

Worldwide pacemaker and defibrillator reuse: Systematic review and meta-analysis of contemporary trials

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Disclosures: The authors have nothing to disclose regarding this study.

Funding Source

We would like to acknowledge support for the statistical analysis from the National Center for Research Resources and the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (Grant Number 1UL1TR001079).

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 vs 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% vs 3.86% respectively, $P = 0.807$, odds ratio = 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. These data provide rationale for proceeding with a prospective multicenter noninferiority randomized control trial.

KEYWORDS

cardiac resynchronization therapy recycling, cardiac resynchronization therapy reuse, defibrillator recycling, defibrillator reuse, pacemaker recycling, pacemaker reuse

1 | 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.

2 | METHODS

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

2.1 | Search strategy

Two study investigators (B.S., S.K.S.) independently searched the medical literature to identify all relevant device studies from January 1, 2008 until December 31, 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.

2.2 | 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 (B.S., S.K.S.) 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).

2.3 | 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 underdetecting 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.

2.4 | 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 interquartile (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% CIs are shown within brackets. All tests were two-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, USA).

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.

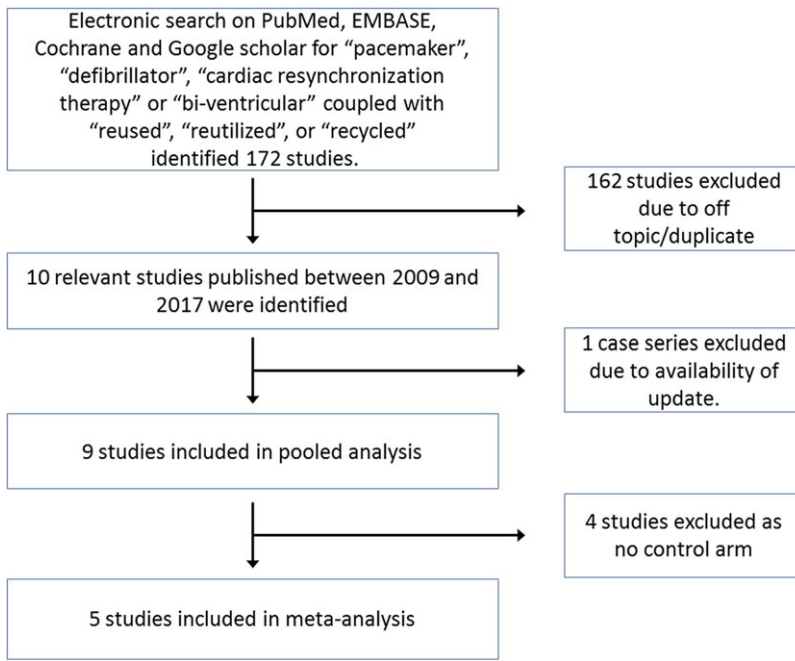


FIGURE 1 Flow diagram of studies selected for pooled analysis and meta-analysis [Color figure can be viewed at wileyonlinelibrary.com]

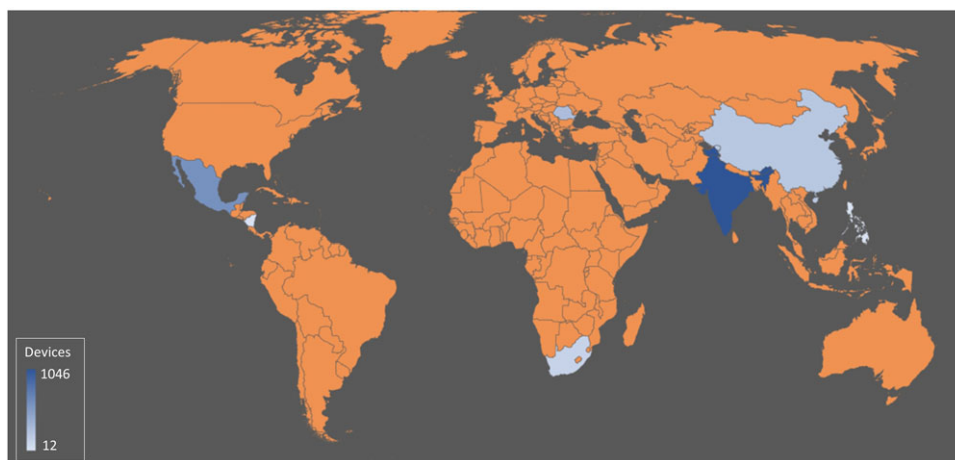


FIGURE 2 Worldwide map of nations participating in contemporary trials of device reuse. Nine clinical trials totaling 2,302 devices examined the safety and efficacy of device reuse in seven nations from 2000 to 2015. The blue color scale correlates with the total device volume in each nation [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of recent uncontrolled and controlled trials

Study	Study country	Publication year	Donation type	Study period	Reused devices	New devices
Baman et al.	Philippines	2009	Postmortem	2008	12	-
Hasan et al.	Nicaragua	2011	Antemortem	2003–2011	17	-
Kantharia et al.	India	2012	Postmortem	2004–2012	53	-
Pavri et al.	India	2012	Ante/Postmortem	2002–2011	106	-
Nava et al.	Mexico	2013	Postmortem	2000–2010	307	296
Feng et al.	China	2014	Antemortem [†]	2007–2012	99	113
Jama et al.	South Africa	2015	Postmortem	2003–2013	63	63
Sosdean et al.	Romania	2015	Ante/Postmortem	2000–2014	127	159
Selvaraj et al.	India	2017	Ante/Postmortem	2010–2015	260	627
Total devices (pacemaker, defibrillator, CRT-D, or CRT-P) in trials: 2,302					1,044	1,258

Note: Nine clinical studies published between 2009 and 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 reimplantation.

TABLE 2 Baseline demographics of recent trial subjects in analysis

Study	Mean age \pm SD (years)		Male number (%)		*Primary pacing indications: AV block (%)/sinus node dysfunction (%)/CRT (%)	
	Reused	New	Reused	New	Reused (900)	New (1,171)
Baman et al.	62.0 \pm 10.0	-	6 (50.0)	-	10/2/0	-
Hasan et al.	42.1 \pm 20.3	-	9 (52.9)	-	8/3/1	-
Kantharia et al.	64.0 \pm 10.0	-	25 (47.2)	-	27/26/0	-
Pavri et al.	52.6 \pm 13.8	-	88 (83.0)	-	0/0/15	-
Nava et al.	59.9 \pm 20.6	60.4 \pm 19.1	158 (51.5)	158 (53.4)	236/65/0	204/82/0
Feng et al.	63.7 \pm 15.0	65.0 \pm 14.3	62 (62.6)	84 (74.3)	48/44/5	62/42/7
Jama et al.	69.7 \pm 17.3	68.6 \pm 16.4	34 (54.0)	34 (54.0)	38/9/0	43/4/0
Sosdean et al.	61.7 \pm 10.1	61.0 \pm 9.4	19 (15.0)	25 (15.7)	0/0/127	0/0/159
Selvaraj et al.	62.3 \pm 12.9	54.7 \pm 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)

Note: 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. AV = atrioventricular; CRT = cardiac resynchronization therapy; SD = standard deviation.

3 | RESULTS

3.1 | Study selection and study patients

An online 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 series¹⁸ due to duplication of data in a larger subsequent trial publication,²⁴ leaving nine 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).

3.2 | Study designs, protocols, and procedures

All studies were single-center, unblinded, nonrandomized, 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 (postmortem) 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} Perioperative antibiotics were used with consistent application for both new and reused devices in all but one uncontrolled study where antibiotics were not employed.²⁰

3.3 | Pooled analysis

The nine studies of contemporary interest included 2,302 devices divided between 1,258 new devices and 1,044 reused devices (Tables 1 and 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 atrioventricular

TABLE 3 Primary and secondary outcomes in recent uncontrolled and controlled trials

Study	Primary composite outcome (%)		Infection (%)		Malfunction (%)		Early depletion (%)	
	Reused (1,044)	New (1,258)	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)

Note: 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.

block (61.8%) followed by sinus node dysfunction (20.6%) followed by requirement for CRT (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 vs 1.7% reused), device malfunction (0.0% new vs 0.2% reused), and premature battery depletion (0.8% new vs 1.7% reused). Of note, there were no device-related deaths reported.

3.4 | 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 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 non-significant (not shown) while the funnel plot did not indicate publication bias (see Figure 3).

3.5 | 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% vs 3.86%, $P = 0.807$, OR = 0.76 [95% CI: 0.45–1.28]; see Figure 4).

3.6 | Secondary outcomes

Four trials totaling 1,988 devices were included in the assessment of infection risk comparing new devices (1,195) to reused devices

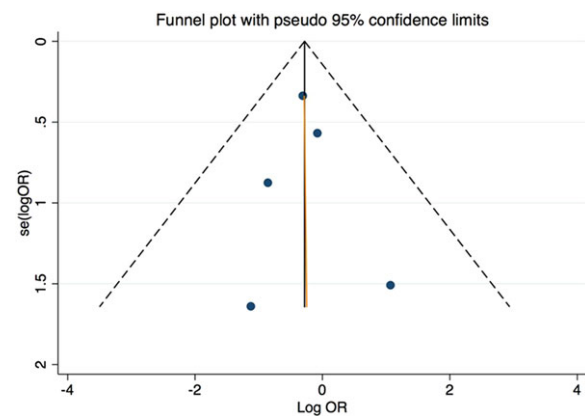


FIGURE 3 Funnel plot for publication bias. This graphic plot indicates no significant publication bias in the five trials included in the meta-analysis of the primary outcome [Color figure can be viewed at wileyonlinelibrary.com]

(793) and no significant difference was seen (1.9% vs 2.3%, $P = 0.785$, OR = 1.09 [95% CI: 0.58–2.07], 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% vs 0.5%, $P = 0.319$, OR = 0.32 [95% CI: 0.03–3.05]; 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% vs 2.6%, $P = 0.084$, OR = 0.43 [95% CI: 0.16–1.12]).

4 | DISCUSSION

4.1 | 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

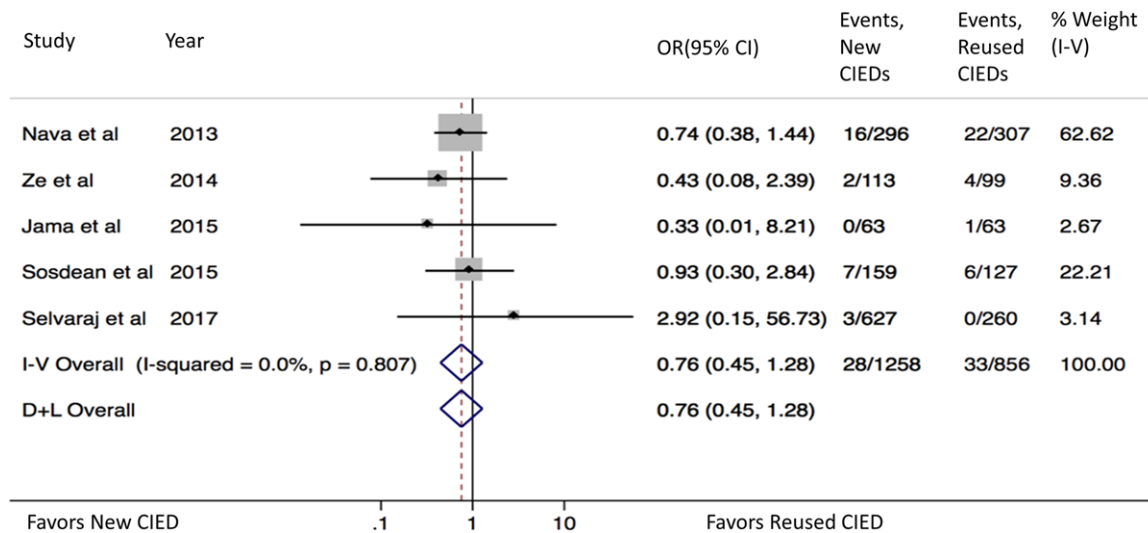


FIGURE 4 Forest plot of primary outcome in trials of new devices versus reused devices: The primary outcome was the composite risk of device infection, device malfunction, premature battery depletion, and device-related death [Color figure can be viewed at wileyonlinelibrary.com]

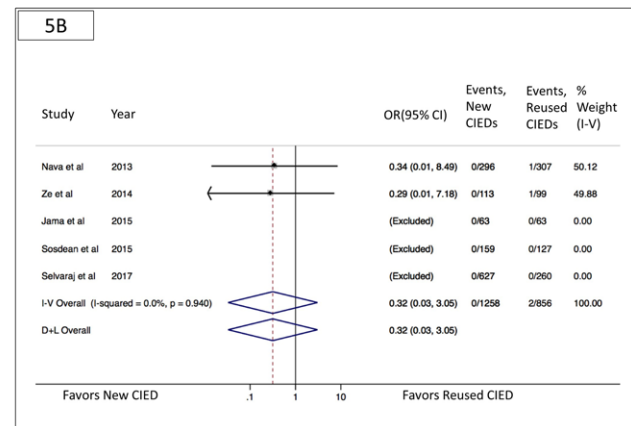
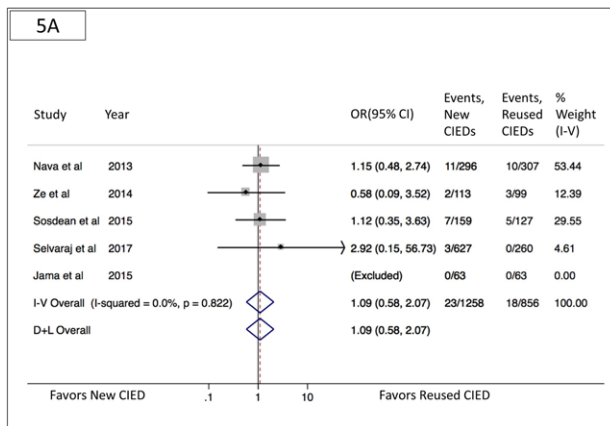


FIGURE 5 (A and B) Forest plots of secondary outcomes in trials of new devices versus reused devices: (A) Risk of device infection, and (B) risk of device malfunction [Color figure can be viewed at wileyonlinelibrary.com]

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.

4.2 | Reuse concerns and regulatory climate

Pacemaker reuse has been the subject of clinical study for more than 40 years now. In fact, a prior systematic review and meta-analysis encompassing 18 studies (completed between 1974 and 2008) that included five controlled trials (completed between 1987 and 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 postmortem to help indigent patients in other nations.^{5,34} 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.³⁵ Unfortunately, such devices are much more likely to be discarded by funeral homes and crematoriums as “medical waste.”³⁶ 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, MI, USA), and Pace4Life (London, United Kingdom).

4.3 | 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 analysis¹¹ 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.

4.4 | Limitations

The main limitation in our systematic review and meta-analysis lies in our reliance upon data from unblinded, nonrandomized, retrospective or ambispective, single-center trials. Thus, we readily acknowledge that retrospective studies predispose to selection bias. Due to the medico-legal constraints on devices currently labeled 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 multicenter 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 multicenter randomized control trial in a handful of underserved nations.³⁰

If such a study confirms the noninferiority 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.

Second, 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.

5 | CONCLUSIONS

Major technological advances in medical care provide new opportunities to benefit all patients who 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 these data help provide the rationale for an adequately powered prospective multicenter noninferiority randomized control trial of this financially inexpensive but clinically invaluable resource.

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How to cite this article: Sinha SK, Sivasambu B, Yenokyan G, et al. Worldwide pacemaker and defibrillator reuse: Systematic review and meta-analysis of contemporary trials. *Pacing Clin Electrophysiol.* 2018;41:1500–1507. <https://doi.org/10.1111/pace.13488>