

## Peer-Review

Chakraborty, Tanya. 2026. "Safety and Long-Term Outcomes of Leadless vs. Conventional Lead-Based Pacemakers." *Journal of High School Science* 10 (1): 60–75. <https://doi.org/10.64336/001c.155396>

A well written paper. However, I have several concerns that need to be addressed.

1. Since the number of studies is small, a random effects model should have been used; not a fixed effects mode; to better model between-study heterogeneity.
2. State under limitations that Publication bias tests such as Funnel plots and Egger's tests were not performed due to the low # of studies.
3. Include a sensitivity analysis (Leave x out) to show how individual studies impact the overall results or estimates. I would particularly like to see this with the all-cause mortality, pericardial effusion and AV synchrony results in the forest plot and/or elsewhere.
4. This manuscript reads like an advertisement for Micra AV. Provide a Conflict of interest section with any links (monetary or otherwise) to the manufacturer or distributor of Micra AV.
5. you state "...additional evidence from meta-analyses supports the overall safety and effectiveness of Micra systems;..." please do not draw conclusions from studies that were not part of your meta-analysis design. You can cite information from those studies but not use them as supporting evidence for your results.
6. Please report TVP AV synchrony results and compare them against Leadless device results.

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### Response to Reviewer Comments

#### Reviewer 1

- **Comment 1 (verbatim):**

*Since the number of studies is small, a random effects model should have been used; not a fixed effects mode; to better model between-study heterogeneity.*

#### **Response:**

We thank the reviewer for this important comment. In response, we revised the statistical approach to use a random-effects model for all pooled analyses to better account for between-study heterogeneity given the small number of included studies. The **Abstract has been updated** to reflect the use of a random-effects model, and the **Methods section** has been revised accordingly (**Section 3.4: Statistical Analysis**).

Between-study heterogeneity was assessed using Cochran's Q test and the  $I^2$  statistic. A fixed-effects model was prespecified only for outcomes demonstrating low heterogeneity ( $I^2 < 25%$ ); however, heterogeneity for all key primary outcomes exceeded this threshold, including the all-cause mortality analysis ( $I^2 = 29.8%$ ). Therefore, a random-effects model was applied to all pooled estimates, which are now reported with 95% confidence intervals.

In addition, the **Methods section was reorganized** into clearly defined subsections to improve transparency of the search strategy, study selection, quality assessment, and statistical analysis. The **forest plot (Figure 2) has also been updated** to reflect the revised random-effects model analyses.

- **Comment 2 (verbatim):**

*State under limitations that Publication bias tests such as Funnel plots and Egger's tests were not performed due to the low # of studies.*

#### **Response:**

We thank the reviewer for this comment. We have revised the Limitations section to explicitly state that publication bias was not assessed using funnel plots or Egger's tests due to the small number of

included studies ( $n < 10$ ), which renders such analyses statistically unreliable. This clarification has now been added to **Section 6. Limitations**.

- **Comment 3 (verbatim):**

*Include a sensitivity analysis (Leave x out) to show how individual studies impact the overall results or estimates. I would particularly like to see this with the all-cause mortality, pericardial effusion and AV synchrony results in the forest plot and/or elsewhere.*

**Response:**

We thank the reviewer for this thoughtful and constructive suggestion. We carefully considered performing leave-one-out sensitivity analyses for the requested outcomes. However, for key endpoints including **all-cause mortality, pericardial effusion, and AV synchrony**, only two studies contributed data to the pooled analyses. In this context, removal of a single study would leave only one remaining data point, rendering **a leave-one-out sensitivity analysis methodologically uninterpretable and statistically unreliable**. Accordingly, a formal sensitivity analysis was not performed for these outcomes, and this has now been explicitly stated in the **Meta-analysis section** (Section 4.4).

To **address the reviewer's intent** of evaluating how individual studies contribute to these outcomes, we **expanded the Results section** by adding a **new subsection (Section 4.3: TVP Comparator Results)** and a **new Table 2**. This table presents available author-reported data for **all-cause mortality, pericardial effusion, and AV synchrony**, as well as **related complication outcomes**, for both leadless pacemakers (LP) and traditional transvenous pacemakers (TVP), where reported. Due to inconsistent reporting of denominators and 95% confidence intervals across studies, these results are presented descriptively, and missing confidence intervals are explicitly noted.

In addition, the **Limitations section has been updated** to clarify that formal sensitivity analyses were not performed due to the limited number of included studies ( $n < 10$ ), which makes such analyses statistically unreliable.

- **Comment 4 (verbatim):**

*This manuscript reads like an advertisement for Micra AV. Provide a Conflict of interest section with any links (monetary or otherwise) to the manufacturer or distributor of Micra AV.*

**Response:**

We thank the reviewer for raising this important concern. In response, we have added a dedicated **Conflict of Interest section** (Section 8) stating that the author has no financial, professional, or personal relationships with Medtronic or any manufacturer or distributor of Micra AV or related leadless pacemaker technologies.

In addition, to further address the **concern regarding tone**, we carefully re-evaluated the manuscript and revised wording in several sections, including the **Results, Discussion, and Conclusion**, to ensure a neutral, objective, and non-promotional scientific tone. These revisions were **limited to lexical and stylistic changes** and did not alter the underlying analyses, interpretations, or reported results.

- **Comment 5 (verbatim):**

*You state "additional evidence from meta-analyses supports the overall safety and effectiveness of Micra systems"; please do not draw conclusions from studies that were not part of your meta-analysis design. You can cite information from those studies but not use them as supporting evidence for your results.*

**Response:**

We thank the reviewer for this important clarification. In response, we revised the **Discussion** to remove language that could be interpreted as drawing supportive conclusions from studies not included in the present meta-analysis. Specifically, the statement referencing external meta-analyses as supporting evidence for the safety and effectiveness of Micra systems has been removed, and such studies are no longer used to support the results of the current analysis.

The revised **paragraph now interprets findings strictly within the scope** of the included studies and emphasizes existing limitations in the evidence base, including the predominance of observational designs, limited follow-up durations, and the absence of randomized controlled trials. The revised text also highlights the need for future large-scale, multicenter randomized studies and longitudinal data to better characterize long-term outcomes, device durability, and generalizability, **without relying on external studies to support the conclusions** of this work.

• **Comment 6 (verbatim):**

*Please report TVP AV synchrony results and compare them against Leadless device results.*

**Response:**

We thank the reviewer for this request. We addressed this comment by adding a dedicated subsection in the **Results section (Section 4.5: Atrioventricular Synchrony with Leadless Versus Transvenous Pacemakers)**, reporting all available AV synchrony data for leadless Micra AV systems and evaluating corresponding data for transvenous pacemaker (TVP) cohorts.

Quantitative AV synchrony values were reported for leadless devices; however, numerical AV synchrony percentages were not reported in the included TVP studies, which limited direct numerical or pooled comparison. This point is now clearly stated in the Results, and the reporting scope of comparative studies (e.g., El-Chami et al., Yu et al.) is noted.

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Thank you for addressing my comments. Your revised manuscript is accepted for publication in the Journal of High School Science.

HOWEVER, we cannot copyedit the manuscript unless all the references present and point to the correct content on the web, have correct author names, have 6 author names listed when there are > 6 authors, are in APA format.

For example, I checked reference 11 and it has incorrect author names, incorrect vol, issue. I did not check other references for veracity.

Please check all references thoroughly and upload the corrected manuscript at the discussion board when done.

We CANNOT PROCEED with copyediting unless this is done.

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Dear Dr.Apte,

Thank you for your email and the reviewer's comments. I have carefully **revised my manuscript, checked all references, and made corrections** to ensure they conform to APA format. This includes verifying author names, journal volumes/issues, and ensuring that references with more than six authors list the first six followed by et al. Any previously incorrect references have been corrected and all references now point to the correct content online.

Please find attached the updated manuscript for your review. I would **greatly appreciate it if you could confirm whether all changes are satisfactory**. I am very excited about the prospect of my manuscript being published and look forward to your feedback.

Thank you so much.

Kind regards,

Tanya Chakraborty

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Dear author,

Thank you for correcting the references. As we continue copyediting, we find that (see attached manuscript)

1. The references in the text do not point to the correct corresponding reference number in the 'references' section of the manuscript. Please check the entire manuscript.
2. Please CLEARLY state what studies were included in the meta-analysis. For example, you seem to state that studies in Table 2 were included but only in a descriptive capacity! What does this mean? Does this mean that some studies were operationalized statistically and other descriptively; yet all of them were included in the meta-analysis? How is that possible? As written, the manuscript is very confusing to the reader. Please check and correct as necessary.
3. Please check for significance at  $p=0.05$ . Remove all qualitative descriptors such as 'markedly', 'slightly'.... and replace with 'significantly'.

Best,

Shireesh Apte

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Dear Dr. Apte,

Thank you for the feedback. I am addressing the points raised.

Could you please let me know whether you would prefer the revisions to be made directly in the Word document you shared, or submitted as a separate revised document with changes clearly highlighted? Thank you so much.

Best regards,

Tanya Chakraborty

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Dear author,

Please make the changes in the document

1. cross out the verbage removed
2. highlight the verbage added

Best,

Shireesh Apte

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Dear Dr. Apte,

I have updated the shared document. Thank you for your feedback and the opportunity to improve it.

All requested revisions have been addressed. I used Track Changes throughout the document: deleted text is crossed out, and newly added or revised text is highlighted in yellow. In-text citation numbers were updated and the reference list reordered accordingly (except for one area in which you may have made a slight change in section 4.2 where ref 15 appears before 14), with changes highlighted. Minor refinements for clarity and accuracy are also highlighted.

Please find the attached word document below.

I hope this version meets the requirements for the next stage of the review process. Thank you so much!

Best regards,

Tanya Chakraborty

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Dear author,

Thank you for addressing my comments. I am still not happy with the way the 2 meta-analysis and the 2 descriptive studies are tangled up in the manuscript. Please separate them completely in different Result sections. References need to be numbered, not referenced by author (although you can do that in addition to the numbers). See manuscript and image attached.

Best,

Shireesh Apte

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Dear author,  
We will be happy to review your manuscript once you have made the changes.  
Best,  
Shireesh Apte

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Dear Dr.Apte,  
Thank you for your message and for your guidance. I have noted the requested changes and will revise the manuscript accordingly.  
Best Regards,  
Tanya Chakraborty

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Dear Dr. Apte,  
Thank you for your suggestion on the manuscript. I have carefully addressed all your comments and would like to summarize the revisions:

- 1.Separation of meta-analysis and descriptive studies:
  - Meta-analysis: Only the two studies with compatible hazard ratios (El-Chami [10], Garweg [15]) are included in the quantitative analyses.
  - Descriptive studies: Yu [11] and Libbus [14] are presented separately, clearly labeled, and their outcomes are not pooled.
- 2.Clariication in Methods: At the start of the Methods section, I explicitly stated that all quantitative results are derived only from the two meta-analyzed studies.
- 3.References and citation format: All in-text citations have been converted to Vancouver style. **For clarity, I have retained the author names before the reference numbers** (e.g., El-Chami et al. (10)) but **removed the year**, ensuring strict Vancouver compliance.
- 4.Statistical qualifiers: Statistical significance is defined globally in Methods as  $p < 0.05$ , and descriptive studies are reported numerically only, without implying significance.

I believe these revisions address all your concerns. Also, please note my preferred email is tanya.cy03@gmail.com. instead of tanyachakraborty.03.07@gmail.com for publications and I will be using this email id for future work, so I have changed it in the manuscript as well (highlighted in blue).

Thank you again for your time and guidance. I hope you're happy with the highlighted changes and I look forward to your feedback!

Best regards,  
Tanya Chakraborty

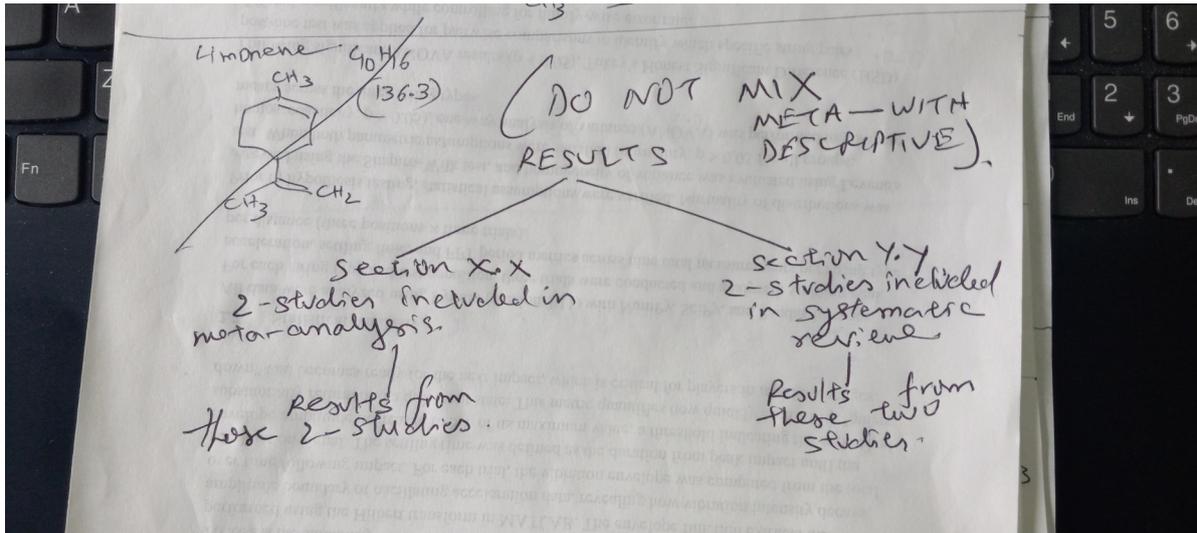
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Dear author,  
Your edits are acceptable. Thank you for addressing my comments.  
To increase the novelty of your paper further, I have written and included a clinical trial design in section 5.3 based on your paper. Please make sure you understand it and agree with it.  
Please also check the attached paper for errors and revert back in 48 hours to ensure a timely publication.  
Best,  
Shireesh Apte

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Dear Dr. Apte,  
Thank you for sharing the Proposed Clinical Trial section. I have reviewed it carefully and find the design, rationale, and statistical framework very well thought out and appropriate. I am generally in agreement with the proposed approach.  
I did notice a few small points where minor adjustments could improve clarity and consistency:

## 1. Sentence clarity and punctuation:



### ● In Section 5.3, **instead of:**

“There is a strong rationale for subgroup learning and; because AV synchrony and valve effects evolve over time; endpoints are event driven.”

Could we use:

“There is a strong rationale for subgroup learning, **and because** AV synchrony and valve effects evolve over time, endpoints are event driven.”

● “Thereafter” could be updated to “Thereafter” to avoid typos

● For consistency in subgroups, perhaps “Baseline HF” could be written as “baseline HF.”

### 2. References formatting-

● In Section 3.1 Study inclusion and analytical framework, references are currently in square brackets [ ]. Could we adjust them to curved brackets ( ) to match the rest of the manuscript?

I would have implemented these minor adjustments myself, but as the document was shared as a PDF, I was not able to directly edit it

Once these small points are addressed, the section looks ready for publication!

Thank you so very much for your guidance and support, and for taking the time to review my manuscript carefully!

Kind regards,

Tanya Chakraborty

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Dear author,

Your manuscript is published in the Journal of High School Science. You can access it at <https://jhss.scholasticahq.com>

Best,

Shireesh Apte