Author’s response to reviews

Title: Point-of-Care Measurement of Activated Clotting Time for Cardiac Surgery as measured by the Hemochron Signature Eliteand the Abbott i-STAT: Agreement, Concordance, and Clinical Reliability

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Author’s response to reviews:

Dear Guangde Tu:

Please find enclosed the revised version of our above-mentioned manuscript, accompanied by a point by point response to the reviewer’s comments.

We hope that you will find our response appropriate and that our revised manuscript can be considered accepted.

Thank you for your consideration.

Sincerely,

Daniel Dirkmann

Response to reviewer No. 1:

We thank this reviewer for his time and effort spent in reviewing our manuscript. We also appreciate that he considers our study well designed.
With respect to this reviewer’s question regarding data on potential preoperative anticoagulation or antithrombotic therapy we are unfortunately not able to provide the suggested data post hoc, due to anonymization. Although we agree with the reviewer that the suggested data would add some potentially interesting information, we also agree that the primary endpoint of our study would not be affected by this information.

Again, thank you for your time and effort spent in reviewing our manuscript.

Response to reviewer No. 2:

We thank this reviewer for his or her time and effort spent and in reviewing our manuscript. We appreciate that he or she considers our manuscript very well written and structured.

The reviewer suggests including additional figures on the results obtained with each device at the three intraoperative times points (i.e., before heparin, during CPB / following heparinization, and after protamine, respectively).

Response: The requested data are already provided in figure 2 of the original manuscript. However, data prior to heparin administration and post protamine infusion have been pooled in the respective graphs and analyses (figure 2A, C and E, respectively), for two reasons. First, for the statistical analyses it does not seem to make a difference if no heparin or only small amounts of heparin have been given, or if heparin has already been bound to protamine to a certain degree. Second, since only one ACT-measurement is usually performed at baseline, according to our clinical standards, only a very limited number of measurements prior to heparin administration was available for our analyses. In order to provide a robust number of data points, we decided to pool these data. Accordingly, we do not feel that the suggested analyses would add any robust information.

The reviewer suggests a more neutral wording in the paragraph measurements with Hemochron devices.

Response: As suggested by this reviewer, we have removed the term “only” throughout the whole paragraph (page 8, lines 6-18 of the revised manuscript), except for the last sentence reading “Of note, in one case the parallel result was only 384 s.” (line 18). This large discrepancy between the two parallel measurements seems noteworthy, because the difference is very high, and this one result is even below the absolute lower limit of 400s while the parallel assay read 1.000s. To further accommodate this reviewer, we also removed the term “worse” and reworded the respective sentence now reading “Bland-Altman analyses demonstrated good agreement, albeit with a relatively broad 95%-cofidence interval (bias: -12.14 s; 95%-confidence interval: 316.3–290 s)”.
The reviewer correctly states that values >1.000s with one of the two identical devices evaluated must strongly contribute to the lower performance of the comparison and wants to know if these values been verified in a second analysis.

Response: According to our clinical standard, non-plausible results such as 1.000s using just one single ACT-device always have to be verified by a second analyses using a new blood sample. In fact, our observation on the high incidence of measurement results reading 1.000s with the one device triggered this clinical evaluation using two types of ACT devices and four parallel measurements. In the present study, re-testing was not considered necessary unless all 4 devices would have concordantly demonstrated 1.000s.

Please note that 22 of 125 measurements were found to provide incongruent results. Thereof 14 measurements included one result reading 1.000s on one device. Please also note that on two occasions both identical devices provided concordant, thus plausible, measurements reading 1.000s. Accordingly, the user cannot be sure if a result of 1.000s is correct or not. Although, as the reviewer correctly states, these parallel measurements with one of the two identical devices strongly contribute to the lower performance, it is still a potentially critical error, essentially limiting the performance of this very device.

The reviewer requests better quality of the figures.

Response: As assumed by the reviewer, the bad quality of the figures seems to result from a conversion problem. The figures uploaded were of high quality. We will assure that high quality images will be included in the publication.

Again, thank you for your time and effort spent in reviewing our manuscript.