World Wide Pacemaker and Defibrillator Reuse: Systematic Review and Meta-Analysis of Contemporary Trials

Short Title: Global Pacemaker and Defibrillator Reuse

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Abstract

BACKGROUND: Patients go without pacemaker, defibrillator, and cardiac resynchronization therapies (devices) each year due to the prohibitive costs of devices.

OBJECTIVE: We sought to examine data available from studies regarding contemporary risks of reused devices in comparison with new devices.

METHODS: We searched online indexing sites to identify recent studies. Peer-reviewed manuscripts reporting infection, malfunction, premature battery depletion, and device related death with reused devices were included. The primary study outcome was the composite risk of infection, malfunction, premature battery depletion, and death. Secondary outcomes were the individual risks.

RESULTS: Nine observational studies (published 2009 – 2017) were identified totaling 2 302 devices (2 017 pacemakers, 285 defibrillators). Five controlled trials were included in meta-analysis (2 114 devices; 1 258 new versus 856 reused). All device reuse protocols employed interrogation to confirm longevity and functionality, disinfectant therapy and, usually, additional biocidal agents, packaging and ethylene oxide gas sterilization. Demographic characteristics, indications for pacing, and median follow-up were similar. There were no device-related deaths reported and no statistically significant difference in risk between new versus reused devices for the primary outcome (2.23% versus 3.86% respectively, p = 0.807, OR = 0.76). There were no significant differences seen in the secondary outcomes for the individual risks of infection, malfunction, and premature battery depletion.

CONCLUSIONS: Device reuse utilizing modern protocols did not significantly increase risk of infection, malfunction, premature battery depletion or device related death in observational studies. This data provides rationale for proceeding with a prospective multi-center non-inferiority randomized control trial.

KEYWORDS: Pacemaker reuse, defibrillator reuse, cardiac resynchronization therapy reuse, pacemaker recycling, defibrillator recycling, cardiac resynchronization therapy recycling

World Wide Pacemaker and Defibrillator Reuse: Systematic Review and Meta-Analysis of Contemporary Trials

BACKGROUND

Major progress has been made in the management of pathologic bradycardia, ventricular tachycardia, and systolic congestive heart failure, utilizing implantable pacemaker, defibrillator, and/or cardiac resynchronization therapy (CRT), respectively.[1,2] However, while these advanced therapies have become commonplace in high income nations, they are rarely available in most low and middle-income nations.[3,4] Annual pacemaker implantation rates of > 700 per million are seen in France, Sweden, and the United States of America (USA), in stark contrast to rates of < 7 per million in Indonesia, Pakistan, and the Philippines.[3] Meanwhile, Germany, the Netherlands, and the USA exhibit annual defibrillator implantation rates of > 200 per million whereas they remain < 2 per million in Bangladesh, India, and Peru.[3] The greatest barrier for device implantations cited by 90% of physicians from underserved regions is the prohibitive cost of such medical devices for most of their patients.[5] Accordingly, many clinicians have undertaken studies examining the safety and efficacy of pacemaker reuse and, as a result, the protocols for retrieval, resterilization, and reimplantation of pacemakers have been greatly refined over the last four decades.[6 - 11]

In light of recently published controlled trials, we sought to systematically review the contemporary data made available in the last decade regarding the safety and efficacy of pacemaker, defibrillator, and CRT (herein termed “device”) reuse and compare to new device use in underserved nations.

METHODS

This study was performed in accordance with the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[12]

Search Strategy

Two study investigators (BS, SKS) independently searched the medical literature to identify all relevant device studies from January 1st, 2008 until December 31st, 2017 using PubMed/MEDLINE (United States National Library of Medicine, Bethesda, MD), EMBASE, the Cochrane Database of

Systematic Reviews, and Google Scholar. We focused upon studies involving humans and utilized the keywords; “pacemaker”, “defibrillator”, “cardiac resynchronization therapy” or “bi-ventricular pacing” coupled with “reused”, “reutilized”, or “recycled” as our search terms. Clinicaltrials.gov was searched to identify relevant ongoing or unpublished trials. In addition, the reference lists of selected trials and reviews were hand searched for potentially relevant citations.

Study Selection

A study was included in the pooled analysis if it was published in a peer reviewed journal and reported the incidence of infection, malfunction, premature battery depletion, and device related death following device reuse. Two investigators (BS, SKS) abstracted and collated comparable data from each study in a standardized manner. Baseline demographic, clinical, and procedural characteristics including procurement source, sterilization technique, antibiotic use, follow-up duration, and device related complications were recorded. Additionally, a study was included in subsequent meta-analysis if the aforementioned outcomes in a new device population (control group) were compared to a reused device population (study group).

Study Outcomes

The primary study outcome was set as the composite risk of device infection, device malfunction, premature battery depletion, and device related death. Secondary study outcomes included the individual risks of infection, malfunction, premature battery depletion, and device related death. Device infection was defined as an early or late local or systemic device related infection warranting device explantation during the study period. Device malfunction was defined as a defect in the structural or electrical integrity of the pulse generator compromising device function. Premature battery depletion was defined as unexpected battery failure prior to the longevity estimation determined at implantation. Only trials with > 2 years of median follow-up were included in the secondary meta-analysis of premature battery depletion to minimize the risk of under-detecting adverse events (beta error). Device-related death was defined as death attributable to device related infection, malfunction, or premature battery depletion as reported by the study authors.

Statistical Methods

Categorical variables were expressed as percentages and continuous variables were expressed as means with standard deviations. Non-normally distributed variables were summarized as medians with inter-quartile (IQR) ranges. All raw data on the primary outcome were pooled and compared between groups using mixed-effect generalized linear models with study as the random effect. Data from studies that included comparison between reused device implantation (study group) and new device implantation (control group) were combined to estimate the pooled effect using random-effect meta-analyses. Odds Ratios [ORs] of study outcomes and their 95% Confidence Intervals (CIs) comparing reused devices with new devices were calculated using the DerSimonian and Laird method.[13] Studies that did not report an event were not included in the meta-analysis for that relevant secondary outcome, and for studies with zero events in one arm, a 0.5 constant continuity correction was used. To assess the potential risk of introducing bias with this approach, sensitivity analyses were performed by adding different constants instead of 0.5.[14] Heterogeneity among trials was assessed with the Higgins and Thompson I^2 index.[15] I^2 can be interpreted as the percentage of variability caused by heterogeneity between studies. The potential for significant small study effects was ascertained utilizing Egger's test.[16] The potential for reporting publication bias was assessed graphically using a funnel plot generated by plotting the standard error versus the DerSimonian and Laird log OR for each controlled study.[17] The analyses are presented as point estimates, and 95% confidence intervals are shown within brackets. All tests were 2-tailed, and a p value of < 0.05 was considered statistically significant. Meta-analysis was conducted using the meta-analysis module in Stata 14 (Stata Statistical Software: Release 14. StataCorp LP, College Station, TX).

Institutional Review Board approval was not required for this study as all primary information included in analysis has been made publicly available in peer reviewed medical journals.

RESULTS

Study Selection and Study Patients

An on-line search using the key search terms identified 172 articles (see Figure 1). Detailed review ascertained 10 relevant clinical studies published between 2009 and 2017 involving device reuse.[18 - 27] We excluded one case series[18] due to duplication of data in a larger subsequent trial publication[24] leaving 9 studies totaling 2 302 devices as summated in the pooled analysis (see Figure 2 and Table 1). The demographic characteristics regarding age, gender, and indication for pacing therapy (when applicable) were similar between the new device and reused device populations (see Table 2).

Study Designs, Protocols, and Procedures

All studies were single center, un-blinded, non-randomized, retrospective or ambispective (initially retrospective but then converted to prospective methodology during the study period) in nature. Specified permission was obtained from patients (ante-mortem) or patients' families (post-mortem) for device donation for reuse. All studies clearly stated that written informed consent was obtained from recipients prior to device implantation or reimplantation with emphasis placed on the potential hazards unique to device reuse.

Every study described interrogation and reprogramming of donated devices. Interrogation was usually undertaken prior to resterilization to confirm software and hardware functionality and ensure adequate device longevity (stipulated by most as > 3 years or > 4 years). Devices subject to manufacturer recall or on advisory were excluded. Pacemakers were reprogrammed to "pacing off" or pacing with minimal voltage output. Defibrillators were programmed to not pace or pace with minimal voltage output and ventricular tachycardia/ventricular fibrillation detection and therapy, as well as auditory or vibratory alerts, were programmed "off". Programmable identifiable patient data (patient's name, physician, medical center, date of initial implant) was routinely erased prior to shipping.

The resterilization protocols employed in the studies reviewed were similar in approach. Initially, donated devices were inspected for signs of external damage and tested for lead port set screw malfunction precluding reuse. They were then cleaned with either pipe cleaners or soft tip brushes to remove debris from the surface and the lead ports. All but one study utilized 3% hydrogen peroxide and/or an alcohol solution (isopropyl alcohol or 70% ethanol) as a disinfectant. All but two studies made use of an additional biocidal measure (five used an enzymatic detergent, one used iodine, and one used benzalkonium chloride). As the final step, all study protocols packaged devices in gas permeable envelopes and utilized ethylene oxide gas sterilization. Three studies also indicated that ethylene oxide gas sterilization was repeated at 3 to 6 month intervals if the device remained unused in the interim.

The implantation of both new and reused devices was undertaken at the same medical center in the recipients' underserved country by an electrophysiologist, interventional cardiologist, or trained general cardiologist, for American College of Cardiology/American Heart Association/Heart Rhythm Society and/or European Society of Cardiology class I or class II guideline directed indications.[1,2] Peri-operative antibiotics were used with consistent application for both new and reused devices in all but one uncontrolled study where antibiotics were not employed.[20]

Pooled analysis

The nine studies of contemporary interest included 2 302 devices divided between 1 258 new devices and 1 044 reused devices (Table 1 and Table 2). Most devices were single or dual-chamber pacemakers (1 748), however, CRT-pacemakers (269), implantable cardioverter-defibrillators (202), and CRT-defibrillators (83) were also included. The baseline demographics (age, gender, and pacing indication) between the new device and reused device groups were similar. In the 2 071 devices with a specific clinical indication for pacing stipulated, the most common diagnosis was second or third degree AV block (61.8%) followed by sinus node dysfunction (20.6%) followed by requirement for cardiac resynchronization therapy (17.6%).

In the analysis of the pooled data (Table 3), the overall risk of the composite primary outcome was not significantly different in the new device population (2.2%) versus the reused device population (3.2%, p = 0.419). Tabulation of each of the sub-categorized secondary outcomes revealed no differences in the risks for device infection (1.8% new versus 1.7% reused), device malfunction (0.0% new versus 0.2% reused), and premature battery depletion (0.8% new versus 1.7% reused). Of note, there were no device related deaths reported.

Meta-analysis

We included data derived from the five controlled trials[23 – 27] totaling 2 114 devices in further analysis comparing the primary and secondary outcomes of patients with new devices (1 258) to reused devices (856). The median follow-up and interquartile range (IQR) was 2.2 years (1.0 – 2.8 years) for the new device group and 2.6 years (1.4 – 3.5 years) for the reused device group. The Egger's test for small study effects (*p* = 0.966) proved nonsignificant (not shown) while the funnel plot did not indicate publication bias (see Figure 3).

Primary Outcome

All five controlled trials were eligible for inclusion in the comparative assessment of the primary outcome (composite of device infection, device malfunction, premature battery depletion, and device related death). Meta-analysis revealed no significant difference in the primary outcome seen between the new device (control) group versus the reused device (study) group (2.23% versus 3.86%, P = 0.807, OR = 0.76 [95% CI: 0.45 to 1.28] see Figure 4).

Secondary Outcomes

Four trials totaling 1 988 devices were included in the assessment of infection risk comparing new devices (1 195) to reused devices (793) and no significant difference was seen (1.9% versus 2.3%, *p* = 0.785, OR = 1.09 [95% CI: 0.58 to 2.07] see Figure 5A). Two trials totaling 815 devices were included in the assessment of malfunction risk comparing new devices (409) to reused devices (406) with no significant difference shown (0.0% versus 0.5%, *p* = 0.319, OR = 0.32 [95% CI: 0.03 to 3.05] see Figure

5B). Three trials totaling 1 015 devices were included in the assessment of premature battery depletion risk comparing new devices (518) with a median follow-up of 3.8 years (IQR: 2.2 – 6.0 years) to reused devices (497) with a median follow-up of 3.5 years (IQR: 2.2 – 5.2 years), and again no significant difference was demonstrated (1.0% versus 2.6%, *p* = 0.084, OR = 0.43 [95% CI: 0.16 to 1.12]).

DISCUSSION

Unmet Global Health Need

There is an urgent need to pursue practical solutions to reduce the global burden of cardiovascular disease which is foremost of the chronic illnesses that have supplanted infectious diseases as the leading cause of death in most low and middle-income nations.[28] An estimated 1.7 million cardiac rhythm device implantations are undertaken worldwide each year.[4] However, it is conservatively estimated that more than 1 million patients who require such device therapy go without treatment annually.[4] Implanting physicians in underserved nations cite device expense as the single greatest barrier to device therapy in their regions.[5] This viewpoint is not surprising as the cost for a new pacemaker pulse generator (approximately $2,500 - $8,000 US dollars) or a new defibrillator generator (approximately $10,000 - $18,000 US dollars) by itself represents a prohibitive obstacle for most people in low and middle-income nations. By contrast, the reported estimated cost of collecting, interrogating, reprocessing, and distributing such devices is $75 - 100 US dollars per device, albeit this is contingent upon volunteer assistance at a variety of levels.[29 – 30] As a consequence, governmental authorities, hospital administrators, physicians, and their patients, in several underserved nations have proven receptive to assisting clinical studies examining the safety and efficacy of reusing devices, most of which were donated by those in high income nations in Europe and the USA where current laws prevent their reuse in humans.

Reuse Concerns & Regulatory Climate

Pacemaker reuse has been the subject of clinical study for more than forty years now. In fact, a prior systematic review and meta-analysis encompassing 18 studies (completed between 1974 – 2008) that included 5 controlled trials (completed between 1987 – 2001) demonstrated a generally favorable safety profile.[11] However, a five-fold increase in pacemaker malfunction (often related to problems with the set screw and grommet in the lead port or premature battery depletion) in reused pacemakers was observed in that analysis.[11] Additionally, larger and more complex cardiac rhythm management devices (defibrillators, CRT-pacemakers, and CRT-defibrillators) were not yet in common clinical practice and thus not included in reuse studies of that era. Importantly, there have been no subsequent alterations in the restrictive USA, Canadian, and European Union laws regulating what manufacturers label as "single use devices" nor medical professional societal recommendations to assist high income nations with such humanitarian efforts in low and middle-income nations.[31-33] This regulatory climate persists even though 87% of both device patients and device physicians surveyed in the United States are willing to donate their devices post-mortem to help indigent patients in other nations.[34,35] In fact, the majority of American device patients in the modern era die with pacemakers and defibrillators that are functional and have > 7 years battery longevity on average.[36] Unfortunately, such devices are much more likely to be discarded by funeral homes and crematoriums as "medical waste".[37] Consequently, the task of transforming our first world medical waste into life saving device therapy has to date fallen upon ad hoc medical volunteer initiatives and international charitable organizations such as Stimubanque (Paris, France), World Medical Relief (Detroit, USA), and Pace4Life (London, United Kingdom).

Contemporary Trials – New Lessons

Our systematic review and meta-analysis of recent controlled trials encompassed studies undertaken in seven distinct countries spanning four continents utilizing 2 302 devices (Figure 2). Despite prominent differences in medical personnel, health care environments, patients, cultural and geographic settings, they yielded similar results, and support the safety and efficacy of device reuse with regards to the composite primary outcome (overall risk < 4%) as well as each of the individual secondary outcomes of infection, malfunction, premature battery depletion, and device related death. Importantly, unlike the previous systematic review by Baman et al[11], the current analysis included studies in which more complex devices (CRT and implantable cardioverter-defibrillators) were used.[20,22,25,27] The consequences of defibrillator malfunction can extend beyond a lack of pacing if shock therapy is also required. In this regard, the four studies included did not reveal malfunction which would render defibrillators ineffective or harmful. We believe that the increased rate of device malfunction noted in the prior pooled analysis[11] has now abated due to the practice of inspection and testing of the hardware with particular scrutiny dedicated to ensuring the functionality of the set screws by reprocessing centers in addition to the adoption of improved lithium battery technologies by manufacturers.

Limitations

The main limitation in our systematic review and meta-analysis lies in our reliance upon data from unblinded, non-randomized, retrospective or ambispective, single center trials. Thusly, we readily acknowledge that retrospective studies predispose to selection bias. Due to the medico-legal constraints on devices currently labelled as "single use only", and the ethical requirement to inform patients of the possible hazards of device reuse, it is likely not feasible to undertake a double-blind multi-center randomized control trial of this nature in high income nations where device cost is not a barrier to receiving therapy. Accordingly, a concerted effort is underway to secure operational funding, donation of new leads, and the standardized clinical care necessary to pursue an adequately powered prospective multi-center randomized control trial in a handful of underserved nations.[30] If such a study confirms the non-inferiority of reused devices, securing large scale lead availability beyond that provided by charitable partners remains a limitation. New pacing and defibrillator leads (approximate cost $200 - $1,500 US dollars) remain a formidable expense for indigent patients and collaboration with industry may be required to fill this void.

Secondly, a handful of different device manufacturers were encompassed in the studies examined. Hence, it is possible that a set of studies with a markedly different distribution of manufacturers may have yielded different results with regards to the risks of device malfunction and/or premature battery depletion.

Finally, given the low adverse event rates seen overall in the studies pooled here (reflected in part by the wide confidence intervals reported), it is possible that a much larger analysis may, in fact, better detect small but significant differences that would otherwise be undiscernible.

CONCLUSIONS

Major technological advances in medical care provide new opportunities to benefit *all* patients that need such therapies. Contemporary device reuse utilizing modern protocols did not significantly increase risk of infection, malfunction, premature battery depletion or device related death in observational studies. It is our belief that this data helps provide the rationale for an adequately powered prospective multi-center non-inferiority randomized control trial of this financially inexpensive but clinically invaluable resource.

REFERENCES

1. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NAM 3rd, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2012; 61: e6-75.
2. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. The task force on cardiac pacing and resynchronization

therapy of the European Society of Cardiology (ESC). Developed in collaboration with European Heart Rhythm Association (EHRA). *Eur Heart J.* 2013; 34: 2281 – 2329.

3. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009 – a World Society of Arrhythmias' project. *Pacing Clin Electrophysiol.* 2011; 34: 1013 – 1027.

4. Mond HG, Mick W, Maniscalco BS. Heartbeat International: making "poor" hearts better. *Heart Rhythm.* 2009; 6: 1538 – 1540.

5. Hughey AB, Desai N, Baman TS, Gakenheimer L, Hagan L, Kirkpatrick JN, Oral H, Eagle KA, Crawford TC. Heart Rhythm Society members' views on pacemaker and implantable cardioverter-defibrillator reuse. *Pacing Clin Electrophysiol.* 2014; 37: 969 – 977.

6. Rosengarten M, Chiu R, Hoffman R. A prospective trial of new versus refurbished cardiac pacemakers: a Canadian experience. *Can J Cardiol.* 1989; 5: 155 – 160.

7. Panja M, Sarkar CN, Kumar S, Kar AK, Mitra S, Sinha DP, Chatterjee A, Roy S, Sarkar NC, Majumder B. Reuse of pacemaker. *Indian Heart J.* 1996; 48: 677 – 680.

8. Grendahl H. Pacemaker re-use. *Tidsskr Nor Leegeforen.* 1994; 114: 3420 – 3423.

9. Linde CL, Bocray A, Jonsson H, Rosenqvist M, Radegran K, Ryden L. Re-used pacemakers: as safe as new? A retrospective case-control study. *Eur Heart J.* 1998; 19: 154 - 157.

10. Pescariu S, Stiubel M, Cozma D, Ioanovici T, Branea H, Luca CT, Luca C, Dragulescu I. La réutilisation des pacemakers, une alternative pour les personnes âgées démunies: Etude rétrospective. *Stimcouer.* 2003; 31: 186 – 189.

11. Baman TS, Pascal M, Romero J, Gakenheimer L, Kirkpatrick JN, Sovitch P, Oral H, Eagle KA. Safety of pacemaker reuse: a meta-analysis with implications for underserved nations. *Circ Arrhythm Electrophysiol.* 2011; 4: 318 – 323.

12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283: 2008 – 2012.

13. DerSimonian R and Laird N. Meta-Analysis in Clinical Trials. *Controlled Clinical Trials.* 1986; 7: 177 – 188.

14. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med.* 2004; 23:1351 – 1375.

15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21: 1539 – 58.

16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997; 315: 629 – 634.

17. Duval S, Tweedie R. A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000; 56: 455 – 463.

18. Jiangbo D, Xuebin L, Ping Z, Long W, Ding L, Xianming C, Feng Z, Yong F, Cuizhen Y, Jihing G. Reuse of infected cardiac rhythm management devices in the same individual. *J Interv Card Electrophysiol.* 2012; 35: 109 – 114.

19. Baman TS, Romero A, Kirkpatrick JN, Romero J, Lange DC, Sison EO, Tangco RV, Abelardo NS, Samson G, Grezlik R, Goldman EB, Oral H, Eagle KA. Safety and efficacy of pacemaker reuse in underdeveloped nations: a case series. *J Am Coll Cardiol.* 2009; 54: 1557 – 1559.

20. Hasan R, Ghanbari H, Feldman D, Menesses D, Rivas D, Zakhem NC, Duarte C, Machado C. Safety, efficacy, and performance of implanted recycled cardiac rhythm management devices in underprivileged patients. *Pacing Clin Electrophysiol.* 2011; 34: 653 – 658.

21. Kantharia BK, Patel SS, Kulkarni G, Shah AN, Lokhandwala Y, Mascarenhas E, Mascarenhas DAN. Reuse of explanted permanent pacemakers donated by funeral homes. *Am J Cardiol.* 2012; 190: 238 – 240.

22. Pavri BB, Lokhandwala Y, Kulkarni GV, Shah M, Kantharia BK, Mascarenhas DAN. Reuse of explanted, resterilized implantable cardioverter-defibrillators: a cohort study. *Ann Intern Med.* 2012; 157: 542 – 548.

23. Nava S, Morales JL, Márquez MF, Barrera F, Gómez J, Colin L, Brugada J, Iturralde P. Reuse of pacemakers: comparison of short and long-term performance. *Circulation.* 2013; 127: 1177 – 1183.

24. Feng Z, Xuebin L, Ping Z, Haicheng Z, Long W, Ding L, Jiangbo D, Fei G, Cuizhen Y, Jihong G. Reuse of infected cardiac rhythm management devices in the same patients: a single center experience. *Pacing Clin Electrophysiol.* 2014; 37: 940 - 946.

25. Jama ZV, Chin A, Badri M, Mayosi BM. Performance of re-used pacemakers and implantable cardioverter defibrillators compared with new devices at Groote Schuur Hospital in Cape Town, South Africa. *Cardiovasc J Afr.* 2015; 26: 181 – 187.

26. Sosdean R, Mornos C, Enache B, Macarie RI, Ianos R, Stefea AM, Pescariu S. Safety and feasibility of biventricular devices reuse in general and elderly population – a single-center retrospective cohort study. *Clinical Interventions in Aging.* 2015; 10: 1311 – 1318.

27. Selvaraj RJ, Sakthivel R, Satheesh S, Pillai AA, Sagnol P, Jouven X, Dodinot B, Balachander J. Reuse of pacemakers, defibrillators, and cardiac resynchronization devices. *Heart Asia.* 2017; 9: 30 – 33.

28. Fuster V, Frazer J, Snair M, Vedanthan R, Dzau V, et al. The future role of the United States in global health: emphasis on cardiovascular disease. *J Am Coll Cardiol.* 2017; 70: 3140 – 3156.

29. Crawford TC, Allmendinger C, Snell J, Weatherwax K, Lavan B, Baman TS, et al. Cleaning and sterilization of used cardiac implantable electronic devices with process validation. *J Am Coll Cardiol EP.* 2017; 3: 623 – 631.

30. Runge MW, Baman TS, Davis S, Weatherwax K, Goldman E, Eagle KA, Crawford TC. Pacemaker recycling: A notion whose time has come. *World J of Cardiol.* 2017; 9: 296 – 303.

31. Vlay SC. Recycling pacemakers and defibrillators: a humanitarian cause – is it feasible? *Heart Rhythm.* 2016; 13: 1977 – 1978.

32. Kirkpatrick JN, Papini C, Baman TS, Kota K, Eagle KA, Verdino RJ, et al. Reuse of pacemakers and defibrillators in developing countries: logistical, legal, and ethical barriers and solutions. *Heart Rhythm.* 2010; 7: 1623 – 1627.

33. Baman TS, Kirkpatrick JN, Romero J, Gakenheimer L, Romero A, Lange DC, et al. Pacemaker reuse: an initiative to alleviate the burden of symptomatic bradyarrhythmia in impoverished nations around the world. *Circulation.* 2010; 122: 1649 – 1656.

34. Gakenheimer L, Lange DC, Romero J, Kirkpatrick JN, Sovitch P, Oral H, et al. Societal views of pacemaker reutilization for those with untreated symptomatic bradycardia in underserved nations. *J Interv Card Electrophysiol.* 2011; 30: 261 – 266.

35. Hughey AB, Desai N, Baman TS, Gakenheimer L, Hagan L, Kirkpatrick JN, et al. Heart Rhythm Society members' views on pacemaker and implantable cardioverter-defibrillator reuse. *Pacing Clin Electrophysiol.* 2014; 37: 969 – 977.

36. Sinha SK, Crain B, Flickinger K, Calkins H, Rickard J, Cheng A, et al. Cardiovascular implantable electronic device function and longevity at autopsy: an underestimated resource. *Heart Rhythm.* 2016; 13: 1971 – 1976.

37. Kirkpatrick JN, Ghani SN, Burke MC, Knight BP. Post-mortem interrogation and retrieval of implantable pacemakers and defibrillators: a survey of morticians and patients. *J Cardiovasc Electrophysiol.* 2007; 18: 478 – 482.

FIGURE AND TABLE LEGENDS

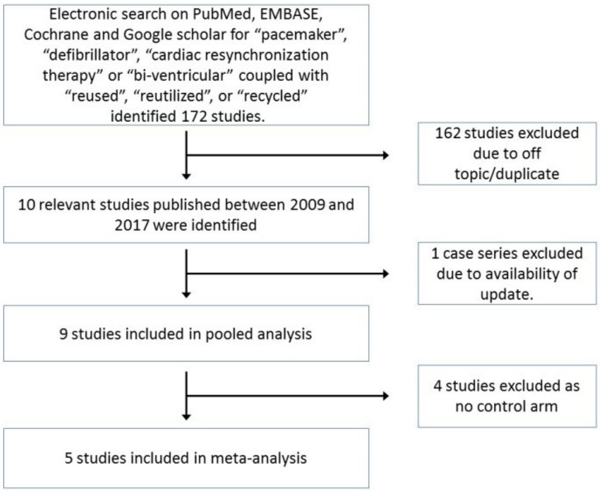

Figure 1. Flow Diagram of Studies Selected for Pooled Analysis and Meta-Analysis

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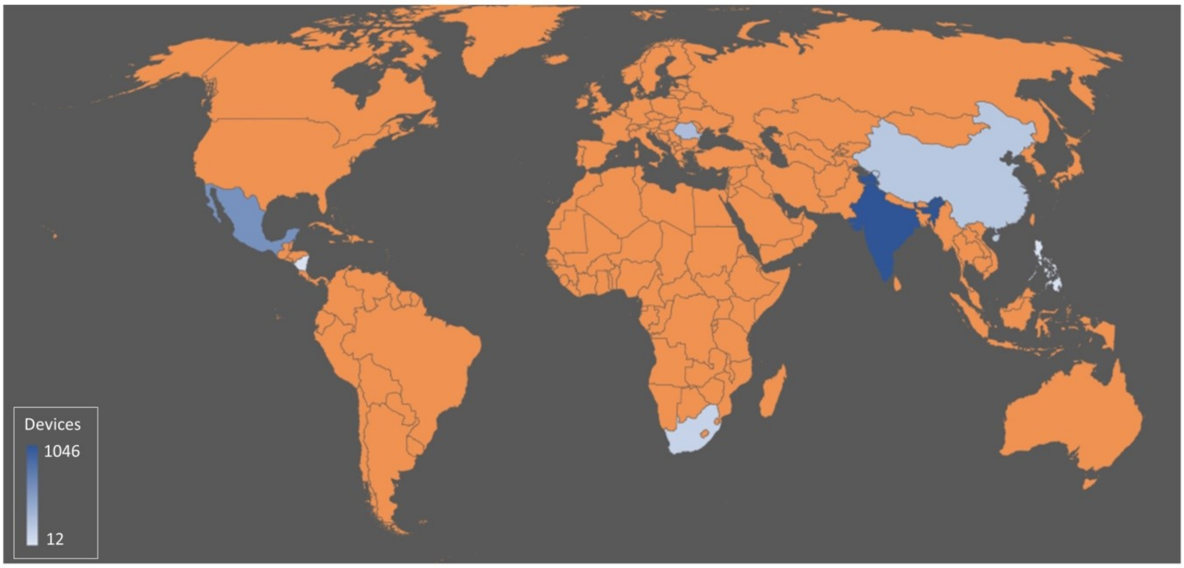

Figure 2. Contemporary Pacemaker, Defibrillator, and CRT Reuse: World Wide Map of Nations Included in Systematic Review

Figure 2. World Wide Map of Nations Participating in Contemporary Trials of Device Reuse: Nine clinical trials totaling 2 302 devices examined the safety & efficacy of device reuse in seven nations from 2000 to 2015. The blue color scale correlates with the total device volume in each nation.

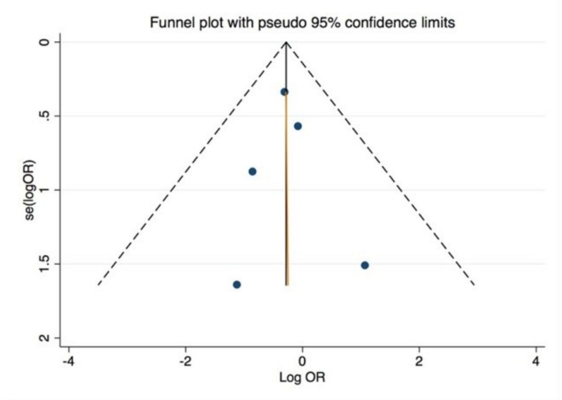

Figure 3. Funnel Plot for Publication Bias.

Figure 3. Funnel Plot for Publication Bias. This graphic plot indicates no significant publication bias in the five trials included in the meta-analysis of the primary outcome.

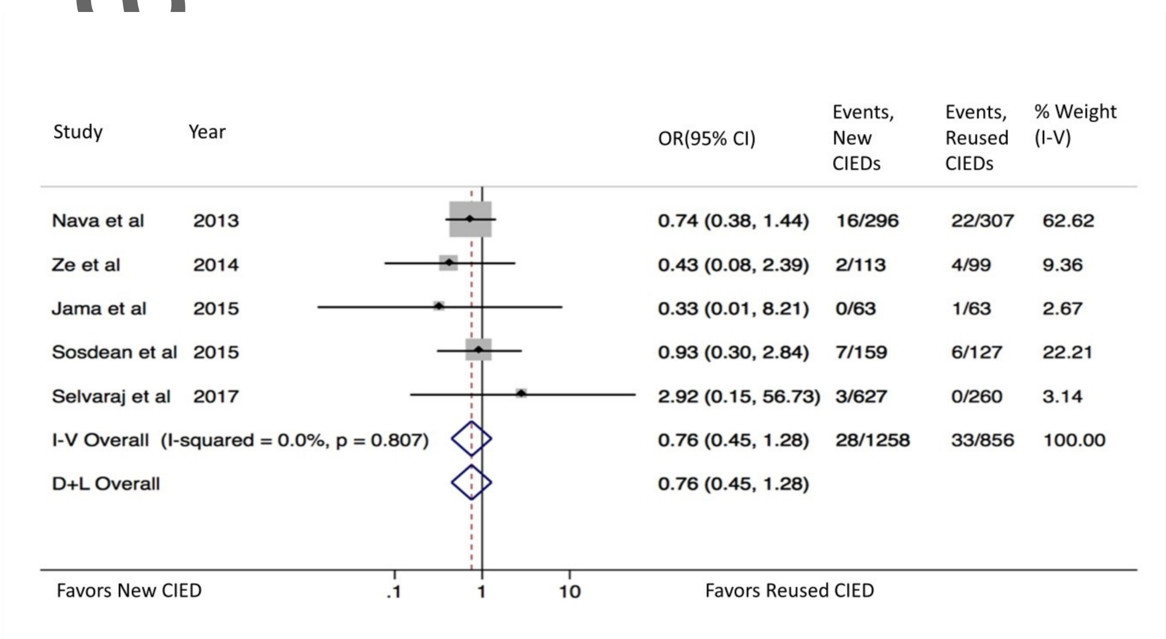

Figure 4. Forest Plot of Primary Outcomes in Trials of Reused Devices versus New Devices

Figure 4. Forest Plot of Primary Outcome in Trials of New Devices versus Reused Devices: The primary outcome was the composite risk of device infection, device malfunction, premature battery depletion, and device related death.

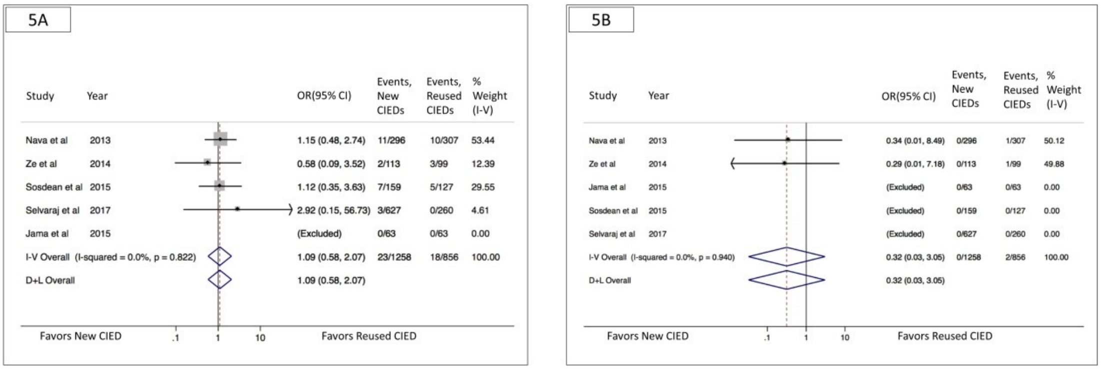

Figure 5: Forest Plots of Secondary Outcomes in Trials of Reused Devices versus New Devices.
5A - Risk of infection. 5B- Device malfunction.

Figures 5A & 5B. Forest Plots of Secondary Outcomes in Trials of New Devices versus Reused Devices: A) Risk of device infection, B) Risk of device malfunction.

Table 1: Characteristics of Recent Uncontrolled & Controlled Trials

Study	Study Country	Publication Year	Donation Type	Study Period	Reused Devices	New Devices
Baman et al	Philippines	2009	Post-mortem	2008	12	-
Hasan et al	Nicaragua	2011	Ante-mortem	2003 - 2011	17	-
Kantharia et al	India	2012	Post-mortem	2004 - 2012	53	-
Pavri et al	India	2012	Ante/Post-mortem	2002 - 2011	106	-
Nava et al	Mexico	2013	Post-mortem	2000 - 2010	307	296
Feng et al	China	2014	Ante-mortem†	2007 - 2012	99	113
Jama et al	South Africa	2015	Post-mortem	2003 - 2013	63	63
Sosdean et al	Romania	2015	Ante/Post-mortem	2000 - 2014	127	159

Selvaraj et al	India	2017	Ante/Post-mortem	2010 - 2015	260	627
Total Devices (Pacemaker, Defibrillator, CRT-D or CRT-P) in Trials: 2302					**1044**	**1258**

Table 1: Characteristics of Recent Uncontrolled & Controlled Trials: Nine clinical studies published between 2009 – 2017 were included in analysis. CRT-D: cardiac resynchronization therapy – defibrillator, CRT-P: cardiac resynchronization therapy - pacemaker, †99 subjects undergoing explantation consented to reuse of the same device for re-implantation.

Table 2: Baseline Demographics of Recent Trial Subjects in Analysis

Study	**Mean Age ± SD (Years)**		**Male Number (%)**		***Primary Pacing Indications: AV Block (%)/Sinus Node Dysfunction (%)/ CRT (%)**	
	Reused	***New***	***Reused***	***New***	***Reused (900)***	***New (1171)***
Baman et al	62.0 ± 10.0	-	6 (50.0)	-	10/2/0	-
Hasan et al	42.1 ± 20.3	-	9 (52.9)	-	8/3/1	-
Kantharia et al	64.0 ± 10.0	-	25 (47.2)	-	27/26/0	-
Pavri et al	52.6 ± 13.8	-	88 (83.0)	-	0/0/15	-
Nava et al	59.9 ± 20.6	60.4 ±19.1	158 (51.5)	158 (53.4)	236/65/0	204/82/0
Feng et al	63.7 ± 15.0	65.0 ± 14.3	62 (62.6)	84 (74.3)	48/44/5	62/42/7
Jama et al	69.7 ± 17.3	68.6 ± 16.4	34 (54.0)	34 (54.0)	38/9/0	43/4/0
Sosdean et al	61.7 ± 10.1	61.0 ± 9.4	19 (15.0)	25 (15.7)	0/0/127	0/0/159
Selvaraj et al	62.3 ± 12.9	54. 7 ± 17.1	108 (48)	272 (50.8)	193/31/12	411/119/38
Mean or Total	**60.5**	**58.5**	**509 (48.8)**	**573 (45.6)**	**560 (62.2)/180 (20.0)/ 160 (17.8)**	**720 (61.5)/247 (21.1)/ 204 (17.4)**

Table 2: Baseline Demographics of Recent Trial Subjects in Analysis: Mean age, male proportion, and primary pacing indications in each study. *Patients with unspecified or less common pacing indication or with defibrillator indication without primary pacing indication not included. CRT: cardiac resynchronization therapy.

Table 3: Primary & Secondary Outcomes of Recent Uncontrolled & Controlled Trials

Study	Primary Composite Outcome (%)		Infection (%)		Malfunction (%)		Early Depletion (%)	
	Reused (1044)	*New (1258)*	*Reused*	*New*	*Reused*	*New*	*Reused*	*New*
Baman et al	0	-	0	-	0	-	N/A	-
Hasan et al	0	-	0	-	0	-	0	-
Kantharia et al	0	-	0	-	0	-	0	-
Pavri et al	0	-	0	-	0	-	0	-
Nava et al	22	16	10	11	1	0	11	5
Feng et al	4	2	3	2	1	0	0	0
Jama et al	1	0	0	0	0	0	1	0
Sosdean et al	6	7	5	7	0	0	1	0
Selvaraj et al	0	3	0	3	0	0	N/A	N/A
Total (%)	**33 (3.16)**	**28 (2.23)**	**18 (1.72)**	**23 (1.83)**	**2 (0.19)**	**0 (0)**	**13 (1.66)**	**5 (0.79)**

Table 3: Primary and Secondary Outcomes in Recent Uncontrolled & Controlled Trials: The primary outcome the composite risk of device infection, device malfunction, and premature battery depletion. No device related deaths were reported. N/A – data outcome was non-applicable as follow-up duration (limited to 2 – 6 months) was deemed inadequate to evaluate for premature battery depletion.