The authors of this paper are grateful for the constructive comments of the reviewers and appreciate the opportunity to respond to these comments.

As you suggested, we have made additional revisions in response to the critiques and suggestions of the reviewers. Our response to the reviewers' comments and the revisions made in accordance with their suggestions are described item by item below.

The changes are highlighted throughout the revised manuscript.

Reviewer #1:

The manuscript, entitled "Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End", discussed past, present, and future clinical trials, factors that influence stem cell therapy outcomes as well as ethical and safety considerations.

We thank the reviewer for the summary of the project and the kind comments.

Several subtitles of Result.

We agree with the reviewer that there are many subtitles in the results section. For this reason, we have reorganized this section and used only 2 subtitles (see page 10, line 7 and page 13, line 1)

The pathophysiology of heart failure and the target of stem cell therapy for HF should be well summarized, such as direct differentiation, paracrine effects, parameter changes of HF after therapy, et al.

We agree that these points need to be better summarized. We have reorganized the introduction and pathophysiology section to make it clearer to the reader and emphasized the main points. Other changes were also made throughout the manuscript.

- Direct differentiation → page 6, line 16
- Paracrine effects → page 6, line 17 and page 9 line 1
- Parameter changes of HF → the last line of page 9, up to page 10, line 2

For endogenous cardiac regeneration, such as YAP signal pathway, plays important roles

Thank you for this important point. Indeed, we agree that this is an important pathway and for that reason, we added a paragraph on the YAP signal pathway (page 9, line 6).

The topic on how stem cells increase the turnover rate of myocytes should be covered.

This is indeed another important point. We have included a new section on how various endogenous pathways including the YAP signaling pathway can increase the turnover rate of cardiomyocytes (page 8, line 27).

Past, present clinical trials should be summarized in a Table for better understanding.

We agree that a summary table would be helpful. As suggested, we have added a table summarizing the landmark clinical trials that have used cellular therapeutics in the treatment of HF, with references (**table 1**, page 19).

Table 1: Safety parameters of various stem cell types, please list the citations in table.
Thank you for your suggestion. We have included a column that lists the references within the table. Please note that it is now **Table 2** (page 21).

Reviewer #2:

This review focused on the pros and cons of the different types of the stem cells used in clinical trials and discussed the limitations of the stem cell therapy and its promising future, which presented an overview of the history of the stem cell therapy in heart failure. The language has high quality and rigorous logic. Overalls, this review is interesting and impressive, and acceptable for publication. There are some suggestions to be addressed.

We thank the reviewer for the summary of the project and the kind comments.

The clinical trials with different stem cell therapies can be summarized in a table, so the readers can easily track the clinical trials and profoundly understand these.
We agree that having a table summarizing the landmark clinical trials would greatly benefit the reader. As suggested, we have added in a table summarizing important clinical trials in the domain of stem cell therapeutics for the treatment of HF. This **table 1** can be found on page 19.

in the part of the "microvesicles and exosomes", as also mentioned in the discussion, the exosomes have been involved as a vital branch of this field, thus a vivid picture of microvesicles and exosomes for therapy in heart may be suitable.
This is an important point. We agree that exosomes may play a vital role in the future of cellular therapeutics for heart failure. For that reason, we have moved the exosomes paragraph to the results section (pages 22, 23) and have included some additional

information on microvesicles. This included discussing a clinical trial using exosomes to treat acute stroke.

Reviewer #3:

The manuscript entitled "Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?" by Rheault-Henry et al rises an important question of modern translational research. Stem cells draw a lot of public attention during last two decades however no significant practical achievements have been done so far and are not seen in the nearest future. The reason for this is the lack of solid scientific basement for the cell therapy of myocardium. The manuscript is interesting and well written however I would advise to introduce some corrections and changes.

We thank the reviewer for the summary of the project and the kind comments.

P.6 section STEM CELLS AND THEIR APPLICATIONS. "Cells derived from the zygote have the ability to differentiate into any embryonic or extraembryonic cell type in the body and are termed totipotent." It is impossible to derive cells from the zygote because it is just one cell. Upon its division two-cell, 4-cell, etc blastomere is formed. On blastomere stage cells are totipotent because they have ability to differentiate into the embryo and the trophectoderm. Later on blactocyst stage cells of the ICM are able to differentiate into embryonic and extraembryonic cell types. Extraembryonic cells and trophectoderm form placenta.
Thank you for pointing this out. We have changed the word zygote to blastocyst on page 6, line 1.

"Human ESCs can differentiate into all three germ layers but lack the potential to create extra-embryonic tissues like the placenta.."- it is incorrect for both human and mouse ESCs, they can form extra-embryonic tissue, however mouse ESCs do not form trophectoderm, although human ESCs do.
Thank you for this comment. We have removed the sentence about ESCs not being able to differentiate into extra-embryonic tissues.

"The successful creation of iPSCs was first documented by Shinya Yamanaka and James Thomson in 2007, and George Q. Daley in 2009[11]." It is incorrect, the creation of iPSCs was first documented by Takahashi&Yamanaks in 2006, later independently Yamanaka and Thomson established human iPSCs in 2007.

Thank you for clarifying this out. We have removed the sentence pertaining to the historical context of iPSCs.

"…although it is apparent that some degree of epigenetic memory is retained with iPSCs making it challenging to reprogram them to a fully pluripotent state[13]." It is incorrect. Recent studies demonstrated that there are no any specific epigenetic memory (see Shutova et al 2016 etc).
We agree with the reviewer's comments regarding epigenetic memory and for this reason, we have removed this sentence.

Section Results, ADULT STEM CELLS Cardiac stem cells. " it is now well established that CSCs express markers of cardiogenesis and can differentiate into cardiomyocytes and vascular endothelial cells[38]." These data are form P.Anversa paper. P.Anversa was blamed for scientific misconduct and majority of his papers about CSCs were retracted https://academic.oup.com/eurheartj/article/40/13/1036/5423360. I am sure that it will be better to avoid the citation of the accused author. Authors also cite another paper by Anversa and mention that it was retracted. There were retracted almost 20 papers and I do not even think that the concept of CSCs is correct and alive. The field was significantly compromised by Anversa misconduct.

We fully agree with the reviewer regarding avoiding any references from Anversa and group. For this reason, we have removed all articles pertaining to Anversa's research and have acknowledged his impact on the field of CSCs in greater detail in the article on page 13, lines 2-14 and page 33 lines 5-8.

Section Discussion. The majority of section is devoted to the ethical issues and unproved therapies. Indeed, the all field and particularly of the adult stem cells is highly compromised and demonstrated no clinical benefits for patients. However, I would recommend to put more attention to scientific basis of therapies rather on the momentary ethical concerns of the nonexistent treatments.
We agree that this section was densely populated with discussion on the ethical concerns of treatments which remain controversial. For this reason, we have condensed the ethical issues section and have included the paragraph at the end of the discussion on page 31.

Reviewer #4: This manuscript authored by Mathieu Rheault-Henry et al. is a comprehensive and well-constructed review, focusing on the stem cell therapy for heart

failure. I fully recommend it for publication, with little changes/proofreading as listed below:

We thank the reviewer for the summary of the project and the kind comments.

There is a lack of the keywords
We have included 6 key words, maximum allowed as per the journal guidelines.
Pg7: at the lower part of the 2nd paragraph, '…Cell and Science[19,20],' change to 'and'. Pg11: guess the word PSCs meant 'iPSCs' in a few places, and also in the 6th line from the bottom in pg25. Pg15: in the middle of the page '… LV function,' finishes with full stop. Pg17: the 8th line in the first paragraph 'mesenchymal precursor cells' should be MPC? Pg21: the last 5th line in the first paragraph, 'The Centers for Disease Control and Prevention (CDC)' Is it CDCP? Pg28: the 8th from the bottom, 'Cardiac progenitor cells …' meant CPC?
Thank you for highlighting these concerns. All issues above have been resolved as suggested.
We have also corrected all abbreviations and grammatical errors at their respective locations.

It would be better to provide a list of abbreviations at the end of the manuscript.
We agree that a list of abbreviations would be helpful for the reader. As suggested, this was added on page 35.

The authors appreciate the suggestions of the reviewers and believe that as a result, this manuscript has improved.

We hope this revised version will meet with your approval.

Sincerely yours

Mathieu Rheault-Henry, MS2
Rony Atoui, MSc, MD, FRCSC, FACS