PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Timing of Device Re-Implantation and Re-Infection Rates Following Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis
AUTHORS	Chew, Derek; Somayaji, Ranjani; Conly, John; Exner, Derek; Rennert-May, Elissa

VERSION 1 - REVIEW

REVIEWER	Michael Doering Heart Centre at the University of Leipzig Leipzig, Germany
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	The present work of Chew et al. is a meta-analysis of 8 studies evaluating re-infection rates following device re-implantation after extraction due to device-related infection. In contrast to clinical reality, the analysis showed a 4 fold higher risk of repeated infection if the device was implanted later than 72 hours after the initial extraction. The authors cannot provide a satisfactory explanation for this circumstance. The manuscript is well written and interesting. Anyway, it has some major limitations: - Only 8 studies fulfilled the inclusion criteria and 2 of these were published more than 15 years ago. The total number of study participants is therefore relatively low with 744. - The cohorts of the individual studies vary widely in patient characteristics, especially with regard to the rate of systemic infections. However, this significantly influences the duration of therapy and the time of reimplantation. Overall, this makes a meaningful analysis of the studies difficult. - The result of the analysis that a time <72 hours before re-implantation is associated with a lower risk of infection makes little sense in a clinical context. The opposite would have been expected. There was probably a significant bias because patients with a lower risk of reinfection were implanted earlier. Please comment on the previous points in more detail in your manuscript. Furthermore, I have some minor comments which may improve the quality of your work.

	- Abstract: it is not clear which patient group has the higher risk of infection in your conclusions. - Introduction: Please also refer to the EHRA-Whitebook. Please also comment on the rates of re-implantation. - Discussion (page 9, line 19): "…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…" - the results of your meta-analysis say exactly the opposite! Please comment on this and try to find an explanation.

REVIEWER	Yohannes Woubishet Woldeamanuel Stanford University, USA Advanced Clinical & Research Center, Ethiopia
REVIEW RETURNED	04-Mar-2019

GENERAL COMMENTS	- This manuscript contains major flaws, some of which I am mentioning below. I recommend it to be rejected. - No a priori estimation of sample size and participant size per study was done. Particularly so when employing random effects weighted analysis. - Please read the following references. - Jackson D, Turner R. Power analysis for random-effects meta-analysis. Res Syn Meth. 2017;8:290–302. https://doi.org/10.1002/jrsm.1240 - Valentine, J. C., Pigott, T. D. & Rothstein, H. R. (2010). How many studies do you need? A primer on statistical power for meta-analysis. Journal of Educational and Behavioral Statistics, 35(2), 215-247.\n– Chapters 4 -6 in Pigott, T. D. (2012). Advances in meta-analysis. New York, NY: Springer - Significant amount of heterogeneity ranging from 61 to as high as 96 %. Authors must disclose p value of I-squared statistics, which will certainly be statistically significant ($p < 0.05$). This indicates significant heterogeneity rendering the studies non-combinable for conducting meta-analysis. - Studies highly variable in terms of study design, patient population, etc..another source of heterogeneity. - $P = 0.06$ not significant result for incidence of CIED infection with respect to 72 hours time to re-implantation. However, authors wrongly claim this as a significant core result of their manuscript. There needs to be adjustment to multiple testing, and hence none of the results become significant enough. - Authors forced result on their meta-regression by increasing p value threshold to 0.10. This is erroneous and misleading.

REVIEWER	Ahmad Farouk Musa Monash University Malaysia
REVIEW RETURNED	03-May-2019

GENERAL COMMENTS	The paper was well written and the statistical analyses were clearly mentioned and correctly chosen. The meta-analysis was correctly undertaken and the results were correctly reported. However, a Flowchart clarifying the PRISMA statement is recommended.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Michael Doering

Institution and Country: Heart Centre at the University of Leipzig, Leipzig, Germany

Please state any competing interests or state ‘None declared’: None declared.

The present work of Chew et al. is a meta-analysis of 8 studies evaluating re-infection rates following device re-implantation after extraction due to device-related infection. In contrast to clinical reality, the analysis showed a 4-fold higher risk of repeated infection if the device was implanted later than 72 hours after the initial extraction. The authors cannot provide a satisfactory explanation for this circumstance.

Thank you for your review of this manuscript. We agree that this finding is contrary to the clinical expectations. As described above, due to the limitations of the available literature (specifically, that the studies variably reported differences in patient characteristics associated with re-infection), we were unable to adjust for important covariates. However, we still believe our findings are a valuable additional to the literature as this exploratory finding, though unexpected, has not been previously described in a systematic review and warrants further evaluation. The discussion has been amended to clarify this limitation:

“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.”

It is also worth noting that while our clinical gestalt (all authors on this manuscript are either cardiologists or infectious diseases physicians) would associate longer re-implantation times with a lower rate of infection, this hypothesis has not been tested rigorously. In fact, the Heart Rhythm Society and American Heart Association recommendation for the 72-hour threshold of device reimplantation is based on low quality evidence (IIaC). Our systematic review resulting in only 8 (mostly retrospective) cohort studies highlights the need to rigorously study the impact of time to re-implantation and other predictors of device re-implantation.

The manuscript is well written and interesting. Anyway, it has some major limitations:

Only 8 studies fulfilled the inclusion criteria and 2 of these were published more than 15 years ago. The total number of study participants is therefore relatively low with 744.

Thank you. We completely agree with the reviewer that this is an important limitation of the study. In fact, our findings highlight the need and provides the rationale for additional studies exploring device re-infections following initial device infection.

As there have been no prior systematic reviews on this topic, we did not know the true extent of this evidence gap. We have amended the limitations section to highlight this limitation and need for further studies in this area:

“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.”

The cohorts of the individual studies vary widely in patient characteristics, especially with regard to the rate of systemic infections. However, this significantly influences the duration of therapy and the time of reimplantation. Overall, this makes a meaningful analysis of the studies difficult.

Thank you for this important point. We agree with the reviewer that there is substantial heterogeneity in the patient populations between studies. In anticipation of the variation in baseline characteristics of the patient cohorts at the study level, we pre-specified use of a random effects model (rather than fixed effects) for our primary analysis using the meta-analysis of proportions method. All pooled incidence rates are reported accompanied by a measure of the degree of heterogeneity (via the I2 statistic) in order to frame the discussion and interpretation. The importance of conditional interpretation of results is highlighted in the conclusion:

“The findings of this study need to be interpreted with circumspection due to the moderate heterogeneity among included studies.”

The result of the analysis that a time <72 hours before re-implantation is associated with a lower risk of infection makes little sense in a clinical context. The opposite would have been expected. There was probably a significant bias because patients with a lower risk of reinfection were implanted earlier.

We agree with the authors that this finding is unexpected. As described above, the meta-regression results should be considered exploratory since we were unable to adjust for important confounders such as risk factors for infection (i.e. severity of initial infection – bacteremia, lead vegetations, or patient factors such as diabetes).

Please comment on the previous points in more detail in your manuscript.

Thank you for your comments and suggestions. These previous points and limitations have been described in greater detail in the manuscript (see above).

Furthermore, I have some minor comments which may improve the quality of your work.

Abstract: it is not clear which patient group has the higher risk of infection in your conclusions.

We have amended the abstract to the following:

“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 (I2 = 61%).”

Introduction: Please also refer to the EHRA-Whitebook. Please also comment on the rates of re-implantation.

We also referred to the EHRA-Whitebook in the discussion of the increasing rates of device implantation worldwide. The following reference has been added:

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)

We have also amended the introduction to mention device re-implantation and replacement for predicted battery depletion, as a contributing factor to the increase rates of CIED infection. The following sentences have been added to the introduction:

“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”

Discussion (page 9, line 19): "…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…" - the results of your meta-analysis say exactly the opposite! Please comment on this and try to find an explanation.

We have amended the discussion to highlight our unexpected findings from the meta-regression, and how this differs from clinical expectation.

"{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."

Reviewer: 2

Reviewer Name: Yohannes Woubishet Woldeamanuel

Institution and Country: Stanford University, USA; Advanced Clinical & Research Center, Ethiopia

Please state any competing interests or state 'None declared': None declared.

This manuscript contains major flaws, some of which I am mentioning below. I recommend it to be rejected.

No a priori estimation of sample size and participant size per study was done. Particularly so when employing random effects weighted analysis.

Please read the following references.

o Jackson D, Turner R. Power analysis for random-effects meta-analysis. Res Syn Meth. 2017;8:290–302. https://doi.org/10.1002/ jrsm.1240

o Valentine, J. C., Pigott, T. D. & Rothstein, H. R. (2010). How many studies do you need? A primer on statistical power for meta-analysis. Journal of Educational and Behavioral Statistics, 35(2), 215-247.\n– Chapters 4 -6 in Pigott, T. D. (2012). Advances in meta-analysis. New York, NY: Springer

Thank you for the comment on the use of power analysis for random-effects meta-analysis. Our primary analysis was to determine the pooled incidence rate of CIED re-infection. Since we were interested in pooling incidence rates (rather than determining the effect size of a binary outcome), we were unable to perform meaningful a priori power calculations. While the provided references discuss three innovative / novel methods for performing power calculations when pooling the results of binary

outcomes, the references do not explicitly discuss methods specifically related to incident rate meta-analyses.

It is worth noting that we did conduct our systematic review and meta-analysis in accordance with the PRISMA statement and Cochrane Handbook (version 5.1), which are considered to be a current standard in methodology and preferred reporting. Neither of these documents have recommended a priori power calculations as part of the current standard protocol (with the exception of prospective individual patient level meta-analyses).

We reviewed the provided references as thoughtfully suggested. The authors from the one of the recommended readings (Valentine et al.) provided above state the following which we believe supports our methodology:

“When the computed prospective power for a planned meta-analysis is low, the reviewers may question whether it is worthwhile for them to invest the time and effort needed to conduct the systematic review. When we are asked this question, we generally answer ‘Yes, it is still worthwhile.’… In this sense, the answer to the question ‘How many studies do you need to do a meta-analysis?’ is ‘two.’ Not because it is ideal but rather because given the need for a conclusion…it is a better analysis strategy than the alternatives.”

While we understand the reviewers concerns and appreciate the important point raised, we respectfully feel we followed appropriate methods and standards for conducting this meta-analysis.

Significant amount of heterogeneity ranging from 61 to as high as 96 %. Authors must disclose p value of I-squared statistics, which will certainly be statistically significant ($p < 0.05$). This indicates significant heterogeneity rendering the studies non-combinable for conducting meta-analysis.

Thank you for highlighting this important point. We agree with the reviewer that there is substantial heterogeneity likely due to a variety of reasons such as the differences in patient characteristics, and individual study methodology.

Recognizing that statistical heterogeneity is unavoidable given the clinical and methodologic diversity of studies (Higgins et al. BMJ 2003; 327: 557-560), we believe that a transparent discussion to explore the meta-analysis results (and inherent limitations) would be a useful and novel contribution to the literature around CIED re-infection rates.

We would like to note that the p values for the chi-squared statistic are already disclosed within Figure 2 and 3. For instance, in Figure 2 the heterogeneity for the overall pooled incidence rate of device re-infection is reported as ($I^2 = 61.30\%$, $p= 0.01$). To provide additional clarity in the text, the following sentences in the results section have been amended:

“…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 (I2 = 61%, Cochran’s Q p = 0.01).”

“…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 (I2 = 96%, Cochran’s Q p < 0.001).”

Studies highly variable in terms of study design, patient population, etc. another source of heterogeneity.

Thank you. We agree that these variations provide reasonable explanations for the cause of the heterogeneity seen in pooled analysis. Sources of heterogeneity are explored in the discussion:

“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.”

P = 0.06 not significant result for incidence of CIED infection with respect to 72 hours time to re-implantation. However, authors wrongly claim this as a significant core result of their manuscript. There needs to be adjustment to multiple testing, and hence none of the results become significant enough.

Authors forced result on their meta-regression by increasing p value threshold to 0.10. This is erroneous and misleading.

We thank the reviewer for clarifying this miscommunication. We did not intend for the meta-regression to claim that a p=0.06 was statistically significant. The manuscript currently describes this as a trend towards significance:

“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).”

We have amended the methods to clarify that the P threshold of < 0.10 refers only to tests of heterogeneity, as recommended by the Cochrane Handbook for Systematic Review and Meta-analysis (5.1) given that these tests are underpowered. The following sentences have been amended:

“All analyses were performed using Stata IC 15.1 with p value <0.05 was considered to indicate statistical significance.”

“A threshold of p < 0.10 was considered significant for tests of heterogeneity.”

Reviewer: 3

Reviewer Name: Ahmad Farouk Musa

Institution and Country: Monash University Malaysia

Please state any competing interests or state ‘None declared’: None declared

The paper was well written and the statistical analyses were clearly mentioned and correctly chosen. The meta-analysis was correctly undertaken and the results were correctly reported. However, a Flowchart clarifying the PRISMA statement is recommended.

Thank you for your comments. Since the studies selected by the systematic review were all observation studies, we have attached the MOOSE checklist. This has been added to the Supplementary Materials as Appendix C. The PRISMA flowchart is illustrated in Figure 1.

VERSION 2 – REVIEW

REVIEWER	Michael Doering Heart Centre at the University of Leipzig Leipzig, Germany
REVIEW RETURNED	04-Jul-2019

GENERAL COMMENTS	The manuscript was adequately revised and the quality of the work improved. Anyway, the small number of patients in your study does not allow to draw any conclusion.

VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 1

Reviewer Name: Michael Doering

Institution and Country: Heart Centre at the University of Leipzig, Leipzig, Germany

Please state any competing interests or state ‘None declared’: None declared.

The manuscript was adequately revised and the quality of the work improved. Anyway, the small number of patients in your study does not allow to draw any conclusion.

Thank you for your comments. We agree that the small number of patients and the substantial heterogeneity in the pooled analyses highlight the need for further study in this area.