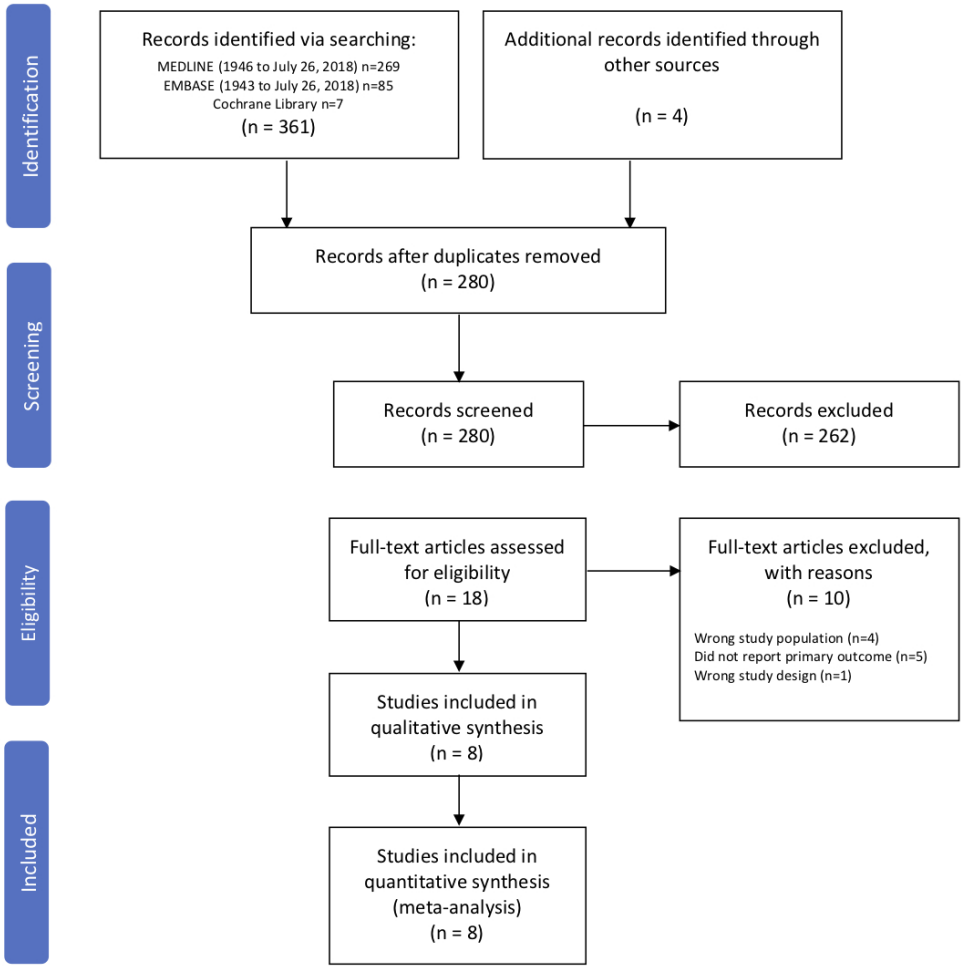
Figure 3. Pooled Incidence Rate of Death Following CIED Infection

TABLES

Table 1. Characteristics of Included Studies

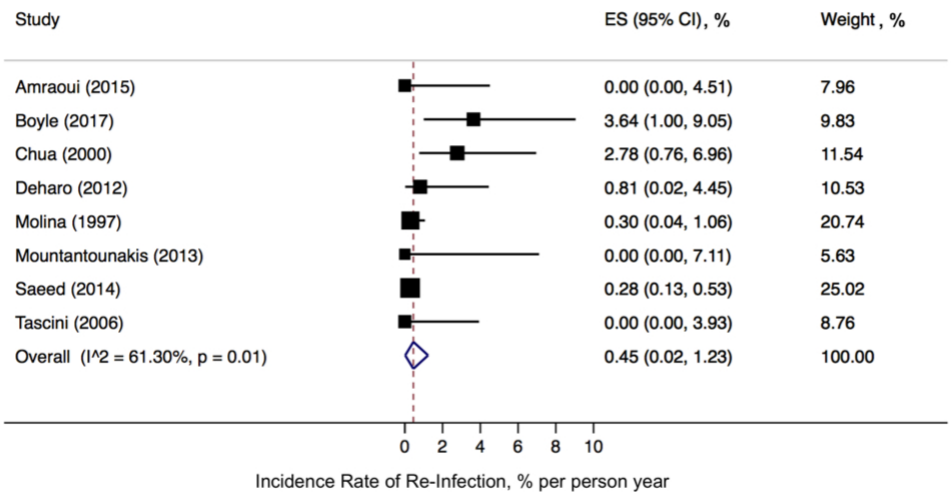
Study (Year)	Ref.	N	Age, yr, mean (SD)	Female, %	Device Type	Pathogen	Local Infection Only, %	Time to Re-implantation	Device Re-Infection, %	Death, %	Follow up, months
Amraoui et al. (2015)	25	80	71 (13)	20	PM, ICD	NR	61	4 to 14 days	0	5.0	12
Boyle et al. (2017)	11	220	68 (14)	19	NR	NR	58	10 days IQR 6 - 19	1.8	11.4	6
Chua et al. (2000)	26	123	66 (16)	29	PM, ICD	CoNS: 46 *S.aureus*: 9.0	74	5 days (range 0 to 68 days)	3	8.1	14
Deharo et al. (2012)	27	59	71 (14)	26	PM, ICD, CRT	CoNS: 42 *S.aureus:* 30 GNB: 11	41	24 days (10 to 1192 days)	1.7	3.3	25
Molina et al. (1997)	28	26	50 (NR)	NR	PM, ICD	NR	NR	2 to 6 weeks	0.09	0	312
Mountantonakis et al. (2013)	29	15	77 (12)	27	PM, ICD	CoNS: 40 *S.aureus:* 27 GNB: 20	100	0 (same day)	0	NR	40
Saeed et al. (2014)	30	168	67 (7)	32	PM, ICD, CRT	NR	82	3 days IQR 1 - 10	5.4	NR	229
Tascini et al. (2006)	31	79	60 (30)	23	PM, ICD	CoNS: 70 *S. aureus*: 14 GNB: 12	72	2 days	0	NR	14

Abbreviations: CoNS = coagulase negative staphylococci, CRT = cardiac resynchronization therapy, GNB = gram negative bacilli, ICD = implantable cardioverter defibrillator, IQR = interquartile range, NR = not reported, PM = pacemaker, Yr = year



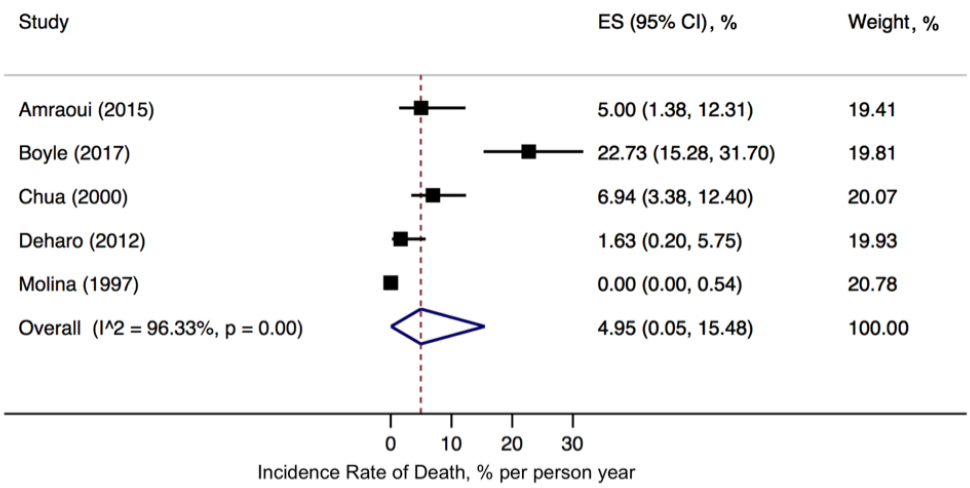
Flow Diagram of Study Selection for Systematic Review

185x185mm (150 x 150 DPI)



Pooled Incidence Rate of Device Re-Infection

169x89mm (150 x 150 DPI)



Pooled Incidence Rate of Death Following CIED Infection

164x85mm (150 x 150 DPI)

APPENDIX A. Detailed Search Strategy

EMBASE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

MEDLINE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

Cochrane Library Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator

2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
5. defibrillator.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	-
3	Description of study outcome(s)	5-6
4	Type of exposure or intervention used	5-6
5	Type of study designs used	5-6
6	Study population	3,5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5, Figure 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5,7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	6
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2,3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Figure 3
28	Indication of statistical uncertainty of findings	7, Figure 2-3

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	7
30	Justification for exclusion (eg, exclusion of non-English language citations)	7
31	Assessment of quality of included studies	7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	9
34	Guidelines for future research	10
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

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Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

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Word Count (excluding abstract, references and tables): 3,266

Short Title: Re-infection Following Management of Initial CIED Infection

ABSTRACT

Objectives: Initial management of cardiac implantable electronic device (CIED) infection requires removal of the infected CIED system and treatment with systemic antibiotics. However, the optimal timing to device re-implantation is unknown. The aim of this study was to quantify the incidence of re-infection after initial management of CIED infection, and to assess the effect of timing to re-implantation on re-infection rates.

Design: Systematic review and meta-analysis

Interventions: A systematic review and meta-analysis was performed of studies published up to February 2018. Inclusion criteria were: (a) documented CIED infection, (b) studies that reported the timing to device re-implantation and (c) studies that reported the proportion of participants with device re-infection. A meta-analysis of proportions using a random effects model was performed to estimate the pooled device re-infection rate.

Primary and secondary outcome measures: The primary outcome measure was the rate of CIED re-infection. The secondary outcome was all-cause mortality.

Results: Of the 280 screened studies, 8 met inclusion criteria with an average of 96 participants per study (range 15 to 220 participants). The pooled incidence rate of device re-infection was 0.45% (95% confidence interval, 0.02 to 1.23%) per person year. A longer time to device re-implantation >72 hours was associated with a trend towards higher rates of re-infection; however, the meta-regression analysis was unable to adjust for important clinical covariates. There did not appear to be a difference in re-infection rates when time to re-implantation was stratified at 1 week. Heterogeneity was moderate (I^2 = 61%).

Conclusions: The incident rate of re-infection following initial management of CIED infection is not insignificant. Time to re-implantation greater >72 hours was associated with an increased risk of re-infection. Our findings highlight the need for larger prospective studies to adequately control for confounders when exploring re-infection risk after initial CIED infection.

PROSERO Registration Number: CRD4201810960

STRENGTHS AND LIMITATIONS

- This is the first systematic review and meta-analysis to assess the rate of re-infection following initial cardiac implantable device infection.
- Pooled incidence rates of re-infection were obtained using random-effects meta-analysis of proportions model, and the impact of timing to device re-implantation was assessed by meta-regression.
- Substantial heterogeneity in the pooled incidence rates estimates limits interpretation.
- The results of our systematic review and meta-analysis highlight the need for additional well-designed studies in this area.

INTRODUCTION

Cardiac implantable electronic device (CIED) infections are a major cause of morbidity and mortality,[1,2] and are associated with substantial healthcare costs.[3,4] In the United States (US), one admission for an infected CIED can range from $14 360 to $53 349 USD.[3] As the number of CIED implantations increase worldwide, the rate of infectious complications is also rising.[5-7] More concerningly, the rate of CIED infections is outpacing the increase in implantations.[8] This is the likely result of the expanding indications for cardiac resynchronization therapy (CRT) and prophylactic implantable cardioverter defibrillators (ICDs) and the increasing need for permanent pacing in an aging patient population; CIEDs are being implanted in increasingly complex patients with multiple comorbidities who are at an increased risk of infectious complications.[2] Additionally, there is an increasing proportion of CIED surgeries for predicted battery depletion.[5] Device pocket re-intervention and repeat surgeries are known risk factors, and increases the risk infection by two to three-fold.[1,9]

Treatment of CIED infections typically requires complete extraction of the infected CIED systems (including generator and leads), debridement and administration of antibiotics to eradicate infection.[10] Delays in device extraction have been associated with significant increase in mortality.[11] Furthermore, failure to remove an infected CIED has been associated with a 7-fold increase in 30-day mortality.[12] There is also an increase in relapse of infection when hardware is not removed,[13] which is postulated to be attributable to biofilm formation.[14]

Following CIED removal, it is critical to evaluate whether or not the CIED requires re-implantation, as over time the indication for CIED may no longer be present.[10] In the majority of patients that require device replacement for infection, the optimal timing to re-implantation is unknown. The ideal re-implantation strategy would minimize the number of procedures and the duration of risk that patients may experience without a CIED (i.e. ventricular arrhythmias, or worsening heart failure without resynchronization). Notably, the optimal timing to re-implantation should not increase the risk of device re-infection.

The evidence regarding timing to re-implantation following CIED infection is relatively sparse and based primarily on consensus opinion.[13] A recent prospective study assessed the relationship between timing of re-implantation to relapse of CIED infection within a six-month time period.[13] Their findings suggested that once the infected hardware was removed timing to re-implantation had little impact on recurrent infection.[13]

Current expert recommendations from the Heart Rhythm Society suggest that blood cultures should be negative for at least 72 hours prior to device re-implantation.[10] A longer duration may be required depending on the clinical scenario (i.e. if there is another untreated source of infection). In the presence of valvular vegetations, it is proposed that device re-implantation be delayed to a minimum of 14 days.

Given the relative paucity of evidence supporting the optimal timing to device re-implantation following CIED infection, our study aims to systematically review the available

literature, to summarize the pooled re-infection rates after initial CIED infection, and to assess if there is a potential association of re-infection with time to device re-implantation.

METHODS

The study protocol and report is based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[15] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (***Appendix A***).[16] The study protocol was designed *a priori* and registered with PROSPERO, CRD4201810960.

Eligibility Criteria

Publications were selected based on the following inclusion criteria: (a) cohort studies or randomized control trials that included patients with documented CIED infection with complete hardware removal as part of the management, (b) studies that reported the timing to device-re-implantation following management of initial CIED infection, and (c) studies that reported the outcome of device re-infection following re-implantation. All publications were limited to those involving adult (age 18 years or older) human participants.

Search Strategy

A systematic electronic search was performed in consultation with a librarian scientist, using MEDLINE (1946-), EMBASE (Excerpta Medica Database 1974-) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Abstracts of Review Effects, Cochrane Central Registry of Controlled Trials, and Health Technology Assessment) databases for observational studies and randomized controlled trials that met inclusion criteria. This was followed with a hand search of the reference lists of relevant articles. The search strategy included both controlled vocabulary (MeSH terms) as well as key words that were identified during the scoping review. The main search concepts included (a) cardiac implantable devices, (b) device infection, and (c) timing to device re-implantation. All searches were conducted without date limitations, and included manuscripts published up to February 22, 2018. The detailed search strategy is included in ***Appendix B***.

Study Selection and Data Extraction

Two reviewers (DC and ERM) independently screened the study titles and abstracts to exclude irrelevant studies. The same reviewers then independently reviewed the full manuscripts for eligible studies and recorded the main reason for exclusion. Disagreements were resolved through consensus, and consultation of a third reviewer (RS) if necessary. Interrater agreement was quantified using Cohen's kappa coefficient. Data extraction was performed in duplicate by the same two reviewers into a standardized electronic spreadsheet. Data elements for extraction were pre-specified, and included the age and sex of participants,

type of CIED infection (i.e. endocarditis or pocket infection), device type (i.e. pacemaker, implantable cardioverter defibrillator or cardiac synchronization therapy), number of leads, microbiology, timing to re-implantation, rate of device re-infection, mortality rate and study follow up time.

Assessment of Study Quality

The risk of bias was assessed using the Newcastle-Ottawa scale[17] and updated Cochrane Risk of Bias Tool[18] for non-randomized and randomized controlled trials respectively. Risk of bias was assessed independently by two reviewers (DC and ER) and discrepancies resolved by consensus.

Patient and Public Involvement

Patients or members of the public were not involved in the study design or analysis

Statistical Analysis

The pooled incidence rate and 95% confidence interval (CI) for outcomes of interest were obtained. The primary outcome of the meta-analysis was the rate of CIED re-infection. The secondary outcome was all-cause mortality. Data were pooled using a random-effects meta-analysis of proportions model using the Dersimonian and Laird method[19] incorporating a Freeman-Tukey double arcsine transformation.[20] A random-effects model was chosen *a priori* on the basis of the anticipated heterogeneity among study baseline characteristics and the impact on device re-infection rates. The Metaprop package in Stata 15.1 (Stata Corp., College Station, TX, USA) was used to obtain the pooled estimate.[21] All analyses were performed using Stata IC 15.1 with p value <0.05 was considered to indicate statistical significance. Rates of CIED re-infection were standardized across studies by the duration of follow up and reported as the incident rate per person-year.

Due to the potential for significant variation in follow up time and the possibility of zero count data in the included studies, we performed a secondary analysis using a mixed-effects Poisson-distribution model to estimate the pooled incidence rate of re-infection.[22] To assess if re-infection rates were affected by time to device re-implantation, a meta-regression of the incidence rates and time to re-implantation was performed. Pre-specified subgroup analyses included stratification of the primary outcome by median time to device re-implantation of greater than 72 hours and those with a median re-implantation time of 72 hours or less. Re-infection rates stratified by re-implantation prior to one week versus at one week or greater were also assessed. The stratification of timing to re-implantation was chosen based on current expert recommendations for CIED infections without or with lead endocarditis, respectively.[10,23]

Heterogeneity across the studies was tested with the Cochran Q and I^2 statistics.[24,25] We considered an I^2 statistic of >25% as a low degree of heterogeneity, >50% as moderate

heterogeneity, and >75% as high heterogeneity.[26] A threshold of $p < 0.10$ was considered significant for the presence of heterogeneity.

RESULTS

Study Selection and Characteristics of Included Studies

Among 280 unique citations identified in the literature search, 18 studies were retrieved for full text review (***Figure 1***). The interrater agreement during the initial screening was substantial (Kappa = 0.61). Following the full text review, a total of eight studies met inclusion criteria.[13,27-33] There were no randomized controlled trials (RCTs) identified in the systematic review that met the inclusion criteria. All eight included studies were observational in design; three were prospective[13,27,29] and five were retrospective.[28,30-33] Of the ten studies that were excluded: four assessed the wrong study population,[34-37] five did not report device re-infection rates,[38-42] and one had the wrong study design.[43]

The characteristics of the included studies are summarized in ***Table 1***. The observation cohorts had a range of 15 to 220 participants, for a total of 744 participants who underwent complete explantation of an infected CIED with subsequent re-implantation of a new device. The range of the mean age was 50 to 71 years and the proportion of women included in the studies was 19 to 32%. The majority of studies reported on device infections related to pacemakers and ICDs,[27,28,31,33] and two studies included CRT infections.[29,32] The microbiology of the CIED infections was not consistently reported among the studies. The most common reported etiology of CIED infection was coagulase negative staphylococci (range 40 to 70%), followed by *Staphylococcus aureus* (range 9 to 30%) and Gram-negative bacilli (range 11 to 20%). The duration of follow up after device re-implantation varied substantially from 6 to 312 months.

Study Quality

As there were no RCTs identified in the systematic review, the Newcastle-Ottawa scale was used to assess risk of bias in each of the included studies (***Appendix C***). Two measures within the scale were not applicable given the design of the included studies; the six measures that were graded were: (a) cohort representativeness, (b) exposure ascertainment, (c) outcome absence at baseline, (d) assessment of outcome, (e) adequacy of observation duration, and (f) completeness of cohort-follow up. The majority of studies had the highest quality-level indicators in all six measures. Two studies selected populations that may not be representative of the overall CIED population: Mountantonakis *et al.* focused on the patients with localized pocket infection for assessing the safety of same day device re-implantation following extraction.[31] The cohort described by Molina did not represent the contemporary population of CIED patients, as a significant proportion of devices in the study cohort underwent CIED implantation by sternotomy or thoracotomy with placement of epicardial patches.[30] Two

studies did not clearly detail if all patients had been accounted for by the end of the study and there were concerns of bias with regards to their completeness of follow up.[30,33]

Re-infection following Management of Infection CIED Infection

In our primary analysis, the incidence rate of first device re-infection for the pooled cohort was 0.45% (95% confidence interval (CI), 0.02 to 1.23%) per person-year (***Figure 2***). There was a moderate degree of heterogeneity (I^2 = 61%, Cochran's Q p = 0.01). In our secondary analysis using a mixed-effects Poisson regression model, the incidence rate of re-infection was similar to our primary analysis at 0.58% (95% CI, 0.21 to 1.55%) per person year.

Effect of Time to Re-implantation

Time to re-implantation >72 hours was associated with a trend toward a higher incidence of CIED re-infection (unadjusted incident rate ratio (IRR) 4.8; 95% CI 0.9 to 24.3, p=0.06 mixed-effects Poisson regression). Given the smaller number of included studies identified by the systematic review, we were unable to adjust for additional variables. When stratifying time to device re-implantation by one week or less, there did not appear to be a significant difference in incidence rate (p=0.7 mixed-effects Poisson regression).

Mortality following CIED Infection

Only five of the included studies reported all-cause mortality.[13,27-30] Among the 508 patients included in these studies, 42 deaths (8.3%) were observed over a median follow up of 14 months. In the random effects analysis, the incidence rate of death was 5.0% (95% CI, 0.1 to 15.5%) per person-year of follow up (***Figure 3***). There was a high degree of heterogeneity (I^2 = 96%, Cochran's Q p < 0.001).

DISCUSSION

Principle Findings

We found that the pooled re-infection rate following initial management of CIED infection was approximately 0.5% per person-year. To our knowledge, this is the first systematic review and meta-analysis reporting the pooled re-infection rates following original management of CIED infection. The substantial heterogeneity seen in the pooled analysis suggests the presence of several variables that can affect the incidence rate of re-infection. Factors may include the presence of bacteremia, response to treatment, or patient factors, such as the presence of immunosuppression.[1]

When we examined infection risk based on timing of re-implantation, a time of greater than 72 hours was associated with a 4-fold higher incidence rate compared to re-implantation at 72 hours or less. Using a one week cut-point for time to device re-implantation, there was no difference in re-infection rates. We consider these results exploratory, as meta-regression is

considered an underpowered analysis. Specifically, given the small number of studies included in the pooled analysis, we were unable to adjust for potentially important confounders. For example, the higher re-infection rate associated with time to re-implantation >72 hours may be due to an increased number of comorbid conditions in the corresponding study populations, or a high proportion of systemic infections requiring additional time to clear the bloodstream of bacteremia. Important covariates, which we were unable to adjust for at the meta-regression level, were the proportions of documented endocarditis, lead vegetations or bacteremia compared to localized pocket infection.

Management of Cardiac Device Infections

Treatment of CIED infections requires complete extraction of the infected CIED systems (including generator and leads) and administration of systemic antibiotics to eradicate infection.[10] In the majority of patients that require device replacement, the optimal timing to re-implantation is unknown. In our study, there was an unexpected association of increased re-infection rates with a time to device re-implantation greater than 72 hours. Although interpretation is limited by lack of adjustment for confounders, this is finding is opposite to the expectation in clinical practice. Conceptually, re-implanting a device too early during the treatment course may result in a higher infection relapse rate if the infection has only been partially eradicated by systemic antibiotics. On the other hand, the longer hospital stays while awaiting device re-implantation are associated with increased health care costs, decreased patient quality of life, and the potential for acquiring non-device related nosocomial infections. Furthermore, there is the potential for adverse events related to the absence of ICD or CRT therapies, such as worsening heart failure or delay to treatment of malignant ventricular arrhythmias.

Time to Device Re-implantation

There is a paucity in the literature exploring the timing of CIED replacement and risk of re-infection. Our systematic review only identified eight studies that reported the time to re-implantation and the rate of device re-infection.[13,27-33] The majority of these studies are limited by their retrospective study design[28,30-33] and small sample sizes. Furthermore, the primary study designs did not focus on assessing the effect of time to re-implantation on subsequent CIED re-infections. Consistent with the relatively paucity in the literature guiding time to device re-implantation, we noted a wide range in the median time to device re-implantation (i.e. same day re-implantation to over two weeks).

One of the largest contemporary prospective cohorts tracking CIED infections found a repeat infection risk of 1.8% among patients who were re-implanted.[13] This study found a high variation in physician practice when determining the time to device re-implantation, yet timing to re-implantation did not seem to affect re-infection rates. With the caveat of a relatively small

sample size and limited follow up, the authors suggested that an array of other risk factors may have a larger role in determining infection relapse rates compared to decisions regarding timing to re-implantation.[13] Consistent with this notion, some studies suggest that factors, such as the presence of hemodialysis for renal failure, pocket hematomas, malignancy, or *Staphylococcus aureus* bacteremia are the leading risk factors in estimating the risk of re-infection.[44,45] In fact, small single-center studies suggested that same-day re-implantation is feasible for patients with isolated CIED pocket infections and is not associated with adverse outcomes.[31,46]

Current expert consensus recommendations from the Heart Rhythm Society and American Heart Association suggest a 72 hour and 14 day waiting period for re-implantation based on blood culture negativity and the presence of valvular vegetations, respectively.[10,23] However, the quality of evidence supporting these recommendations are weak (Grade IIaC), and based mainly on a single retrospective study of 127 patients.[42] Our findings do not support this conclusion as re-implantation at greater than 72 hours was associated with increased infection rates. However, there are significant limitations to our findings since only eight studies were available for inclusion in the meta-regression, and these individual studies did not reliably report differences in patient characteristics among those who developed a device re-infection versus those who remained infection-free. Thus, we were unable to adjust for important covariates such as severity of initial infection (i.e. presence of bacteremia, lead endocarditis, causative micro-organism), patient comorbidities, or choice of antibiotic treatment for initial infection. Our meta-regression findings should be considered exploratory and reinforces the need for additional research to guide recommendations regarding timing to re-implantation.

Study Limitations

Our study requires interpretation in the context of a number of limitations. Firstly, time to re-implantation and device re-infection rates were inconsistently reported in the literature. Five studies were excluded at the level of the full text screen as they did not report device re-infection rates. Additionally, the adopted diagnostic criteria for device infection were inconsistently reported among the included studies, which may contribute to the heterogeneity in the pooled estimate of incidence rate of CIED re-infection. Secondly, the meta-analyses included mainly retrospective studies that varied in patient population, study quality, and follow-up, contributing to the clinical variability and heterogeneity in our pooled analysis. Thirdly, we did not anticipate the relatively small number of studies and patients derived from the systematic review. Nonetheless, our study highlights the importance of additional research in the area of cardiac device infection, and further study assessing re-infection rates and long-term outcome.

Finally, we attempted to explore the relationship between time to re-implantation and re-infection rates. An important limitation is the unavailability of patient level data and times to follow up. To explore the potential association, we performed a Poisson-distribution meta-

regression. However, given the small number of studies that met inclusion criteria, the meta-regression was underpowered, and we were unable to properly adjust for other confounders with the potential to affect re-infection rates. This may explain the unexpected association of increased re-infection rates with time to device re-implantation greater than 72 hours. Nevertheless, this highlights the need for larger prospective studies to adequate control for confounders when exploring re-infection risk after initial CIED infection.

Implications for Future Research

Additional prospective, well-designed studies are required to explore the effect of timing to re-implantation on re-infection rates, with adequate adjustment for patient comorbidities, extent of infection (i.e. localized pocket infection, vegetation or bacteremia) and the causative pathogen. Based on the several small studies reporting on the safety of same day re-implantation and in light of our findings, larger studies are necessary to validate the safety of the one-stage contralateral device replacement approach compared with delayed device replacement. Given the potential impact on hospital length of stay, an economic evaluation comparing these strategies will also be an important component.

Finally, the advent of new technology such as leadless pacemakers and subcutaneous ICDs may obviate the need to delay device re-implantation following extraction of infected CIED systems. The current assumption is that these newer devices are associated with a lower risk of infection: leadless pacemakers have significantly less surface area for bacterial seeding, and subcutaneous ICDs do not contain any components exposed to the bloodstream. Nevertheless, the use of these novel devices to replace infected conventional CIEDs following antimicrobial therapy, or the rates of infection associated with these devices have yet to be assessed.

CONCLUSION

The incident rate of re-infection following initial management of CIED infection is not insignificant. Our findings suggest a trend that time to re-implantation affects rates of re-infection when device re-implantation occurs at ≤ 72 hours compared to >72 hours. The findings of this study need to be interpreted with circumspection due to the moderate heterogeneity among included studies.

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AUTHOR CONTRIBUTIONS

JC, DVE, ER and DC were responsible for conception of this research study and methodology. DS and ER wrote the manuscript. DS, ER and RS were responsible for data collection and analysis. All authors reviewed the manuscript and analyses.

DATA AVAILABILITY STATEMENT

The data used to compile the meta-analysis is available upon request.

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COMPETING INTERESTS

DVE has received research grants from Medtronic Inc, GE Healthcare, and St Jude Medical outside of the submitted work. The remaining authors have no conflicts of interest to disclose.

REFERENCES

1 Polyzos, K. A., Konstantelias, A. A. & Falagas, M. E. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace* **17**, 767-777, doi:10.1093/europace/euv053 (2015).

2 Greenspon, A. J. *et al.* 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* **58**, 1001-1006, doi:10.1016/j.jacc.2011.04.033 (2011).

3 Sohail, M. R., Henrikson, C. A., Braid-Forbes, M. J., Forbes, K. F. & Lerner, D. J. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* **171**, 1821-1828, doi:10.1001/archinternmed.2011.441 (2011).

4 Tarakji, K. G. *et al.* Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* **7**, 1043-1047, doi:10.1016/j.hrthm.2010.05.016 (2010).

5 Mond, H. G. & Proclemer, A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* **34**, 1013-1027, doi:10.1111/j.1540-8159.2011.03150.x (2011).

6 Valzania, C., Torbica, A., Tarricone, R., Leyva, F. & Boriani, G. Implant rates of cardiac implantable electrical devices in Europe: A systematic literature review. *Health Policy* **120**, 1-15, doi:10.1016/j.healthpol.2015.11.001 (2016).

7 Raatikainen, M. J. P. *et al.* A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *Europace* **19**, ii1-ii90, doi:10.1093/europace/eux258 (2017).

8 Voigt, A., Shalaby, A. & Saba, S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol* **33**, 414-419, doi:10.1111/j.1540-8159.2009.02569.x (2010).

9 Arana-Rueda, E. *et al.* Repeated procedures at the generator pocket are a determinant of implantable cardioverter-defibrillator infection. *Clin Cardiol* **40**, 892-898, doi:10.1002/clc.22743 (2017).

10 Kusumoto, F. M. *et al.* 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm* **14**, e503-e551, doi:10.1016/j.hrthm.2017.09.001 (2017).

11 Viganego, F. *et al.* Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol* **109**, 1466-1471, doi:10.1016/j.amjcard.2012.01.360 (2012).

12 Le, K. Y. *et al.* Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm* **8**, 1678-1685, doi:10.1016/j.hrthm.2011.05.015 (2011).

13 Boyle, T. A. *et al.* Reimplantation and Repeat Infection After Cardiac-Implantable Electronic Device Infections: Experience From the MEDIC (Multicenter Electrophysiologic Device Infection Cohort) Database. *Circulation. Arrhythmia and electrophysiology* **10**, doi:10.1161/CIRCEP.116.004822 (2017).

14 Gaynor, S. L. *et al.* Laser assistance for extraction of chronically implanted endocardial leads: infectious versus noninfectious indications. *Pacing Clin Electrophysiol* **29**, 1352-1358, doi:10.1111/j.1540-8159.2006.00547.x (2006).

15 Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **339**, b2535, doi:10.1136/bmj.b2535 (2009).

16 Stroup, D. F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* **283**, 2008-2012 (2000).

17 Wells GA *et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* , <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]> (2000).

18 Higgins, J. P. *et al.* in *Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.* Vol. 10 (Issue 1) (eds J. Chandler, J. McKenzie, I. Boutron, & B. Welch) (2016).

19 DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177-188 (1986).

20 Freeman, M. & Turkey, J. Transformations related to the angular and the square root. *Ann Math Stats* **21**, 607-611 (1950).

21 Nyaga, V. N., Arbyn, M. & Aerts, M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* **72**, 39, doi:10.1186/2049-3258-72-39 (2014).

22 Spittal, M. J., Pirkis, J. & Gurrin, L. C. Meta-analysis of incidence rate data in the presence of zero events. *BMC Med Res Methodol* **15**, 42, doi:10.1186/s12874-015-0031-0 (2015).

23 Baddour, L. M. *et al.* Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* **121**, 458-477, doi:10.1161/CIRCULATIONAHA.109.192665 (2010).

24 Cochran, W. G. The comparison of percentages in matched samples. *Biometrika* **37**, 256-266 (1950).

25 Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539-1558, doi:10.1002/sim.1186 (2002).

26 Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560, doi:10.1136/bmj.327.7414.557 (2003).

27 Amraoui, S. *et al.* Comparison of delayed transvenous reimplantation and immediate surgical epicardial approach in pacing-dependent patients undergoing extraction of infected permanent pacemakers. *Heart Rhythm* **12**, 1209-1215, doi:10.1016/j.hrthm.2015.02.023 (2015).

28 Chua, J. D. *et al.* Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* **133**, 604-608 (2000).

29 Deharo, J. C. *et al.* Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study. *Heart* **98**, 724-731, doi:10.1136/heartjnl-2012-301627 (2012).

30 Molina, J. E. Undertreatment and overtreatment of patients with infected antiarrhythmic implantable devices. *Ann Thorac Surg* **63**, 504-509 (1997).
31 Mountantonakis, S. E., Tschabrunn, C. M., Deyell, M. W. & Cooper, J. M. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. *Europace* **16**, 252-257, doi:10.1093/europace/eut220 (2014).
32 Saeed, O., Gupta, A., Gross, J. N. & Palma, E. C. Rate of cardiovascular implantable electronic device (CIED) re-extraction after recurrent infection. *Pacing Clin Electrophysiol* **37**, 963-968, doi:10.1111/pace.12407 (2014).
33 Tascini, C. *et al.* Management of cardiac device infections: A retrospective survey of a non-surgical approach combining antibiotic therapy with transvenous removal. *J Chemother* **18**, 157-163, doi:10.1179/joc.2006.18.2.157 (2006).
34 Amraoui, S. *et al.* Single surgical procedure combining epicardial pacemaker implantation and subsequent extraction of the infected pacing system for pacemaker-dependent patients. *J Thorac Cardiovasc Surg* **146**, 302-305, doi:10.1016/j.jtcvs.2012.07.026 (2013).
35 Le Franc, P. *et al.* Extraction of endocardial implantable cardioverter-defibrillator leads. *The American journal of cardiology* **84**, 187-191 (1999).
36 O'Nunain, S. *et al.* The treatment of patients with infected implantable cardioverter-defibrillator systems. *J Thorac Cardiovasc Surg* **113**, 121-129, doi:10.1016/S0022-5223(97)70407-0 (1997).
37 Rickard, J. *et al.* Cardiac venous left ventricular lead removal and reimplantation following device infection: a large single-center experience. *J Cardiovasc Electrophysiol* **23**, 1213-1216, doi:10.1111/j.1540-8167.2012.02392.x (2012).
38 Cassagneau, R. *et al.* Long-term outcomes after pocket or scar revision and reimplantation of pacemakers with preerosion. *Pacing Clin Electrophysiol* **34**, 150-154, doi:10.1111/j.1540-8159.2010.02950.x (2011).
39 Kennelly, B. M. & Piller, L. W. Management of infected transvenous permanent pacemakers. *Br Heart J* **36**, 1133-1140 (1974).
40 Margey, R. *et al.* Contemporary management of and outcomes from cardiac device related infections. *Europace* **12**, 64-70, doi:10.1093/europace/eup362 (2010).
41 Rickard, J. *et al.* Survival of patients with biventricular devices after device infection, extraction, and reimplantation. *JACC Heart Fail* **1**, 508-513, doi:10.1016/j.jchf.2013.05.009 (2013).
42 Sohail, M. R. *et al.* Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* **49**, 1851-1859, doi:10.1016/j.jacc.2007.01.072 (2007).
43 Vogt, P. R. *et al.* Surgical management of infected permanent transvenous pacemaker systems: ten year experience. *J Card Surg* **11**, 180-186 (1996).
44 Essebag, V. *et al.* Clinically Significant Pocket Hematoma Increases Long-Term Risk of Device Infection: BRUISE CONTROL INFECTION Study. *J Am Coll Cardiol* **67**, 1300-1308, doi:10.1016/j.jacc.2016.01.009 (2016).
45 Leung, S. & Danik, S. Prevention, Diagnosis, and Treatment of Cardiac Implantable Electronic Device Infections. *Curr Cardiol Rep* **18**, 58, doi:10.1007/s11886-016-0733-x (2016).

46 Nandyala, R. & Parsonnet, V. One stage side-to-side replacement of infected pulse generators and leads. *Pacing Clin Electrophysiol* **29**, 393-396, doi:10.1111/j.1540-8159.2006.00359.x (2006).

FIGURES

Figure 1. Flow Diagram of Study Selection for Systematic Review

Figure 2. Pooled Incidence Rate of Device Re-Infection

Figure 3. Pooled Incidence Rate of Death Following CIED Infection

TABLES

Table 1. Characteristics of Included Studies

Study (Year)	Ref.	N	Age, yr, mean (SD)	Female, %	Device Type	Pathogen	Local Infection Only, %	Time to Re-implantation	Device Re-Infection, %	Death, %	Follow up, months
Amraoui et al. (2015)	25	80	71 (13)	20	PM, ICD	NR	61	4 to 14 days	0	5.0	12
Boyle et al. (2017)	11	220	68 (14)	19	NR	NR	58	10 days IQR 6 - 19	1.8	11.4	6
Chua et al. (2000)	26	123	66 (16)	29	PM, ICD	CoNS: 46 *S.aureus*: 9.0	74	5 days (range 0 to 68 days)	3	8.1	14
Deharo et al. (2012)	27	59	71 (14)	26	PM, ICD, CRT	CoNS: 42 *S.aureus:* 30 GNB: 11	41	24 days (10 to 1192 days)	1.7	3.3	25
Molina et al. (1997)	28	26	50 (NR)	NR	PM, ICD	NR	NR	2 to 6 weeks	0.09	0	312
Mountantonakis et al. (2013)	29	15	77 (12)	27	PM, ICD	CoNS: 40 *S.aureus:* 27 GNB: 20	100	0 (same day)	0	NR	40
Saeed et al. (2014)	30	168	67 (7)	32	PM, ICD, CRT	NR	82	3 days IQR 1 - 10	5.4	NR	229
Tascini et al. (2006)	31	79	60 (30)	23	PM, ICD	CoNS: 70 *S. aureus*: 14 GNB: 12	72	2 days	0	NR	14

Abbreviations: CoNS = coagulase negative staphylococci, CRT = cardiac resynchronization therapy, GNB = gram negative bacilli, ICD = implantable cardioverter defibrillator, IQR = interquartile range, NR = not reported, PM = pacemaker, Yr = year

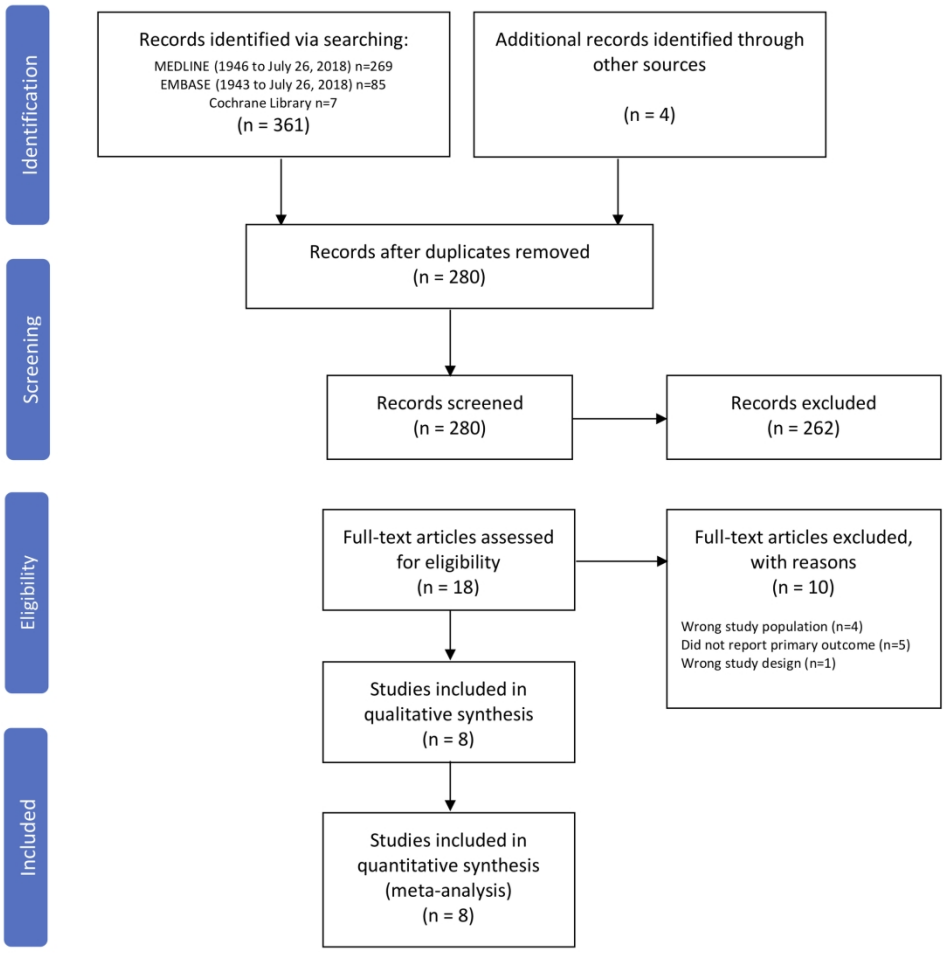

Figure 1. Flow Diagram of Study Selection for Systematic Review

189x186mm (300 x 300 DPI)

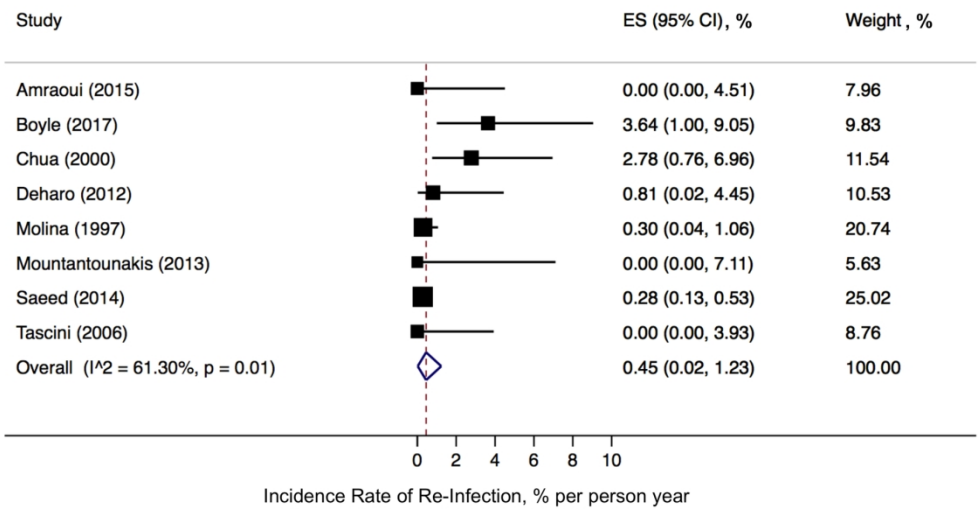

Figure 2. Pooled Incidence Rate of Device Re-Infection

164x86mm (300 x 300 DPI)

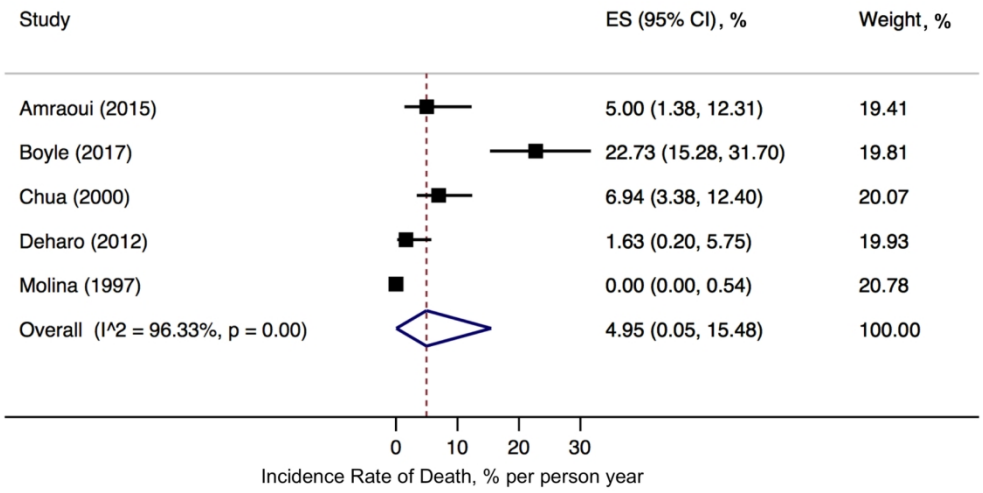

Figure 3. Pooled Incidence Rate of Death Following CIED Infection

162x83mm (300 x 300 DPI)

APPENDIX A. MOOSE Checklist for Reporting of Meta-analyses of Observation Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5, Figure 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Table 1, Figures 1-3

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2,3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	8, Figure 3
28	Indication of statistical uncertainty of findings	8, Figure 2-3
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	-
31	Assessment of quality of included studies	Appendix
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10-11
34	Guidelines for future research	10-11
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

APPENDIX B. Detailed Search Strategy

EMBASE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

MEDLINE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

Cochrane Library Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.

3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
5. defibrillator.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

APPENDIX C1. Summary of Study Quality Assessment

Study ID	Selection				Comparability	Outcome			Total (⋆)
	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome shown to be absent at study start		Assessment of outcome	Adequacy of follow up duration	Adequacy of cohort follow up	
Amraoui (2015)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Boyle (2017)	A (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Chua (2000)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	B (⋆)	**6**
Deharo (2012)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Molina (1997)	C	--	A (⋆)	B	--	B (⋆)	A (⋆)	D	**3**
Saaed (2014)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Tascini (2006)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	C (⋆)	**6**
Mountantounakis (2013)	C	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**5**

APPENDIX C2. Newcastle Ottawa Quality Assessment Form for Cohort Studies

*(Reference: Wells GA et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)_*

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ⍰
   b) somewhat representative of the average _____ in the community ⍰
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ⍰
   b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
a) secure record (eg surgical records) ☐
b) structured interview ☐
c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes ☐
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) ☐
b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
a) independent blind assessment ☐
b) record linkage ☐
c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ☐
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ☐
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

APPENDIX A. MOOSE Checklist for Reporting of Meta-analyses of Observation Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5, Figure 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Table 1, Figures 1-3

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2,3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	8, Figure 3
28	Indication of statistical uncertainty of findings	8, Figure 2-3
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	-
31	Assessment of quality of included studies	Appendix
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10-11
34	Guidelines for future research	10-11
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

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Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

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Short Title: Re-infection Following Management of Initial CIED Infection

ABSTRACT

Objectives: Initial management of cardiac implantable electronic device (CIED) infection requires removal of the infected CIED system and treatment with systemic antibiotics. However, the optimal timing to device re-implantation is unknown. The aim of this study was to quantify the incidence of re-infection after initial management of CIED infection, and to assess the effect of timing to re-implantation on re-infection rates.

Design: Systematic review and meta-analysis

Interventions: A systematic review and meta-analysis was performed of studies published up to February 2018. Inclusion criteria were: (a) documented CIED infection, (b) studies that reported the timing to device re-implantation and (c) studies that reported the proportion of participants with device re-infection. A meta-analysis of proportions using a random effects model was performed to estimate the pooled device re-infection rate.

Primary and secondary outcome measures: The primary outcome measure was the rate of CIED re-infection. The secondary outcome was all-cause mortality.

Results: Of the 280 screened studies, 8 met inclusion criteria with an average of 96 participants per study (range 15 to 220 participants). The pooled incidence rate of device re-infection was 0.45% (95% confidence interval (CI), 0.02 to 1.23%) per person year. A longer time to device re-implantation >72 hours was associated with a trend towards higher rates of re-infection (unadjusted incident rate ratio 4.8; 95% CI 0.9 to 24.3, p=0.06); however, the meta-regression analysis was unable to adjust for important clinical covariates. There did not appear to be a difference in re-infection rates when time to re-implantation was stratified at 1 week. Heterogeneity was moderate (I^2 = 61%).

Conclusions: The incident rate of re-infection following initial management of CIED infection is not insignificant. Time to re-implantation may affect subsequent rates of device re-infection. Our findings are considered exploratory and significant heterogeneity limits interpretation.

PROSERO Registration Number: CRD4201810960

STRENGTHS AND LIMITATIONS

- This is the first systematic review and meta-analysis to assess the rate of re-infection following initial cardiac implantable device infection.
- Pooled incidence rates of re-infection were obtained using random-effects meta-analysis of proportions model, and the impact of timing to device re-implantation was assessed by meta-regression.
- Substantial heterogeneity in the pooled incidence rates estimates limits interpretation.
- The results of our systematic review and meta-analysis highlight the need for additional well-designed studies in this area.

INTRODUCTION

Cardiac implantable electronic device (CIED) infections are a major cause of morbidity and mortality,[1,2] and are associated with substantial healthcare costs.[3,4] In the United States (US), one admission for an infected CIED can range from $14 360 to $53 349 USD.[3] As the number of CIED implantations increase worldwide, the rate of infectious complications is also rising.[5-7] More concerningly, the rate of CIED infections is outpacing the increase in implantations.[8] This is the likely result of the expanding indications for cardiac resynchronization therapy (CRT) and prophylactic implantable cardioverter defibrillators (ICDs) and the increasing need for permanent pacing in an aging patient population; CIEDs are being implanted in increasingly complex patients with multiple comorbidities who are at an increased risk of infectious complications.[2] Additionally, there is an increasing proportion of CIED surgeries for predicted battery depletion.[5] Device pocket re-intervention and repeat surgeries are known risk factors, and increases the risk infection by two to three-fold.[1,9]

Treatment of CIED infections typically requires complete extraction of the infected CIED systems (including generator and leads), debridement and administration of antibiotics to eradicate infection.[10] Delays in device extraction have been associated with significant increase in mortality.[11] Furthermore, failure to remove an infected CIED has been associated with a 7-fold increase in 30-day mortality.[12] There is also an increase in relapse of infection when hardware is not removed,[13] which is postulated to be attributable to biofilm formation.[14]

Following CIED removal, it is critical to evaluate whether or not the CIED requires re-implantation, as over time the indication for CIED may no longer be present.[10] In the majority of patients that require device replacement for infection, the optimal timing to re-implantation is unknown. The ideal re-implantation strategy would minimize the number of procedures and the duration of risk that patients may experience without a CIED (i.e. ventricular arrhythmias, or worsening heart failure without resynchronization). Notably, the optimal timing to re-implantation should not increase the risk of device re-infection.

The evidence regarding timing to re-implantation following CIED infection is relatively sparse and based primarily on consensus opinion.[13] A recent prospective study assessed the relationship between timing of re-implantation to relapse of CIED infection within a six-month time period.[13] Their findings suggested that once the infected hardware was removed timing to re-implantation had little impact on recurrent infection.[13]

Current expert recommendations from the Heart Rhythm Society suggest that blood cultures should be negative for at least 72 hours prior to device re-implantation.[10] A longer duration may be required depending on the clinical scenario (i.e. if there is another untreated source of infection). In the presence of valvular vegetations, it is proposed that device re-implantation be delayed to a minimum of 14 days.

Given the relative paucity of evidence supporting the optimal timing to device re-implantation following CIED infection, our study aims to systematically review the available

literature, to summarize the pooled re-infection rates after initial CIED infection, and to assess if there is a potential association of re-infection with time to device re-implantation.

METHODS

The study protocol and report is based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[15] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (***Appendix A***).[16] The study protocol was designed *a priori* and registered with PROSPERO, CRD4201810960.

Eligibility Criteria

Publications were selected based on the following inclusion criteria: (a) cohort studies or randomized control trials that included patients with documented CIED infection with complete hardware removal as part of the management, (b) studies that reported the timing to device-re-implantation following management of initial CIED infection, and (c) studies that reported the outcome of device re-infection following re-implantation. All publications were limited to those involving adult (age 18 years or older) human participants.

Search Strategy

A systematic electronic search was performed in consultation with a librarian scientist, using MEDLINE (1946-), EMBASE (Excerpta Medica Database 1974-) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Abstracts of Review Effects, Cochrane Central Registry of Controlled Trials, and Health Technology Assessment) databases for observational studies and randomized controlled trials that met inclusion criteria. This was followed with a hand search of the reference lists of relevant articles. The search strategy included both controlled vocabulary (MeSH terms) as well as key words that were identified during the scoping review. The main search concepts included (a) cardiac implantable devices, (b) device infection, and (c) timing to device re-implantation. All searches were conducted without date limitations, and included manuscripts published up to February 22, 2018. The detailed search strategy is included in ***Appendix B***.

Study Selection and Data Extraction

Two reviewers (DC and ERM) independently screened the study titles and abstracts to exclude irrelevant studies. The same reviewers then independently reviewed the full manuscripts for eligible studies and recorded the main reason for exclusion. Disagreements were resolved through consensus, and consultation of a third reviewer (RS) if necessary. Interrater agreement was quantified using Cohen's kappa coefficient. Data extraction was performed in duplicate by the same two reviewers into a standardized electronic spreadsheet. Data elements for extraction were pre-specified, and included the age and sex of participants,

type of CIED infection (i.e. endocarditis or pocket infection), device type (i.e. pacemaker, implantable cardioverter defibrillator or cardiac synchronization therapy), number of leads, microbiology, timing to re-implantation, rate of device re-infection, mortality rate and study follow up time.

Assessment of Study Quality

The risk of bias was assessed using the Newcastle-Ottawa scale[17] and updated Cochrane Risk of Bias Tool[18] for non-randomized and randomized controlled trials respectively. Risk of bias was assessed independently by two reviewers (DC and ER) and discrepancies resolved by consensus.

Patient and Public Involvement

Patients or members of the public were not involved in the study design or analysis

Statistical Analysis

The pooled incidence rate and 95% confidence interval (CI) for outcomes of interest were obtained. The primary outcome of the meta-analysis was the rate of CIED re-infection. The secondary outcome was all-cause mortality. Data were pooled using a random-effects meta-analysis of proportions model using the Dersimonian and Laird method[19] incorporating a Freeman-Tukey double arcsine transformation.[20] A random-effects model was chosen *a priori* on the basis of the anticipated heterogeneity among study baseline characteristics and the impact on device re-infection rates. The Metaprop package in Stata 15.1 (Stata Corp., College Station, TX, USA) was used to obtain the pooled estimate.[21] All analyses were performed using Stata IC 15.1 with p value <0.05 was considered to indicate statistical significance. Rates of CIED re-infection were standardized across studies by the duration of follow up and reported as the incident rate per person-year.

Due to the potential for significant variation in follow up time and the possibility of zero count data in the included studies, we performed a secondary analysis using a mixed-effects Poisson-distribution model to estimate the pooled incidence rate of re-infection.[22] To assess if re-infection rates were affected by time to device re-implantation, a meta-regression of the incidence rates and time to re-implantation was performed. Pre-specified subgroup analyses included stratification of the primary outcome by median time to device re-implantation of greater than 72 hours and those with a median re-implantation time of 72 hours or less. Re-infection rates stratified by re-implantation prior to one week versus at one week or greater were also assessed. The stratification of timing to re-implantation was chosen based on current expert recommendations for CIED infections without or with lead endocarditis, respectively.[10,23]

Heterogeneity across the studies was tested with the Cochran Q and I^2 statistics.[24,25] We considered an I^2 statistic of >25% as a low degree of heterogeneity, >50% as moderate

heterogeneity, and >75% as high heterogeneity.[26] A threshold of $p < 0.10$ was considered significant for the presence of heterogeneity.

RESULTS

Study Selection and Characteristics of Included Studies

Among 280 unique citations identified in the literature search, 18 studies were retrieved for full text review (***Figure 1***). The interrater agreement during the initial screening was substantial (Kappa = 0.61). Following the full text review, a total of eight studies met inclusion criteria.[13,27-33] There were no randomized controlled trials (RCTs) identified in the systematic review that met the inclusion criteria. All eight included studies were observational in design; three were prospective[13,27,29] and five were retrospective.[28,30-33] Of the ten studies that were excluded: four assessed the wrong study population,[34-37] five did not report device re-infection rates,[38-42] and one had the wrong study design.[43]

The characteristics of the included studies are summarized in ***Table 1***. The observation cohorts had a range of 15 to 220 participants, for a total of 744 participants who underwent complete explantation of an infected CIED with subsequent re-implantation of a new device. The range of the mean age was 50 to 71 years and the proportion of women included in the studies was 19 to 32%. The majority of studies reported on device infections related to pacemakers and ICDs,[27,28,31,33] and two studies included CRT infections.[29,32] The microbiology of the CIED infections was not consistently reported among the studies. The most common reported etiology of CIED infection was coagulase negative staphylococci (range 40 to 70%), followed by *Staphylococcus aureus* (range 9 to 30%) and Gram-negative bacilli (range 11 to 20%). The duration of follow up after device re-implantation varied substantially from 6 to 312 months.

Study Quality

As there were no RCTs identified in the systematic review, the Newcastle-Ottawa scale was used to assess risk of bias in each of the included studies (***Appendix C***). Two measures within the scale were not applicable given the design of the included studies; the six measures that were graded were: (a) cohort representativeness, (b) exposure ascertainment, (c) outcome absence at baseline, (d) assessment of outcome, (e) adequacy of observation duration, and (f) completeness of cohort-follow up. The majority of studies had the highest quality-level indicators in all six measures. Two studies selected populations that may not be representative of the overall CIED population: Mountantonakis *et al.* focused on the patients with localized pocket infection for assessing the safety of same day device re-implantation following extraction.[31] The cohort described by Molina did not represent the contemporary population of CIED patients, as a significant proportion of devices in the study cohort underwent CIED implantation by sternotomy or thoracotomy with placement of epicardial patches.[30] Two

studies did not clearly detail if all patients had been accounted for by the end of the study and there were concerns of bias with regards to their completeness of follow up.[30,33]

Re-infection following Management of Infection CIED Infection

In our primary analysis, the incidence rate of first device re-infection for the pooled cohort was 0.45% (95% confidence interval (CI), 0.02 to 1.23%) per person-year (***Figure 2***). There was a moderate degree of heterogeneity (I^2 = 61%, Cochran's Q p = 0.01). In our secondary analysis using a mixed-effects Poisson regression model, the incidence rate of re-infection was similar to our primary analysis at 0.58% (95% CI, 0.21 to 1.55%) per person year.

Effect of Time to Re-implantation

Time to re-implantation >72 hours was associated with a trend toward a higher incidence of CIED re-infection (unadjusted incident rate ratio (IRR) 4.8; 95% CI 0.9 to 24.3, p=0.06 mixed-effects Poisson regression). Given the smaller number of included studies identified by the systematic review, we were unable to adjust for additional variables. When stratifying time to device re-implantation by one week or less, there did not appear to be a significant difference in incidence rate (p=0.7 mixed-effects Poisson regression).

Mortality following CIED Infection

Only five of the included studies reported all-cause mortality.[13,27-30] Among the 508 patients included in these studies, 42 deaths (8.3%) were observed over a median follow up of 14 months. In the random effects analysis, the incidence rate of death was 5.0% (95% CI, 0.1 to 15.5%) per person-year of follow up (***Figure 3***). There was a high degree of heterogeneity (I^2 = 96%, Cochran's Q p < 0.001).

DISCUSSION

Principle Findings

We found that the pooled re-infection rate following initial management of CIED infection was approximately 0.5% per person-year. To our knowledge, this is the first systematic review and meta-analysis reporting the pooled re-infection rates following original management of CIED infection. The substantial heterogeneity seen in the pooled analysis suggests the presence of several variables that can affect the incidence rate of re-infection. Factors may include the presence of bacteremia, response to treatment, or patient factors, such as the presence of immunosuppression.[1]

When we examined infection risk based on timing of re-implantation, a time of greater than 72 hours was associated with a 4-fold higher incidence rate compared to re-implantation at 72 hours or less. Using a one week cut-point for time to device re-implantation, there was no difference in re-infection rates. We consider these results exploratory, as meta-regression is

considered an underpowered analysis. Specifically, given the small number of studies included in the pooled analysis, we were unable to adjust for potentially important confounders. For example, the higher re-infection rate associated with time to re-implantation >72 hours may be due to an increased number of comorbid conditions in the corresponding study populations, or a high proportion of systemic infections requiring additional time to clear the bloodstream of bacteremia. Important covariates, which we were unable to adjust for at the meta-regression level, were the proportions of documented endocarditis, lead vegetations or bacteremia compared to localized pocket infection.

Management of Cardiac Device Infections

Treatment of CIED infections requires complete extraction of the infected CIED systems (including generator and leads) and administration of systemic antibiotics to eradicate infection.[10] In the majority of patients that require device replacement, the optimal timing to re-implantation is unknown. In our study, there was an unexpected association of increased re-infection rates with a time to device re-implantation greater than 72 hours. Although interpretation is limited by lack of adjustment for confounders, this is finding is opposite to the expectation in clinical practice. Conceptually, re-implanting a device too early during the treatment course may result in a higher infection relapse rate if the infection has only been partially eradicated by systemic antibiotics. On the other hand, the longer hospital stays while awaiting device re-implantation are associated with increased health care costs, decreased patient quality of life, and the potential for acquiring non-device related nosocomial infections. Furthermore, there is the potential for adverse events related to the absence of ICD or CRT therapies, such as worsening heart failure or delay to treatment of malignant ventricular arrhythmias.

Time to Device Re-implantation

There is a paucity in the literature exploring the timing of CIED replacement and risk of re-infection. Our systematic review only identified eight studies that reported the time to re-implantation and the rate of device re-infection.[13,27-33] The majority of these studies are limited by their retrospective study design[28,30-33] and small sample sizes. Furthermore, the primary study designs did not focus on assessing the effect of time to re-implantation on subsequent CIED re-infections. Consistent with the relatively paucity in the literature guiding time to device re-implantation, we noted a wide range in the median time to device re-implantation (i.e. same day re-implantation to over two weeks).

One of the largest contemporary prospective cohorts tracking CIED infections found a repeat infection risk of 1.8% among patients who were re-implanted.[13] This study found a high variation in physician practice when determining the time to device re-implantation, yet timing to re-implantation did not seem to affect re-infection rates. With the caveat of a relatively small

sample size and limited follow up, the authors suggested that an array of other risk factors may have a larger role in determining infection relapse rates compared to decisions regarding timing to re-implantation.[13] Consistent with this notion, some studies suggest that factors, such as the presence of hemodialysis for renal failure, pocket hematomas, malignancy, or *Staphylococcus aureus* bacteremia are the leading risk factors in estimating the risk of re-infection.[44,45] In fact, small single-center studies suggested that same-day re-implantation is feasible for patients with isolated CIED pocket infections and is not associated with adverse outcomes.[31,46]

Current expert consensus recommendations from the Heart Rhythm Society and American Heart Association suggest a 72 hour and 14 day waiting period for re-implantation based on blood culture negativity and the presence of valvular vegetations, respectively.[10,23] However, the quality of evidence supporting these recommendations are weak (Grade IIaC), and based mainly on a single retrospective study of 127 patients.[42] Our findings do not support this conclusion as re-implantation at greater than 72 hours was associated with increased infection rates. However, there are significant limitations to our findings since only eight studies were available for inclusion in the meta-regression, and these individual studies did not reliably report differences in patient characteristics among those who developed a device re-infection versus those who remained infection-free. Thus, we were unable to adjust for important covariates such as severity of initial infection (i.e. presence of bacteremia, lead endocarditis, causative micro-organism), patient comorbidities, or choice of antibiotic treatment for initial infection. Our meta-regression findings should be considered exploratory and reinforces the need for additional research to guide recommendations regarding timing to re-implantation.

Study Limitations

Our study requires interpretation in the context of a number of limitations. Firstly, time to re-implantation and device re-infection rates were inconsistently reported in the literature. Five studies were excluded at the level of the full text screen as they did not report device re-infection rates. Additionally, the adopted diagnostic criteria for device infection were inconsistently reported among the included studies, which may contribute to the heterogeneity in the pooled estimate of incidence rate of CIED re-infection. Secondly, the meta-analyses included mainly retrospective studies that varied in patient population, study quality, and follow-up, contributing to the clinical variability and heterogeneity in our pooled analysis. Thirdly, we did not anticipate the relatively small number of studies and patients derived from the systematic review. Nonetheless, our study highlights the importance of additional research in the area of cardiac device infection, and further study assessing re-infection rates and long-term outcome.

Finally, we attempted to explore the relationship between time to re-implantation and re-infection rates. An important limitation is the unavailability of patient level data and times to follow up. To explore the potential association, we performed a Poisson-distribution meta-

regression. However, given the small number of studies that met inclusion criteria, the meta-regression was underpowered, and we were unable to properly adjust for other confounders with the potential to affect re-infection rates. This may explain the unexpected association of increased re-infection rates with time to device re-implantation greater than 72 hours. Nevertheless, this highlights the need for larger prospective studies to adequate control for confounders when exploring re-infection risk after initial CIED infection.

Implications for Future Research

Additional prospective, well-designed studies are required to explore the effect of timing to re-implantation on re-infection rates, with adequate adjustment for patient comorbidities, extent of infection (i.e. localized pocket infection, vegetation or bacteremia) and the causative pathogen. Based on the several small studies reporting on the safety of same day re-implantation and in light of our findings, larger studies are necessary to validate the safety of the one-stage contralateral device replacement approach compared with delayed device replacement. Given the potential impact on hospital length of stay, an economic evaluation comparing these strategies will also be an important component.

Finally, the advent of new technology such as leadless pacemakers and subcutaneous ICDs may obviate the need to delay device re-implantation following extraction of infected CIED systems. The current assumption is that these newer devices are associated with a lower risk of infection: leadless pacemakers have significantly less surface area for bacterial seeding, and subcutaneous ICDs do not contain any components exposed to the bloodstream. Nevertheless, the use of these novel devices to replace infected conventional CIEDs following antimicrobial therapy, or the rates of infection associated with these devices have yet to be assessed.

CONCLUSION

The incident rate of re-infection following initial management of CIED infection is not insignificant. Our findings suggest a trend that time to re-implantation affects rates of re-infection when device re-implantation occurs at ≤ 72 hours compared to >72 hours. The findings of this study need to be interpreted with circumspection due to the moderate heterogeneity among included studies.

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AUTHOR CONTRIBUTIONS

JC, DVE, ER and DC were responsible for conception of this research study and methodology. DS and ER wrote the manuscript. DS, ER and RS were responsible for data collection and analysis. All authors reviewed the manuscript and analyses.

DATA AVAILABILITY STATEMENT

The data used to compile the meta-analysis is available upon request.

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COMPETING INTERESTS

DVE has received research grants from Medtronic Inc, GE Healthcare, and St Jude Medical outside of the submitted work. The remaining authors have no conflicts of interest to disclose.

REFERENCES

1 Polyzos, K. A., Konstantelias, A. A. & Falagas, M. E. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace* **17**, 767-777, doi:10.1093/europace/euv053 (2015).

2 Greenspon, A. J. *et al.* 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* **58**, 1001-1006, doi:10.1016/j.jacc.2011.04.033 (2011).

3 Sohail, M. R., Henrikson, C. A., Braid-Forbes, M. J., Forbes, K. F. & Lerner, D. J. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* **171**, 1821-1828, doi:10.1001/archinternmed.2011.441 (2011).

4 Tarakji, K. G. *et al.* Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* **7**, 1043-1047, doi:10.1016/j.hrthm.2010.05.016 (2010).

5 Mond, H. G. & Proclemer, A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* **34**, 1013-1027, doi:10.1111/j.1540-8159.2011.03150.x (2011).

6 Valzania, C., Torbica, A., Tarricone, R., Leyva, F. & Boriani, G. Implant rates of cardiac implantable electrical devices in Europe: A systematic literature review. *Health Policy* **120**, 1-15, doi:10.1016/j.healthpol.2015.11.001 (2016).

7 Raatikainen, M. J. P. *et al.* A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *Europace* **19**, ii1-ii90, doi:10.1093/europace/eux258 (2017).

8 Voigt, A., Shalaby, A. & Saba, S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol* **33**, 414-419, doi:10.1111/j.1540-8159.2009.02569.x (2010).

9 Arana-Rueda, E. *et al.* Repeated procedures at the generator pocket are a determinant of implantable cardioverter-defibrillator infection. *Clin Cardiol* **40**, 892-898, doi:10.1002/clc.22743 (2017).

10 Kusumoto, F. M. *et al.* 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm* **14**, e503-e551, doi:10.1016/j.hrthm.2017.09.001 (2017).

11 Viganego, F. *et al.* Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol* **109**, 1466-1471, doi:10.1016/j.amjcard.2012.01.360 (2012).

12 Le, K. Y. *et al.* Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm* **8**, 1678-1685, doi:10.1016/j.hrthm.2011.05.015 (2011).

13 Boyle, T. A. *et al.* Reimplantation and Repeat Infection After Cardiac-Implantable Electronic Device Infections: Experience From the MEDIC (Multicenter Electrophysiologic Device Infection Cohort) Database. *Circulation. Arrhythmia and electrophysiology* **10**, doi:10.1161/CIRCEP.116.004822 (2017).

14 Gaynor, S. L. *et al.* Laser assistance for extraction of chronically implanted endocardial leads: infectious versus noninfectious indications. *Pacing Clin Electrophysiol* **29**, 1352-1358, doi:10.1111/j.1540-8159.2006.00547.x (2006).

15 Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **339**, b2535, doi:10.1136/bmj.b2535 (2009).

16 Stroup, D. F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* **283**, 2008-2012 (2000).

17 Wells GA *et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* , <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]> (2000).

18 Higgins, J. P. *et al.* in *Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.* Vol. 10 (Issue 1) (eds J. Chandler, J. McKenzie, I. Boutron, & B. Welch) (2016).

19 DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177-188 (1986).

20 Freeman, M. & Turkey, J. Transformations related to the angular and the square root. *Ann Math Stats* **21**, 607-611 (1950).

21 Nyaga, V. N., Arbyn, M. & Aerts, M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* **72**, 39, doi:10.1186/2049-3258-72-39 (2014).

22 Spittal, M. J., Pirkis, J. & Gurrin, L. C. Meta-analysis of incidence rate data in the presence of zero events. *BMC Med Res Methodol* **15**, 42, doi:10.1186/s12874-015-0031-0 (2015).

23 Baddour, L. M. *et al.* Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* **121**, 458-477, doi:10.1161/CIRCULATIONAHA.109.192665 (2010).

24 Cochran, W. G. The comparison of percentages in matched samples. *Biometrika* **37**, 256-266 (1950).

25 Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539-1558, doi:10.1002/sim.1186 (2002).

26 Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560, doi:10.1136/bmj.327.7414.557 (2003).

27 Amraoui, S. *et al.* Comparison of delayed transvenous reimplantation and immediate surgical epicardial approach in pacing-dependent patients undergoing extraction of infected permanent pacemakers. *Heart Rhythm* **12**, 1209-1215, doi:10.1016/j.hrthm.2015.02.023 (2015).

28 Chua, J. D. *et al.* Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* **133**, 604-608 (2000).

29 Deharo, J. C. *et al.* Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study. *Heart* **98**, 724-731, doi:10.1136/heartjnl-2012-301627 (2012).

30 Molina, J. E. Undertreatment and overtreatment of patients with infected antiarrhythmic implantable devices. *Ann Thorac Surg* **63**, 504-509 (1997).
31 Mountantonakis, S. E., Tschabrunn, C. M., Deyell, M. W. & Cooper, J. M. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. *Europace* **16**, 252-257, doi:10.1093/europace/eut220 (2014).
32 Saeed, O., Gupta, A., Gross, J. N. & Palma, E. C. Rate of cardiovascular implantable electronic device (CIED) re-extraction after recurrent infection. *Pacing Clin Electrophysiol* **37**, 963-968, doi:10.1111/pace.12407 (2014).
33 Tascini, C. *et al.* Management of cardiac device infections: A retrospective survey of a non-surgical approach combining antibiotic therapy with transvenous removal. *J Chemother* **18**, 157-163, doi:10.1179/joc.2006.18.2.157 (2006).
34 Amraoui, S. *et al.* Single surgical procedure combining epicardial pacemaker implantation and subsequent extraction of the infected pacing system for pacemaker-dependent patients. *J Thorac Cardiovasc Surg* **146**, 302-305, doi:10.1016/j.jtcvs.2012.07.026 (2013).
35 Le Franc, P. *et al.* Extraction of endocardial implantable cardioverter-defibrillator leads. *The American journal of cardiology* **84**, 187-191 (1999).
36 O'Nunain, S. *et al.* The treatment of patients with infected implantable cardioverter-defibrillator systems. *J Thorac Cardiovasc Surg* **113**, 121-129, doi:10.1016/S0022-5223(97)70407-0 (1997).
37 Rickard, J. *et al.* Cardiac venous left ventricular lead removal and reimplantation following device infection: a large single-center experience. *J Cardiovasc Electrophysiol* **23**, 1213-1216, doi:10.1111/j.1540-8167.2012.02392.x (2012).
38 Cassagneau, R. *et al.* Long-term outcomes after pocket or scar revision and reimplantation of pacemakers with preerosion. *Pacing Clin Electrophysiol* **34**, 150-154, doi:10.1111/j.1540-8159.2010.02950.x (2011).
39 Kennelly, B. M. & Piller, L. W. Management of infected transvenous permanent pacemakers. *Br Heart J* **36**, 1133-1140 (1974).
40 Margey, R. *et al.* Contemporary management of and outcomes from cardiac device related infections. *Europace* **12**, 64-70, doi:10.1093/europace/eup362 (2010).
41 Rickard, J. *et al.* Survival of patients with biventricular devices after device infection, extraction, and reimplantation. *JACC Heart Fail* **1**, 508-513, doi:10.1016/j.jchf.2013.05.009 (2013).
42 Sohail, M. R. *et al.* Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* **49**, 1851-1859, doi:10.1016/j.jacc.2007.01.072 (2007).
43 Vogt, P. R. *et al.* Surgical management of infected permanent transvenous pacemaker systems: ten year experience. *J Card Surg* **11**, 180-186 (1996).
44 Essebag, V. *et al.* Clinically Significant Pocket Hematoma Increases Long-Term Risk of Device Infection: BRUISE CONTROL INFECTION Study. *J Am Coll Cardiol* **67**, 1300-1308, doi:10.1016/j.jacc.2016.01.009 (2016).
45 Leung, S. & Danik, S. Prevention, Diagnosis, and Treatment of Cardiac Implantable Electronic Device Infections. *Curr Cardiol Rep* **18**, 58, doi:10.1007/s11886-016-0733-x (2016).

46 Nandyala, R. & Parsonnet, V. One stage side-to-side replacement of infected pulse generators and leads. *Pacing Clin Electrophysiol* **29**, 393-396, doi:10.1111/j.1540-8159.2006.00359.x (2006).

FIGURES

Figure 1. Flow Diagram of Study Selection for Systematic Review

Figure 2. Pooled Incidence Rate of Device Re-Infection

Figure 3. Pooled Incidence Rate of Death Following CIED Infection

TABLES

Table 1. Characteristics of Included Studies

Study (Year)	Ref.	N	Age, yr, mean (SD)	Female, %	Device Type	Pathogen	Local Infection Only, %	Time to Re-implantation	Device Re-Infection, %	Death, %	Follow up, months
Amraoui et al. (2015)	25	80	71 (13)	20	PM, ICD	NR	61	4 to 14 days	0	5.0	12
Boyle et al. (2017)	11	220	68 (14)	19	NR	NR	58	10 days IQR 6 - 19	1.8	11.4	6
Chua et al. (2000)	26	123	66 (16)	29	PM, ICD	CoNS: 46 *S.aureus*: 9.0	74	5 days (range 0 to 68 days)	3	8.1	14
Deharo et al. (2012)	27	59	71 (14)	26	PM, ICD, CRT	CoNS: 42 *S.aureus:* 30 GNB: 11	41	24 days (10 to 1192 days)	1.7	3.3	25
Molina et al. (1997)	28	26	50 (NR)	NR	PM, ICD	NR	NR	2 to 6 weeks	0.09	0	312
Mountantonakis et al. (2013)	29	15	77 (12)	27	PM, ICD	CoNS: 40 *S.aureus:* 27 GNB: 20	100	0 (same day)	0	NR	40
Saeed et al. (2014)	30	168	67 (7)	32	PM, ICD, CRT	NR	82	3 days IQR 1 - 10	5.4	NR	229
Tascini et al. (2006)	31	79	60 (30)	23	PM, ICD	CoNS: 70 *S. aureus*: 14 GNB: 12	72	2 days	0	NR	14

Abbreviations: CoNS = coagulase negative staphylococci, CRT = cardiac resynchronization therapy, GNB = gram negative bacilli, ICD = implantable cardioverter defibrillator, IQR = interquartile range, NR = not reported, PM = pacemaker, Yr = year

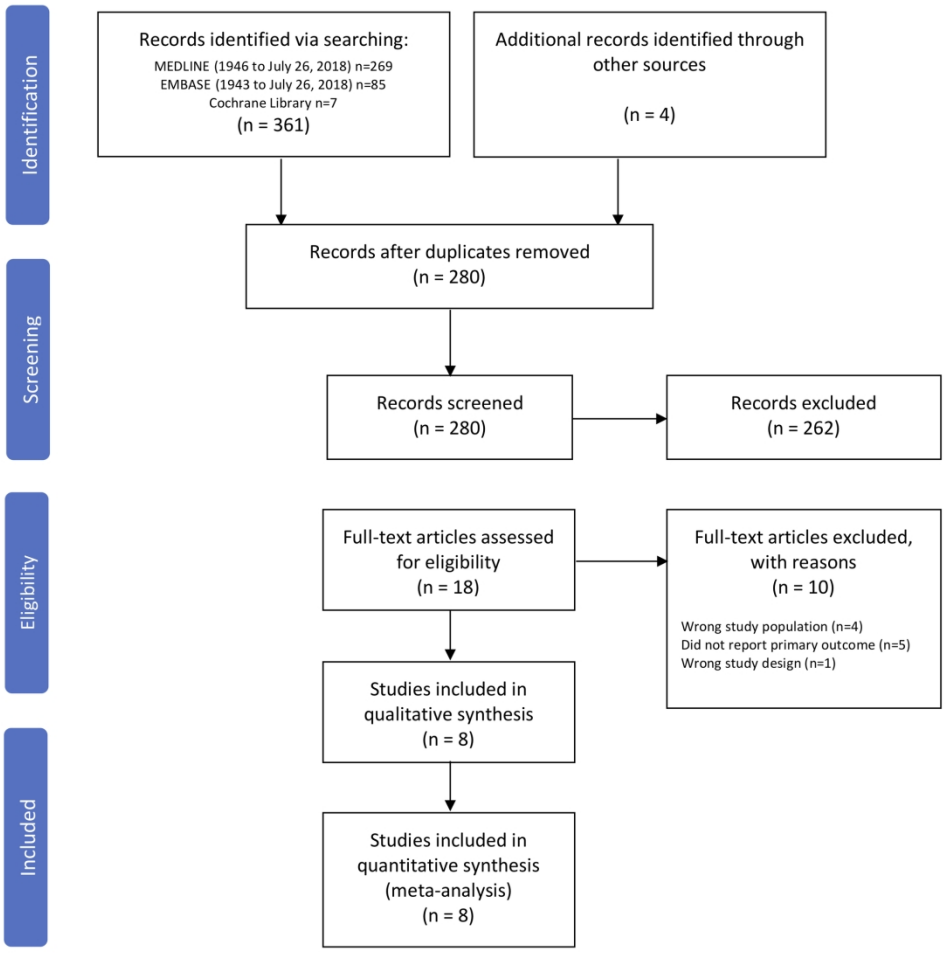

Figure 1. Flow Diagram of Study Selection for Systematic Review

189x186mm (300 x 300 DPI)

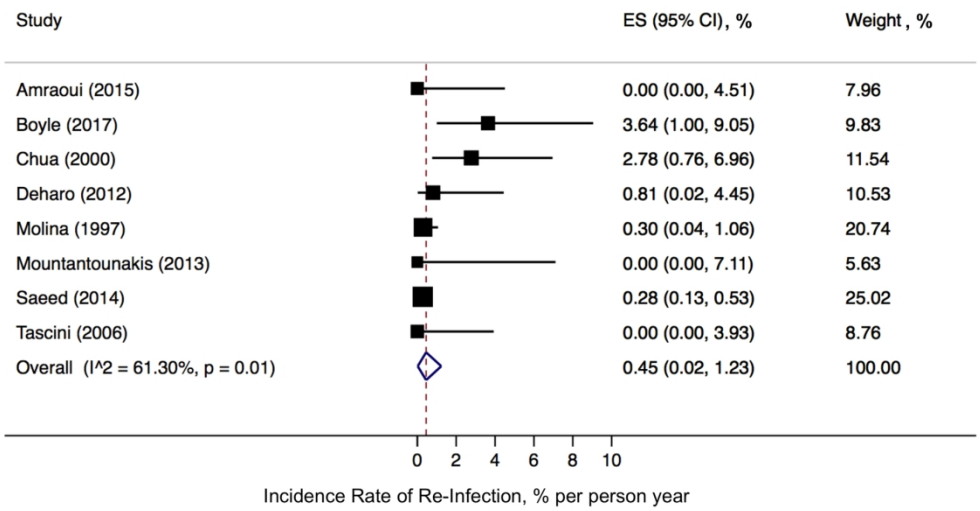

Figure 2. Pooled Incidence Rate of Device Re-Infection

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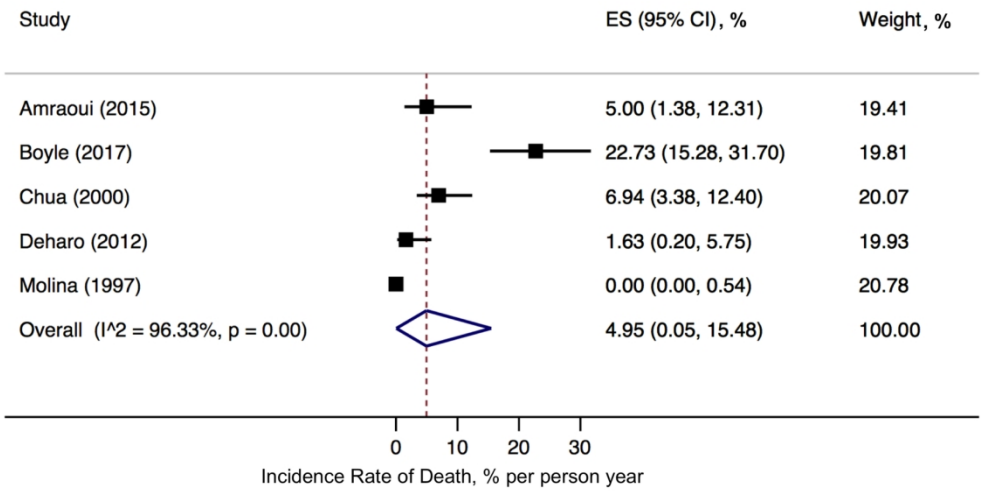

Figure 3. Pooled Incidence Rate of Death Following CIED Infection

162x83mm (300 x 300 DPI)

APPENDIX A. MOOSE Checklist for Reporting of Meta-analyses of Observation Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5, Figure 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Table 1, Figures 1-3

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2,3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	8, Figure 3
28	Indication of statistical uncertainty of findings	8, Figure 2-3
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	-
31	Assessment of quality of included studies	Appendix
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10-11
34	Guidelines for future research	10-11
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

APPENDIX B. Detailed Search Strategy

EMBASE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

MEDLINE Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.
3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. defibrillator.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

Cochrane Library Search Strategy

1. exp pacemaker/ or exp implantable cardioverter defibrillator/ or exp artificial heart pacemaker/ or exp defibrillator
2. cardiac implantable electronic device.mp.

3. cardiovascular implantable electronic device.mp.
4. pacemaker.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
5. defibrillator.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
6. cardiac resynchronization therapy.mp. or exp cardiac resynchronization therapy/
7. 1 or 2 or 3 or 4 or 5 or 6
8. device infection.mp. or exp infection/ or exp device infection/
9. infection.mp.
10. 8 or 9
11. reimplantation or exp Reimplantation/
12. 7 and 10 and 11

APPENDIX C1. Summary of Study Quality Assessment

Study ID	Selection				Comparability	Outcome			Total (⋆)
	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome shown to be absent at study start		Assessment of outcome	Adequacy of follow up duration	Adequacy of cohort follow up	
Amraoui (2015)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Boyle (2017)	A (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Chua (2000)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	B (⋆)	**6**
Deharo (2012)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Molina (1997)	C	--	A (⋆)	B	--	B (⋆)	A (⋆)	D	**3**
Saaed (2014)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**6**
Tascini (2006)	B (⋆)	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	C (⋆)	**6**
Mountantounakis (2013)	C	--	A (⋆)	A (⋆)	--	B (⋆)	A (⋆)	A (⋆)	**5**

APPENDIX C2. Newcastle Ottawa Quality Assessment Form for Cohort Studies

*(Reference: Wells GA et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)_*

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ⍰
   b) somewhat representative of the average _____ in the community ⍰
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ⍰
   b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
a) secure record (eg surgical records) ☐
b) structured interview ☐
c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes ☐
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) ☐
b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
a) independent blind assessment ☐
b) record linkage ☐
c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ☐
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ☐
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

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Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5, Figure 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
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