Author’s response to reviews

Title: Effect of pocket irrigation with antimicrobial on prevention of pacemaker pocket infection: a Meta-analysis

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Author’s response to reviews:

Revision for "Effect of pocket irrigation with antimicrobial on prevention of pacemaker pocket infection: a Meta-analysis" (Manuscript ID: BCAR-D-17-00358)

Dear Prof. Marzia Cottini,

Thank you very much for giving us the opportunity to revise the manuscript "Effect of pocket irrigation with antimicrobial on prevention of pacemaker pocket infection: a Meta-analysis", which has been modified according to the reviewers' comments. Besides, we have checked the other parts of the manuscript to ensure data were correctly presented. For example, Figure 3 and Figure 4 were replaced by results from fixed-effects model.
We are sorry for making so much typing and grammar mistakes. We really want to make some contribution to this area. I hope that with your thoughtful and valuable suggestions and our effort, the manuscript is useful to this area. All changes of the manuscript were highlighted in red.

I would appreciate it very much if the manuscript could be re-reviewed and considered for publication in your journal.

Sincerely,

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Point-by-point response to the reviewers' comments

Rita Pavasini (Reviewer 1): This is an interesting meta-analysis on the effect of pocket irrigation with antimicrobial on device infection. The paper is statistically well conducted, unfortunately an extensive revision of English grammar is needed. I also suggest to perform if possible.

Comment 1: Subgroup analysis or meta-regression for the type of implantation (PM vs. ICD vs. CRT).

Answer: Thank you for your comment. Each enrolled study included patients with pacemakers (PM) implantation and some studies included both pacemakers and implanted cardiac defibrillator (ICD)/cardiac resynchronization therapy (CRT) implantations as well. Using PM only or PM plus ICD/CRT in each study as co-variable, we performed meta-regression which revealed a non-significant influence on the pooled results ($P = 0.72$).

According to this results, we revised the result section (line 24, page 8 to line 8, page 9) as follows: Meta-regression using mean age, region, study design, including patients receiving ICD (or CRT) or not, antibiotics/non-antibiotics and first/second line therapy against staphylococcus aureus as co-variables were done. Results indicated that age, study design, including CRT or ICD patients, or early/late infections were not the sources of heterogeneity (mean age: $P = 0.34$;
region: P = 0.05; study design: P = 0.24; CRT or ICD included: P = 0.72; antibiotics or not: P = 0.11; first or second line therapy for staphylococcus aureus: P = 0.18; early/late infections: P = 0.33). However, both region and antibiotics/non-antibiotic may account for heterogeneity (region: P = 0.03; antibiotics/non-antibiotics: P = 0.08).

Comment 2: Meta-regression for the mean age of the patients in every study population.

Answer: Thank you for your comment. Similar with the previous comment, we used mean age as co-variable in the meta-regression and found a non-significant results (P = 0.34). Corresponding descriptions in the manuscript were revised as above.

Comment 3: It is not clear the time for infection, were the event related to the implantation or were they mainly happening in the long term follow-up, if this is the case, how authors thinks that the initial irrigation of the pocket could have affect the outcome?

Answer: Thank you for your insightful comment. All the reported studies, expect one (Yang, 2015), reported the time for infection after PM/ICD/CRT-D implantation. The durations ranged from one week to seven years. To be more clearly clarified the issue, we divided infection happened within one month as early infection, otherwise as late infection. Two studies reported early infection only, five ones reported late infection only and another two reported both. Pooled analysis was performed independently within the two groups. Results revealed that pocket irrigation conferred protective effects in both early and late infection, with a slightly larger effect size of in early infection (early infection: RR = 0.48, 95% CI: 0.25 to 0.93; late infection: RR = 0.50, 95% CI: 0.30-0.83).

According to this, we revised the results section (line 14 to 16, page 8) as follows: Pocket irrigation reduced both early (within one month) and late (longer than one month) infections, but with a slightly larger effect size in protecting early infection (Figure 4E).

Comment 4: Is there any difference in the time of the occurrence of the infections between antibiotics vs. antimicrobial vs. saline?

Answer: Thank you for your comment. Only one study focusing on the protective effects of antimicrobial agent and results were non-significant. Moreover, early and late infections in this study were non-statistically significance (Lakkireddy et al., 2005). Therefore, it could be inferred from current evidence that anti-microbial agents is inferior to antibiotics, either in early or late infection.
Since only one study focusing on antimicrobial and the rest are investigating effects of antibiotics, which were already analyzed in comment 3, we did not duplicately present early and late infection of the antimicrobial study as the original publication.

Matteo Serenelli (Reviewer 2): This is an interesting meta-analysis, simple work and well done. I suggest some minor changes.

Comment 1: Some typographic errors are present.
Answer: Thank you for your comment. We have checked it and corrected some typing and grammar errors. We hope it could be better and reach your standard this time.

Comment 2: Please attach as supplemental online material the PRISMA checklist.
Answer: Thank you for your comment and we have appended the PRISMA checklist as supplementary materials.

Comment 3: At page 5, row 3, you wrote that "pacemakers are the unique effective way to treat bradycardia arrhythmia" which is not true because ICD and CRT both may perform as pacemakers & You also state "ICD and CRT are effective strategies for sudden death and heart failure", I suggest you to change it into "ICD and CRT are effective strategies to prevent sudden death and improve heart failure".
Answer: Thank you for your preciseness and we have revised them all in the manuscript. For your convenience we present them here.

We think that CRT could not prevent but improve heart failure, so we revised this as follow: Of these, pacemakers are the most common and effective way to treat bradycardia arrhythmia (pacemaker), while ICD and CRT are effective strategies to prevent sudden death and improve heart failure, respectively (line 3 to line 6 in page 4).

Besides, we also checked other parts of the manuscript to ensure correct expression.
Comment 4: In the statistical analysis paragraph you said the you use a significance level of P<0.1 rather than 0.05 for the I2 statistic test and the Cochrane Q-test, can you explain why?

Answer: Thank you for your comment. In the meta-analysis, the power of the Cochrane Q-test is believed to be low. Therefore, in some studies, the level of significance for the test is set at larger than 0.05 to increased its sensitivity (Bown MJ and Sutton. Quality Control in Systematic Reviews and Meta-analyses. 2010,40(5):669-677; Sedgwick Philip. Meta-analyses: what is heterogeneity? BMJ 2015;350:h1435 doi: 10.1136/bmj.h1435).