Author’s response to reviews

Title: Long Term Surgical Outcomes for Infective Endocarditis in People Who Inject Drugs: A Systematic Review and Meta-Analysis

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Author’s response to reviewers’ comments:

Arnar Geirsson (Reviewer 1):

The manuscript is a systematic review and meta-analysis of long-term outcome of people who inject drugs who underwent cardiac surgery for infective endocarditis. They included 27 studies for review and 19 for data analysis. The PWID group was younger, likely to have S. aureus infection, had greater hazard of death and reoperation than non-PWID group.

The subject of the study is very relevant in current era of the opioid epidemic and the perceived dramatic increase in the burden on hospital systems and cardiac surgery programs treating this challenging group of patients.

The manuscript is well written with sound statistical methodology and analysis.

We appreciate the reviewer’s summary and positive comments.
I have two minor comments to consider:

The current opioid epidemic in the US has resulted in dramatic increase in endocarditis and although not based on hard data is felt by some physicians to be different than prior PWID IE cases. The publications included in this manuscript obviously does not include recent publication that have been published in 2019. It is worth mentioning that in the discussion about study limitation.

This has been added to the study limitations. This reads as follows: “Due to the wide range in publication dates of the included articles, cardiac surgery techniques and supportive care likely has improved over the time period but this temporal variation was not assessed. As well, patterns of injection drug use have changed over time and geographic space (i.e., increased fentanyl use or increased injection of stimulants) that may lead to different degrees of severity of IE in PWID. The present results may not be reflective of the current epidemiology of injection drug use.”

Supplementary figure 3 is important and recommend including in the main manuscript

This figure has now been included in the main manuscript and uploaded as a TIFF. All references to the figures within the manuscript have been updated.

Lucas Castellani (Reviewer 2):

I want to congratulate you on your review of this topic. With the current opiate crisis and rise in infective endocarditis related to substance use, understanding the long term outcomes of surgical approaches in this patient population is very important. As clearly pointed out in the background and discussion, this is a progressive issue that requires study as there is limited information on the best approach in this population.

The authors did a good job at reviewing the literature and attempting to obtain individual patient data. The use of an estimate for IPD was creative and I believe helped to build the data. The results will help to provide some insight into the true prognosis and course for this patient population given the follow up was long in the study.

We appreciate the reviewer’s summary and positive comments.

As per all studies with a review of retrospective data there will be selection bias, but this is the only literature available currently. Unfortunately the actual surgical information was not included (repair or replacement), and whether there were more intraoperative findings of complicated infection to explain the difference rather than the post operative time period alone. I suspect this was due to the information being not available in the studies.

We agree that more nuanced surgical information that includes type of surgery, intraoperative findings (e.g., abscesses, valve rupture) and post-operative complications may provide more detail into the relationship between injection drug use and death, however, this was inconsistently reported by the included studies. We have added the following section to the limitations section:

“Surgical technique, intraoperative findings (e.g., abscesses, valve rupture), and post-operative complications may be other variables that may differ between PWID and non-PWID to explain differences in survival but were not assessed as part of this study.”
Regardless, I think this was a well done review of the available evidence and I would recommend the article be published with some discretionary changes as noted below.

Abstract:
Pg2 Line 6 - I'm not clear it needs to be US-centered as the IE and opiate use issue is global.

The reference to the United States has been removed. The opening line of the abstract now reads: “In recent years, the number of infective endocarditis (IE) cases associated with injection drug use has increased.”

Pg2 Line 39 - I'm not sure if putting "PWID were younger" is required, unless you also put the reoperation was higher also. Either consider removing or rewording.

The reference to younger has been removed. The abstract’s conclusion now starts: “PWID had shorter survival that non-PWID.”

Background:
Pg3 Line 17 - Somewhat unclear statement in terms of flow. Consider "In PWID, however, other bacterial and fungal infectious complications including Infective endocarditis are often overlooked."

In the Introduction section the last sentence of paragraph 1, has now been changed to the reviewer’s suggestions.

Pg4 Line 12 - Happy to see this study included as your study adds on to the understanding of these patients given the prior study's short follow up time.

Methods:
Variables - Pg5 Line46 - Does Culture negative include classic Culture negative organisms (ie. Bartonella, Coxiella)? Should one separate Group A Streptococcus (if there were enough) given the issues in PWID? Were there any other organisms that were seen (ie. GPB, other fungal?) to warrant an "other" section?

Other bacteria or fungus were rarely individually reported, and when reported, there was large heterogeneity in these reported “other” organisms. Most were typical gram negative organisms (E. coli, Enterobacter, Pseudomonas, Serratia, Klebsiella). Examples of other organisms include Lactobacillus ramosus, N gonorrhea, Rothia dentocariosa. These organisms were too varied and inconsistently reported to separate in another column. These other organisms where included in the “Gram negative rods” column. For this version of the manuscript, we have renamed this column as “Gram negative rods or others.”

Studies that reported “culture-negative (or marantic) endocarditis” typically did not report specific agents. However, when traditional agents of culture negative endocarditis were reported (e.g. Bartonella, Coxiella, HACEK), we included the case under “gram negative rods or others.” For example, Nelson reported a case of Q fever (at the time of that publication the organism was still under the genus Rickettsia) and Mestres reported a case of Coxiella. Both of these organisms were counted in the “gram negative rods or others” column.

Regarding group A streptococci (GAS), most papers reported streptococci as Streptococci spp. If
broken down, most mentioned viridans group streptococci (or alpha-hemolytic), enterococcus (or group D) and other streptococci (where GAS maybe included). Carrell and Thalme each reported a case of GAS. We do not believe the reported studies provided enough cases of GAS to merit a separate column.

Was there any thought to include intraoperative findings or was this not available?

Intraoperative findings were inconsistently reported. A reference to this has been added as a limitation as noted above.

Statistical analysis - This seems a reasonable methodology for the study and I applaud the creativity in using the estimate individual patient data (eIPD), however statistical analysis is not my expertise and so I would recommend this be looked into.

Results:
Valve data - Pg7 Line46 - I would caution in using the absolute terms "more common" without significance. Either remove or state something like "there is a trend to".

The term more common has been removed. In the results section, under the Valve data subsection, the sentence has been reworded to:

“The in PWID, 39.7% of surgical procedures involved the aortic valve, 33.5% the tricuspid valve, and 25.6% the mitral valve. In non-PWID, 53.1% of surgical procedures involved the aortic valve, 36.8% the mitral valve, and 9.6% the tricuspid valve.”

Discussion:
Pg9 Line39 - I truly appreciate the discussion of access to and treatment for the substance use disorder. This is a large component and may have a huge effect on outcomes in these patients.

We agree that interventions that provide substance use disorder therapy and the research measuring the impact of these intervention are urgently needed.