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May 20, 2020

**Re: A Comprehensive Review of Hemolysis in Ventricular Assist Devices (ID 54539)**

Dear Editors,

We would like to thank you for the opportunity you kindly gave us to revise and improve our manuscript.

We would also like to thank the reviewers for their thoughtful comments that much enhanced the quality of our work. We have addressed their comments in the revised manuscript and a point-by-point response can be found in the attached pages below. We have also addressed editorial comments of April 13<sup>th</sup>.

Kind regards,

A handwritten signature in blue ink, appearing to be 'L. Palaiodimos', with a stylized flourish at the end.

Leonidas Palaiodimos, MD MSc  
Assistant Professor of Medicine  
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**Response to reviewer #1:**

On behalf of my co-authors I would like to thank you for your thoughtful comment. In response to the specific point that was raised:

**Interesting topic the article should be re written so it becomes somewhat easier to read  
maybe some figures or tables**

Authors' response:

The manuscript has been carefully revised and 2 tables have been drawn up and incorporated into the revised version so as the paper to become more comprehensible.

## **Response to reviewer #2:**

On behalf of my co-authors I would like to thank you for your valuable comments. In response to the specific points that were raised:

**"A Comprehensive Review of Hemolysis in Ventricular Assist Devices" must be revised with respect to 1.Improve in grammatical errors and typographical errors 2.Literature review till date as it sites researches up to 2017 3.Provide a table showing the modification done to VAD overtime to reduce the hemolysis 4.Follow international standard during revision/follow instruction to the author for writing a review article/meta-analysis.**

Authors' response:

1. The manuscript has been carefully revised and all typos and grammatical errors have been corrected.
2. We have updated our manuscript with the latest evidence on the topic. More specifically,

**Page 3, Incidence section, 2nd paragraph, last lines** now read: *"Along these lines, a recent study from Japan showed that hemolysis was the most frequent adverse event among HeartMate II receivers, of whom 14% developed a major hemolytic event." (ref 12: Seguchi O, Kuroda K, Kumai Y, Nakajima S, Yanase M, Wada K, et al. Clinical Outcomes of Patients With the HeartMate II Left Ventricular Assist Device: A Single-center Experience From Japan. Transplant Proc. 2018;50(9):2726-32)*

**Page 3, Incidence section, 3rd paragraph, last lines** now read: *"More impressive were the results of two small-sized studies for the Heartmate 3 LVAS, where no cases of hemolysis were observed." (ref 16: Nowacka A, Hullin R, Tozzi P, Barras N, Regamey J, Yerly P, et al. Short-term single-centre experience with the HeartMate 3 left ventricular assist device for advanced heart failure. Eur J Cardiothorac Surg. 2020).*

**Page 7, Prognosis section, last lines** now read: *"Interestingly, in a recent study by Xia et al., hemolysis or pump thrombosis were found to be a significant predictors of poor long-term survival, even after adjusting for potential confounders."(ref 38: Xia Y, Forest S, Friedmann P, Chou LC, Patel S, Jorde U, et al. Factors Associated With Prolonged Survival in Left Ventricular Assist Device Recipients. Ann Thorac Surg. 2019;107(2):519-26).*

3. In the revised manuscript we provide a table presenting the basic characteristics of different types of LVAD and their association with hemolysis (Page 3, Incidence Section, 1<sup>st</sup> Paragraph, last line).

4. Thank you for your comment. However, our manuscript is a narrative review and not a systematic review and meta-analysis. Therefore, the PRISMA statement does not apply to our

manuscript.

**Response to reviewer #3:**

On behalf of my co-authors I would like to thank you for your detailed comments. In response to the specific points that were raised:

**Dear author, this is a review paper that is focused on critical issues of the hemolysis from the perspective of long-term (durable) ventricular assist devices (VADs), covering the entire clinical spectrum of this expected but potentially life-threatening complication. The article is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly. The most discussable options in the article are: 1) Would you please kindly correct all your typos and grammar errors throughout the manuscript. 2) I would suggest drawing the summarizing table with the main studies, different types of devices (this is what I am missing in the paper; there is a question about the role of the type of device), outcomes. Generally, the paper is of very good quality**

Authors' response:

1. The manuscript has been carefully revised and all typos and grammatical errors have been corrected.
2. 2 tables have been drawn up and incorporated into the revised manuscript (Page 3, Incidence Section, 1<sup>st</sup> paragraph, **Table 1: Basic Characteristics of Different Types of Left Ventricular Assist Devices**; Page 7, Prognosis Section, **Table 2: Baseline Characteristics, Demographics and Results of Studies Investigating hemolysis in LVADs**)