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Methodological and Evidence Synthesis Quality Evaluation of Meta-Analyses Assessing the Effect of Antibacterial Envelopes to Reduce CIED-Related Infections

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ABSTRACT

Purpose: *Antibacterial envelopes have been demonstrated to be therapeutically helpful in patients with Cardiac Implantable Electronic Devices (CIEDs). We examined the methodological and evidence synthesis quality of meta-analyses evaluating the effect of envelopes to reduce CIED infections.* ***Methods:*** *Full-text English systematic reviews published in peer-reviewed journals that described meta-analyses of the therapeutic efficacy of envelope on CIED-related infection were explored. A complete literature search was conducted from conception to September 27, 2021, using the electronic databases PubMed, Scopus, and Web of Science. On the 2nd of January 2022, the search was updated. Two reviewers independently screened the titles/abstracts and full-texts and extracted the data. The methodological quality of the included studies was assessed using the AMSTAR-2 tool. The GRADE technique was used to evaluate the quality of evidence synthesis.* ***Results:*** *Six reviews with a total of 15 outcomes were included. All of the reviews had a critically low methodological quality. Nine (60%) and six (40%) outcomes had low and moderate-quality evidence synthesis, respectively. Regarding the GRADE criteria, all outcomes were at risk of bias (n=15, 100%), followed by inconsistency (n=12, 80%), and publication bias (n=10, 67%). Researchers in the field should use the AMSTAR-2 scale and GRADE to perform high-quality studies in the future.* ***Conclusion:*** *To our knowledge, the current study is the first to analyze the methodological and evidence quality of systematic reviews providing meta-analyses on the effect of antibacterial envelopes on CIED-related infections. This is to help physicians, policymakers, and researchers to make better therapeutic decisions by revealing the methodological and evidence synthesis quality of systematic reviews.*

Keywords: Cardiac implantable electronic device, Methodological quality, Certainty of evidence, AMSTAR-2, GRADE, CIED

INTRODUCTION

Infection is one of the most common side effects of treatment with Cardiovascular Implantable Electronic Devices (CIED), and it's associated with a high mortality rate and substantial healthcare costs [1-4]. Cardiac implantables are approaches and treatments available to people at risk of life-threatening ventricular arrhythmias, and their efficacy and effectiveness have been demonstrated in several randomized controlled trials [5-12]. According to current statistics, an estimated 1.5 million persons worldwide receive cardiac implantables each year, according to recent statistics [13]. Despite this, infection is one of the most common reasons for implantation failure [14].

Despite the effectiveness of systemic antibiotics in reducing infections caused by implanted electronic devices,

infection is widespread, and the frequency of infections is continuously increasing to alarming levels [11,15-19]. According to a consensus paper published by the European Heart Rhythm Association (EHRA) in 2020, the risk of implantable electronic heart device infection is of particular concern because it is linked to significant morbidity, increased hospitalizations, lower survival, and higher healthcare costs [20]. According to the findings of a study, the average cost of treating a patient with severe CIED-related infection is over $50,000, with an average hospital stay of 13 days [21]. According to reports, infection rates may increase faster than the implantation rate [17,18]. As a result, novel infection-prevention measures could help to improve the outcome of implantation therapy.

As previously indicated, preventative measures appear crucial, given the high cost of implanted electronic device-related infections to healthcare systems [22]. The Food and Drug Administration (FDA) approved the use of an Antibacterial Envelope (AE) to decrease the risk of infection during device installation to address these concerns [13]. Thanks to technological developments, this has been replaced by a single-use absorbable sheath [13]. Even though multiple meta-analyses have found antibacterial envelopes therapeutically effective in CIED patients, large-scale research to examine the validity of the current evidence synthesis is still needed [23-27]. We studied systematic reviews comparing the use of an antibacterial envelope in patients undergoing electronic device implantation to assess the quality of the evidence on the efficacy of an antibacterial envelope in preventing CIED-related infections. Systematic flaws or deficiencies in the design or conduct of articles in the field may mislead the findings. As a result, the methodology and evidence synthesis quality assessments should help improve evidence-based therapeutic management of infections caused by implantation.

One of the tools created to assess the quality of evidence is the GRADE which has universal validity and acceptance acknowledged by the World Health Organization (WHO) and recommended in the Cochrane Handbook [28]. Evidence quality is divided into four categories by the GRADE system: high, moderate, low, and very low. While more studies are unlikely to affect our confidence in the effect estimate if the quality is high, we have very little confidence in the effect estimate if the quality is low [29]. As a result, this study aims to assess the overall quality of evidence derived from systematic reviews that provide a quantitative synthesis of the impact of an antibacterial envelope on CIED-related infection versus alternative therapies that do not use an antibacterial envelope. The current study provides a thorough assessment of the existing evidence on the effects of AE-based treatments in CIED patients.

MATERIALS AND METHODS

Eligibility Criteria

English systematic reviews in the original full text published in peer-reviewed journals describing meta-analyses of the clinical effect of AE on CIED-related infection in human populations of both genders and any age group compared to other comparators without AE. This research did not include any animal-based studies. We did not confine our analysis to a particular period, clinical environment, or geographic location.

Search Strategy

We conducted a complete literature search from conception to September 27, 2021, using the electronic databases PubMed, Scopus, and Web of Science. On the 2nd of January 2022, we also updated our search. The final qualifying studies' reference lists were also reviewed to see any additional potentially relevant studies. For further information on the search techniques used in each database, see Table 1.

Table 1 Search strategies

N	Searched database	Applied search formula
1	PubMed	(((((("antibacterial Envelope"[Title/Abstract] OR "antibiotic envelope"[Title/Abstract] OR "antimicrobial envelope"[Title/Abstract]) OR (defibrillator[Title/Abstract] AND infection[Title/Abstract] AND envelope[Title/Abstract])) OR (ICD[Title/Abstract] AND infection[Title/Abstract] AND envelope[Title/Abstract])) OR (ICDs[Title/Abstract] AND infection[Title/Abstract] AND envelope[Title/Abstract])) OR (CIED[Title/Abstract] AND infection[Title/Abstract] AND envelope[Title/Abstract])) OR ("cardiac implantable electronic device"[Title/Abstract] AND infection[Title/Abstract] AND envelope[Title/Abstract])

2	Scopus	(TITLE-ABS-KEY ("antibacterial envelope" OR "antimicrobial envelope" OR "antibiotic envelope") OR TITLE-ABS-KEY (defibrillator AND infection AND envelope) OR TITLE-ABS-KEY (ICD AND infection AND envelope) OR TITLE-ABS-KEY (ICDs AND infection AND envelope) OR TITLE-ABS-KEY (CIED AND infection AND envelope) OR TITLE-ABS-KEY ("cardiac implantable electronic device" AND infection AND envelope))
3	Web of science	"Antibacterial Envelope" OR "antibiotic envelope" OR "antimicrobial envelope" (Topic) or defibrillator AND infection AND envelope (Topic)
		or ICD AND infection AND envelope (Topic)
		or ICDs AND infection AND envelope (Topic)
		or CIED AND infection AND envelope (Topic)
		or “cardiac implantable electronic device” AND infection AND envelope (Topic)

Study Selection

The documents found during the searches were organized and entered into the Microsoft Excel program. DOI numbers were used to identify duplicates. The titles were utilized to identify duplication without a DOI number. Two reviewers separately evaluated the titles and abstracts of included articles based on the following criteria: Is this a study based on a systematic review? (yes/unsure, no) Is it an antibacterial envelope-based study (yes/unsure, no)? Studies with yes/unsure answers were eligible for the next round of the screening process (full-text screening). The reviewers then evaluated the studies using the following factors: Is this a study in English? (Yes, no) Is this a human study? (Yes, no) Is it a meta-analysis (yes, no)? Does the study explore the effect of the envelope on CIED infections? (Yes, or no.). We could find qualified systematic reviews by limiting “Yes” to all questions. Reviewers discussed disagreements throughout both titles/abstract and full-text screening to achieve a consensus. The PRISMA flowchart illustrates the screening findings and the selection of eligible research. Two reviewers worked individually to obtain data from the qualifying studies [30].

Data Items

In terms of data extraction, the following variables were collected by the reviewers from the studies: Year of publication, authors’ names, first author’s country using the ISO 3166-1 code, population, intervention, comparator, outcome, the total number of populations in each outcome, effect size, and confidence intervals.

The Methodological Quality of Systematic Reviews

Two reviewers independently assessed the quality of the eligible systematic reviews using the AMSTAR-2 instrument, which consists of 16 questions with answers of yes, partially yes, or no [31]. Disagreements in the ratings of the 16 items on the AMSTAR-2 checklist were addressed through debate and consensus. We utilized the following methodology to report the review’s methodological quality: 1 point for questions with a yes response, 0.5 points for questions with a partial yes answer, and 0 points for questions with a no answer.

Assessment of the Quality of Evidence

As previously stated, two reviewers independently assessed the quality of evidence for each outcome in meta-analyses using the GRADE tool, which evaluates the quality of synthesis of each outcome based on five domains: 1) risk of bias, 2) inconsistency, 3) imprecision, 4) publication bias, and 5) indirectness. The GRADE tool recommends 0, 1, or 2 downgrades depending on the severity of each domain. As a result, we used the techniques listed below [29]:

Concerning the risk of bias, if at least 75% of the included studies had a low risk of bias for each outcome, we did not assign any downgrade. Conversely, we set one downgrade to the outcome. We gave one downgrade if the risk of bias score was not reported in the reviews. When it comes to inconsistency, we considered the reported heterogeneity (I^2) for each outcome. Accordingly, we assigned one downgrade if the calculated heterogeneity was reported to be at least 50% for each outcome, as according to the Cochrane handbook, the heterogeneity more than 50% may represent substantial heterogeneity [28]. Otherwise, we did not consider any downgrades. We also assigned one downgrade if no heterogeneity was reported [32]. We did not give a downgrade to any outcome if the pooled sample size was more than 2000 in line with imprecision, as recommended by the GRADE Handbook [29]. We assigned one downgrade if the pooled sample size was less than 200 [32]. Optimal information size was calculated when pooled sample sizes

were between 200 and 2000. We gave one downgrading if the calculated optimal information size was more than the pooled sample size of the outcome [33]. Otherwise, there was no consideration for a downgrading. Stata software 16 and Power calculation were used to calculate optimal information size.

There is publication bias in a pooled estimate when only some of the publications that may be included are entered in the analysis. A bias in the meta-analysis may be shown visually using a funnel plot. Consequently, the funnel plot may not adequately identify publication bias and may lead to incorrect findings [34-37]. As a result, we used the trim-and-fill approach of Duval and Tweedie to investigate publication bias [38]. The pooled effect size is calculated using the results of the imputed studies. We degrade the outcome if the imputation of the possibly missing study alters the meta-analysis results [39]. If there were discrepancies between included studies in terms of intervention, population, or comparator, we considered 1 or 2 downgrades, depending on the severity of the differences, to measure indirectness in each outcome. No downgrading was considered if the included studies were compatible with the review questions in each outcome and were coherent in terms of population, intervention, or comparator [36]. Finally, we graded the quality of every piece of evidence on a four-point scale: 0 downgrade equals high quality, 1-2 downgrades equal moderate quality. 3-4 and 5-6 downgrades also equal low and very low quality of evidence synthesis [32].

RESULTS

Literature Search

In PubMed, Scopus, and the Web of Science, we found 60, 77, and 105 documents, respectively. After removing duplicates, one hundred twenty-three studies were suitable for title/abstract screening. Five studies were eliminated because they did not focus on an antibacterial envelope, and 91 records were excluded because they were not systematic reviews. As a result, 32 studies were selected for full-text screening. Six systematic reviews that reported a meta-analysis of the impact of an antibacterial envelope as an intervention on CIED infection outcomes vs. non-antibacterial envelope fulfilled the inclusion criteria and were included in the final analysis. After checking the reference lists of the qualifying research, no further studies were discovered to be eligible (Figure 1).

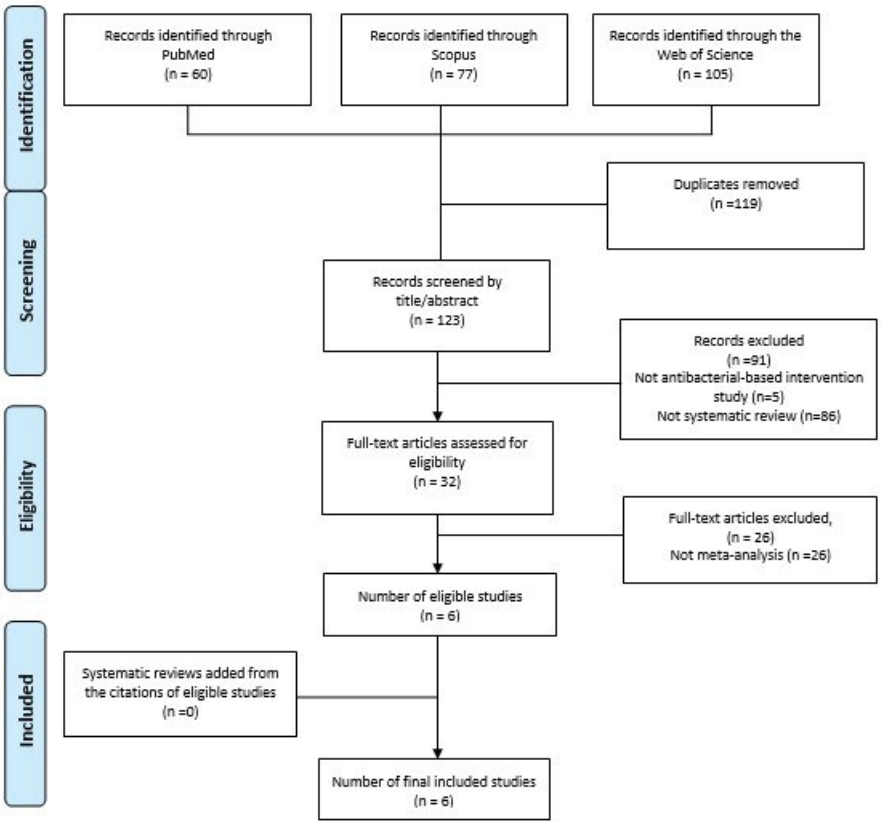

Figure 1 PRISMA flowchart of study selection

Characteristics of the Included Systematic Reviews

Six systematic reviews published in 2017, 2018, 2019, and 2020 in the United States of America, India, and Indonesia satisfied the inclusion criteria, providing meta-analyses evaluating the influence of AE on CIED infections. There were 35 primary studies in all that were included in the reviews (Table 2) [23-27,40].

Table 2 Characteristics of the included systematic reviews

References	Country	Population	Intervention	Comparator	Outcome(s)	Conclusion Summary
[23]	United States of America	Patients with CIED	Antibacterial envelope	Matched controls	CIED infections	The use of an antibiotic envelope at the time of device installation or update helps to prevent severe CIED infections, especially in individuals who are thought to be at higher risk.
[27]	United States of America	High-risk patients with CIED	Antibacterial envelope	Control group	Major CIED infections	AE-CIED may reduce the likelihood of CIED infections in high-risk individuals.
[25]	India	Patients with CIED	Antibiotic envelope	standard infection prevention strategies	Major and/or minor CIED infections	Antibiotic envelopes are used prophylactically as an adjuvant treatment to normal infection prevention methods to help reduce the incidence of CIED infections.
[26]	Indonesia	CIED	Antibiotic envelope	Control group	CIED major infections	Antibiotic envelope (TYRX) has been proven to be safe and effective in decreasing the incidence of severe infections in high-risk patients undergoing CIED implantation, particularly in those undergoing high-power CIED implantation.
[24]	United States of America	CIED patients	Antibiotic envelope	Without antibiotic envelope	CIED infections	The use of antibiotic envelopes in CIED implants has been linked to a reduced infection rate.
[41]	United States of America	CIED patients	AE	Without antibiotic envelope	CIED infection	The findings show that the TYRX antibiotic envelope has a substantial positive effect on the prevention of CIED infections.

Methodological Quality Results

The average methodological quality score was approximately 8.2 out of 16 points; the highest score was 10.5, and the lowest was 6.5 [25,26]. All included systematic reviews achieved a critically low methodological quality score using the AMSTAR-2 tool guideline [31]. Although all included studies were able to meet the criteria of items 1, 11, and 14, i.e., the inclusion of components of PICO, use of appropriate methods for statistical combination of results, and satisfactory explanation of heterogeneity, five items were not met by the reviews, namely: item 2: registration of the protocol before the main review, item 7: Provision of a list of excluded studies and rationale for exclusions, Item 10: Indication of the source of funding of included studies, Item 12: Assessment of the potential impact of risk of bias in individual studies on the results of the meta-analysis and Item 13: Consideration of risk of bias in individual studies when interpreting/discussing the results of the review. The study designs for inclusion were explained in half of the reviews but not in the other three studies [23-27,40]. Most of the reviews employed double study selection [23-26]. Data extraction was also not duplicated in one document [27]. In addition, the characteristics of the included studies were not described in sufficient detail in one study [25]. The risk of bias in the included studies was only assessed in two reviews [26,27]. Only one systematic review did not mention potential sources of conflict of interest [24]. The likelihood of publication bias was not analyzed (Table 3) [24,25].

Table 3 Assessment of the methodological quality of reviews

Studies	Items																Overall score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
[23]	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Y	Y	10 (CL)
[27]	Y	N	N	PY	N	N	N	Y	Y	N	Y	N	N	Y	Y	Y	7/5 (CL)
[25]	Y	N	N	PY	Y	Y	N	N	N	N	Y	N	N	Y	N	Y	6/5 (CL)
[27]	Y	N	Y	PY	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	10/5 (CL)
[24]	Y	N	Y	PY	Y	Y	N	PY	N	N	Y	N	N	Y	N	N	7 (CL)
[41]	Y	N	N	PY	N	Y	N	Y	N	N	Y	N	N	Y	Y	Y	7/5 (CL)

AMSTAR-2 Items: 1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed a quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
Y: Yes. PY: partially yes. N: No. CL: Critically Low methodological quality

GRADE Results

The six reviews included in this study comprised fifteen outcomes. Although none of the reported outcomes (0%) had high-quality evidence synthesis, nine (60%) and six (40%) outcomes had low and moderate-quality evidence synthesis, respectively. Regarding the GRADE criteria, all outcomes were at risk of bias (n=15, 100%), followed by inconsistency (n= 12, 80%), and publication bias (n=10, 67%). In contrast, imprecision and indirectness were not found in the outcomes (Table 4).

Table 4 GRADE results for quality of evidence synthesis

Studies	Interventions	Outcomes (number of included studies)	Effect size/ (95% confidence intervals)	Risk of Bias	Inconsi-stency	Impre-cision	Publication bias	Indirect-ness	Overall quality rating
[23]	Antimicrobial envelope enrolling higher risk patients	Major CIED related infections (3)	0.26 (0.08, 0.85) RR	-1	-1	0	0	0	Moderate
	Antimicrobial envelope enrolling any risk patients	Major CIED related infections (3)	0.53 (0.06, 4.52) RR	-1	-1	0	-1	0	Low
	Antimicrobial envelope enrolling any risk patients and higher risk patients	Major CIED related infections (6)	0.34 (0.14, 0.86) RR	-1	-1	0	-1	0	Low
	Antibacterial envelope among randomized and propensity score-matched patients	major CIED related infections (4)	0.30 (0.11, 0.83) RR	-1	0	0	-1	0	Moderate
	Antibacterial envelope in high-risk patients with CIED	Major CIED infections (6)	0.34 (0.13, 0.86) OR	-1	-1	0	-1	0	Low
[27]	Non-absorbable antibiotic envelope	Major and/or minor infection (5)	0.26 (0.14, 0.49) RR	-1	-1	0	-1	0	Low
[25]	Absorbable antibiotic envelope	Major and/or minor infection (2)	0.48 (0.35, 0.65) RR	-1	-1	0	NA	0	Moderate
	Non-absorbable and absorbable antibiotic envelope	Major and/or minor infection (7)	0.41 (0.31, 0.54) RR	-1	-1	0	0	0	Moderate
	Non-absorbable antibiotic envelope	Major infection (4)	0.33 (0.17, 0.64) RR	-1	-1	0	-1	0	Low
	Absorbable antibiotic envelope	Major infection (1)	0.59 (0.36, 0.97) RR	-1	NA	0	NA	0	Moderate
	Non-absorbable and absorbable antibiotic envelope	Major infection (5)	0.48 (0.32, 0.70) RR	-1	-1	0	-1	0	Low
[26]	Antibiotic envelope	major infections (6)	0.42 (0.19, 0.97) OR	-1	-1	0	-1	0	Low
[24]	Antibiotic envelope	Pooled cohort CIED infection (5)	0.31 (0.17, 0.58) OR	-1	-1	0	-1	0	Low
	Antibiotic envelope	Propensity-matched cohort CIED infection (3)	0.14 (0.05, 0.41) OR	-1	0	0	0	0	Moderate
[41]	Antibiotic envelope	CIED infection (5)	0.29 (0.09, 0.94) OR	-1	-1	0	-1	0	Low

RR: Risk Ratio, CIED: Cardiac Implantable Electronic Device, OR: odds ratio, NA: not applicable

DISCUSSION

Methodological examination and appraisal of the quality of evidence are strongly advocated in evidence-based medicine before making medical decisions [42,43]. The most important sources of evidence that influence medical decision-making are systematic reviews of high methodological quality that provide a high degree of certainty [44,45]. To our knowledge, the current study is the first to analyze the methodological and evidence quality of systematic reviews providing meta-analyses on the effect of antibacterial envelopes on CIED-related infections. This is to help physicians, policymakers, and researchers to make better therapeutic decisions by revealing the methodological

and evidence synthesis quality of systematic reviews. Six reviews were included in the final analysis based on the inclusion criteria. As the findings revealed, the included systematic reviews had critically low methodological quality, underlining the need for quality improvement. Most included reviews failed to meet the five criteria of the Amstar-2 tool. None of the included studies followed a published and registered protocol. According to the Cochrane Handbook, a protocol for systematic reviews should be registered to minimize bias in the results of systematic reviews [28]. Most authors of systematic reviews are unaware that a protocol for systematic reviews must be registered in advance, so a standard method is needed that requires authors to register protocols before conducting systematic reviews [46].

Another criterion not met by the included studies is the justification for exclusions. One of the critical areas of the AMSTAR-2 tool is presenting the list of excluded studies in systematic reviews and the reasons for exclusion of each excluded study, as highlighted in the conduct of screening in systematic reviews [47]. Therefore, researchers are highly advised to justify the exclusion of studies in systematic reviews. Because most reasons for exclusions in systematic reviews are intervention, comparison group, randomized controlled trial design, and outcomes, reporting reasons for exclusions can minimize any likely bias in systematic reviews [48]. Another criterion of the AMSTAR-2 tool that was not met by all systematic reviews is assessing the effect of risk of bias on the pooled effect size and the discussion of this effect on the results in systematic reviews. The reliability of randomized trials depends on how well they are organized and how well bias is minimized. In a review, it is crucial to examine the possibility of bias in the results of individual studies [28]. Authors performing meta-analyses must consider the possibility of bias in the results of the included studies. Analyses and conclusions based on the results of all studies, even if errors are overlooked in measuring bias, are inappropriate. More caution should be exercised in analyzing and interpreting results, and the quality of the evidence should be rated lower if more studies contain bias [28]. To account for the effects of risk of bias on the pooled effect size, authors can employ several strategies. The most important are subgroup analyses that stratify by the risk of bias of the included studies and meta-regression or sensitivity analyses. Consequently, researchers should conduct optimal analyses in their systematic reviews to account for the risk of bias. The AMSTAR tool requires systematic reviews to report the funding sources of included studies, which was not done in the included reviews. Most systematic reviews do not report or explain the funding source for included papers [49]. The main reason funding sources affect study results is sponsor bias [49]. To make appropriate therapeutic treatment recommendations, it is necessary to analyze, disclose, and critically evaluate any sponsor bias in meta-analytic estimates [49]. Previous studies in spinal surgery, treatment of major depression in adults, dance therapy, exercise therapy for chronic low back pain, bariatrics, and child sexual abuse interventions also rated the methodological quality of most systematic reviews as critically low [50-55]. In contrast, the methodological quality of most systematic reviews in antibiotics in third molar surgeries was reported as moderate [56].

We also found that the calculated outcomes in the included systematic reviews had evidence synthesis of low and moderate quality, primarily due to risk of bias in the included studies, significant inconsistency between included studies in the meta-analyses, and publication bias, which means that we have moderate and low confidence in these calculated effect sizes. According to the Cochrane Handbook, including studies in meta-analyses with a high risk of bias reduces the certainty of pooled effect sizes. Including only studies with a low risk of bias or conducting subgroup or sensitivity analyses to uncover the effects of risk of bias on the measured effect size may help address this issue. Researchers should consider these guidelines and strategies in the future to minimize the impact of risk of bias on the quality of evidence synthesis, contributing to high-quality meta-analyses [28]. Inconsistency of included studies in meta-analyses decreases the quality of evidence synthesis, as the results of the current systematic review showed that the quality of most measured outcomes in this study decreased due to inconsistency. Therefore, researchers in this field are advised to identify the source of heterogeneity of included studies in meta-analyses by conducting subgroup analyses or meta-regression [57].

The following are some of our study's strengths. We assessed the methodological quality and the quality of evidence synthesis of the literature using two well-validated techniques, namely AMSTAR-2, a new version of AMSTAR, and GRADE, which improved the research quality.

CONCLUSION

Our investigation includes six systematic reviews assessing the effect of antibacterial envelopes on CIED-related infection with 15 outcomes, all rated as having critically low methodological quality by the AMSTAR-2 instrument.

The GRADE rating of the meta-analysis results in the included SRs revealed that all evidence was of low and moderate quality. Systematic flaws or shortcomings in the design or conduct of articles in this field may skew the results. Before making any medical decisions, the Cochrane Handbook strongly advises evaluating the quality of evidence synthesis. As a result, assessing methodology and evidence synthesis could improve evidence-based therapeutic management of infections induced by cardiac implantation. According to the results of this systematic review, some critical flaws should be considered before making any clinical decision making. According to the current study results, the actual effects of the antibacterial envelopes to reduce CIED-related infection might differ from the estimated effects in the analyzed outcomes. This recommends that cardiologists, healthcare policymakers, and clinicians consider the current study results before making any medical decisions. Moreover, researchers in the field should receive more training and use the AMSTAR 2 scale and GRADE to perform high-quality studies in the future. For CIED-related infections, this method will provide improved clinical therapy recommendations.

DECLARATIONS

Author Contributions

HMN, and AS did searching, screening, and data extracting. MM interpreted the data. The first draft of the manuscript was written by HMN. HMN did the statistical analysis and supervised the research. All authors reviewed the results and approved the final version of the manuscript.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] de Bie, Mihaly K., et al. "Cardiac device infections are associated with a significant mortality risk." *Heart Rhythm,* Vol. 9, No. 4, 2012, pp. 494-98.

[2] Henrikson, Charles A., et al. "Antibacterial envelope is associated with low infection rates after implantable cardioverter-defibrillator and cardiac resynchronization therapy device replacement: Results of the citadel and centurion studies." *JACC: Clinical Electrophysiology,* Vol. 3, No. 10, 2017, pp. 1158-67.

[3] Sohail, Muhammad R., et al. "Mortality and cost associated with cardiovascular implantable electronic device infections." *Archives of Internal Medicine,* Vol. 171, No. 20, 2011, pp. 1821-28.

[4] Tarakji, Khaldoun G., et al. "Cardiac implantable electronic device infections: Presentation, management, and patient outcomes." *Heart Rhythm,* Vol. 7, No. 8, 2010, pp. 1043-47.

[5] Bundgaard, Johan S., et al. "The impact of implantable cardioverter-defibrillator implantation on health-related quality of life in the DANISH trial." *EP Europace,* Vol. 21, No. 6, 2019, pp. 900-08.

[6] Elayi, Claude S., et al. "Randomized trial comparing the effectiveness of internal (through implantable cardioverter defibrillator) versus external cardioversion of atrial fibrillation." *Journal of Interventional Cardiac Electrophysiology,* Vol. 58, No. 3, 2020, pp. 261-67.

[7] Moser, Robert H. "Diseases of medical progress." *New England Journal of Medicine,* Vol. 255, No.13, 1956, pp. 606-14.

[8] Poole, Jeanne E., et al. "Long-term outcomes of implantable cardioverter-defibrillator therapy in the SCD-HeFT." *Journal of the American College of Cardiology,* Vol. 76, No. 4, 2020, pp. 405-15.

[9] Rorth, Rasmus, et al. "Efficacy of an implantable cardioverter-defibrillator in patients with diabetes and heart failure and reduced ejection fraction." *Clinical Research in Cardiology,* Vol. 108, No. 8, 2019, pp. 868-77.

[10] Rorth, Rasmus, et al. "The effect of implantable cardioverter-defibrillator in patients with diabetes and non-ischaemic systolic heart failure." *EP Europace,* Vol. 21, No. 8, 2019, pp. 1203-10.

[11] Sapp, John L., et al. "Cardiac resynchronization therapy reduces ventricular arrhythmias in primary but not secondary prophylactic implantable cardioverter defibrillator patients: insight from the Resynchronization in Ambulatory Heart Failure trial." *Circulation: Arrhythmia and Electrophysiology,* Vol. 10, No. 3, 2017, p. e004875.

[12] Vamos, Mate, et al. "Implantable cardioverter–defibrillator therapy in hypertrophic cardiomyopathy: A SIMPLE substudy." *Heart Rhythm,* Vol. 15, No. 3, 2018, pp. 386-92.

[13] Tarakji, Khaldoun G., et al. "Antibacterial envelope to prevent cardiac implantable device infection." *New England Journal of Medicine,* Vol. 380, No. 20, 2019, pp. 1895-905.

[14] Connelly, Tara, et al. "Automated implantable cardioverter defibrillator lead infection in a patient with previous superior vena cava thrombosis." *Case Reports,* Vol. 2015, 2015, p. bcr2015211772.

[15] Tyers, G. F., and K. R. Tyson. "Pacemaker implantation." *The Journal of Thoracic and Cardiovascular Surgery,* Vol. 77, No. 4, 1979, p. 631.

[16] Cabell, Christopher H., et al. "Increasing rates of cardiac device infections among Medicare beneficiaries: 1990-1999." *American Heart Journal,* Vol. 147, No. 4, 2004, pp. 582-86.

[17] Greenspon, Arnold J., et al. "16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States: 1993 to 2008." *Journal of the American College of Cardiology,* Vol. 58, No. 10, 2011, pp. 1001-06.

[18] Voigt, Andrew, Alaa Shalaby, and Samir Saba. "Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003." *Journal of the American College of Cardiology,* Vol. 48, No. 3, 2006, pp. 590-91.

[19] Voigt, Andrew, Alaa Shalaby, and Samir Saba. "Continued rise in rates of cardiovascular implantable electronic device infections in the United States: Temporal trends and causative insights." *Pacing and Clinical Electrophysiology,* Vol. 33, No. 4, 2010, pp. 414-19.

[20] Blomstrom-Lundqvist, Carina, et al. "European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-Endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)" *EP Europace,* Vol. 22, No. 4, 2020, pp. 515-49.

[21] Shariff, Nasir, et al. "Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation." *Journal of Cardiovascular Electrophysiology,* Vol. 26, No. 7, 2015, pp. 783-89.

[22] Burnhope, Emma, et al. "A systematic approach towards implementing value-based health care in heart failure: Understandings from retrospective analysis methods in South London." *Health Services Management Research,* 2020, p. 0951484820971442.

[23] Asbeutah, Abdul Aziz A., et al. "The role of an antibiotic envelope in the prevention of major cardiac implantable electronic device infections: A systematic review and meta-analysis." *Medicine,* Vol. 99, No. 26, 2020.

[24] Koerber, Scott M., et al. "Use of antibiotic envelopes to prevent cardiac implantable electronic device infections: A meta-analysis." *Journal of Cardiovascular Electrophysiology,* Vol. 29, No. 4, 2018, pp. 609-15.

[25] Kumar, Ashish, Rajkumar Doshi, and Mariam Shariff. "Role of antibiotic envelopes in preventing cardiac implantable electronic device infection: A meta-analysis of 14 859 procedures." *Journal of Arrhythmia,* Vol. 36, No. 1, 2020, pp. 176-79.

[26] Pranata, Raymond, et al. "Antibiotic envelope is associated with reduction in cardiac implantable electronic devices infections especially for high-power device-Systematic review and meta-analysis." *Journal of Arrhythmia,* Vol. 36, No. 1, 2020, pp. 166-73.

[27] Ullah, Waqas, et al. "Efficacy of antibacterial envelope in prevention of cardiovascular implantable electronic device infections in high-risk patients: A systematic review and meta-analysis." *International Journal of Cardiology,* Vol. 315, 2020, pp. 51-56.

[28] Higgins, Julian PT, et al., eds. "Cochrane handbook for systematic reviews of interventions." *John Wiley & Sons*, 2019.

[29] Schunemann, Holger, et al. "GRADE handbook. 2013." 2015.

[30] Page, Matthew J., et al. "The PRISMA 2020 statement: An updated guideline for reporting systematic

reviews." *International Journal of Surgery,* Vol. 88, 2021, p. 105906.

[31] Shea, Beverley J., et al. "AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both." *BMJ,* Vol. 358, 2017.

[32] Pollock, Alex, et al. "An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews." *Journal of Clinical Epidemiology,* Vol. 70, 2016, pp. 106-10.

[33] Pogue, Janice M., and Salim Yusuf. "Cumulating evidence from randomized trials: Utilizing sequential monitoring boundaries for cumulative meta-analysis." *Controlled Clinical Trials,* Vol. 18, No. 6, 1997, pp. 580-93.

[34] Mavridis, Dimitris, and Georgia Salanti. "How to assess publication bias: Funnel plot, trim-and-fill method and selection models." *Evidence-Based Mental Health,* Vol. 17, No. 1, 2014, p. 30.

[35] Zhang, Yuan, et al. "GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences-Inconsistency, imprecision, and other domains." *Journal of Clinical Epidemiology,* Vol. 111, 2019, pp. 83-93.

[36] Terrin, Norma, Christopher H. Schmid, and Joseph Lau. "In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias." *Journal of Clinical Epidemiology,* Vol. 58, No. 9, 2005, pp. 894-901.

[37] Zwetsloot, Peter-Paul, et al. "Standardized mean differences cause funnel plot distortion in publication bias assessments." *Elife,* Vol. 6, 2017, p. e24260.

[38] Duval, Sue, and Richard Tweedie. "Trim and fill: A simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis." *Biometrics,* Vol. 56, No. 2, 2000, pp. 455-63.

[39] Motahari-Nezhad, Hossein, et al. "Outcomes of digital biomarker-based interventions: Protocol for a systematic review of systematic reviews." *JMIR Research Protocols,* Vol. 10, No. 11, 2021, p. e28204.

[40] Santenna, Chenchula, et al. "The safety, tolerability and mortality reduction efficacy of remdesivir; based on randomized clinical trials, observational and case studies reported safety outcomes: An updated systematic review and meta-analysis." *Therapeutic Advances in Drug Safety,* Vol. 12, 2021, p. 20420986211042517.

[41] Ali, Sajid, et al. "A meta-analysis of antibacterial envelope use in prevention of cardiovascular implantable electronic device infection." *Therapeutic Advances in Infectious Disease,* Vol. 4, No. 3, 2017, pp. 75-82.

[42] Lunny, Carole, et al. "Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: Rationale and design." *Systematic Reviews,* Vol. 5, No. 1, 2016, pp. 1-8.

[43] Manchikanti, Laxmaiah, et al. "Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: part 3: Systematic reviews and meta-analyses of randomized trials." *Pain Physician,* Vol. 12, No. 1, 2009, pp. 35-72.

[44] Gopalakrishnan, S., and P. Ganeshkumar. "Systematic reviews and meta-analysis: Understanding the best evidence in primary healthcare." *Journal of Family Medicine and Primary Care,* Vol. 2, No. 1, 2013, pp. 9-14.

[45] Johnson, Blair T., and Emily A. Hennessy. "Systematic reviews and meta-analyses in the health sciences: Best practice methods for research syntheses." *Social Science & Medicine,* Vol. 233, 2019, pp. 237-51.

[46] Tawfik, Gehad Mohamed, et al. "Protocol registration issues of systematic review and meta-analysis studies: A survey of global researchers." *BMC Medical Research Methodology, Vol.* 20, No. 1, 2020, pp. 1-9.

[47] Meline, Timothy. "Selecting studies for systemic review: Inclusion and exclusion criteria." *Contemporary Issues in Communication Science and Disorders,* Vol. 33, Spring, 2006, pp. 21-27.

[48] Edinger, Tracy, and Aaron M. Cohen. "A large-scale analysis of the reasons given for excluding articles that are retrieved by literature search during systematic review." *AMIA Annual Symposium Proceedings*, Vol. 2013, 2013, pp. 379-87.

[49] Faggion, C. M., M. Atieh, and D. G. Zanicotti. "Reporting of sources of funding in systematic reviews in periodontology and implant dentistry." *British Dental Journal,* Vol. 216, No. 3, 2014, pp. 109-12.

[50] Dettori, Joseph R., Andrea C. Skelly, and Erika D. Brodt. "Critically low confidence in the results produced by spine surgery systematic reviews: An AMSTAR-2 evaluation from 4 spine journals." *Global Spine Journal,* Vol. 10, No. 5, 2020, pp. 667-73.

[51] Matthias, Katja, et al. "The methodological quality of systematic reviews on the treatment of adult major depression needs improvement according to AMSTAR 2: A cross-sectional study." *Heliyon,* Vol. 6, No. 9, 2020, p. e04776.

[52] Kim, Hye-Ryeon, Chang-Hwan Choi, and Eunhye Jo. "A methodological quality assessment of meta-analysis studies in dance therapy using AMSTAR and AMSTAR 2." *Healthcare*, Vol. 8, No. 4, 2020.

[53] Almeida, Matheus Oliveira, et al. "Overall confidence in the results of systematic reviews on exercise therapy for chronic low back pain: A cross-sectional analysis using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 tool." *Brazilian Journal of Physical Therapy,* Vol. 24, No. 2, 2020, pp. 103-17.

[54] Storman, Monika, et al. "The quality of systematic reviews/meta-analyses published in the field of bariatrics: a cross-sectional systematic survey using AMSTAR 2 and ROBIS." *Obesity Reviews,* Vol. 21, No. 5, 2020, p. e12994.

[55] de Ribera, Olga Sanchez, Nicolas Trajtenberg, and Larissa S. Christensen. "Evaluating the quality of meta-analytical reviews using the AMSTAR-2: A systematic review of meta-analytical reviews regarding child sexual abuse interventions." *Child Abuse & Neglect,* Vol. 104, 2020, p. 104463.

[56] Chugh, Ankita, et al. "Critical analysis of methodological quality of systematic reviews and meta-analysis of antibiotics in third molar surgeries using AMSTAR 2." *Journal of Oral Biology and Craniofacial Research,* Vol. 10, No. 4, 2020, pp. 441-49.

[57] Guyatt, Gordon H., et al. "GRADE guidelines: 7. Rating the quality of evidence-inconsistency." *Journal of Clinical Epidemiology,* Vol. 64, No. 12, 2011, pp. 1294-302.