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# Response to the Comments on 'Point of Care D-Dimer Testing in the Emergency Department–A Bioequivalence Study' and Erratum to the Results

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We have read with interest the comments made on our study titled 'Point of care (POC) D-dimer testing in the Emergency department–a bioequivalence study' [1].

Ekelund and Heilmann, referring to the results and conclusions of the study, have suggested that one of the discrepancies may be caused by a typographical error, and this inference probably stems from the use of the term 'range' in the published article. This should have been termed 'Bland-Altman limits of agreement' (0.24-2.13) for all the cases where both tests were ordered and not just for the 8 POC-negative VIDAS (VIDAS D-dimer assay; bioMérieux SA, RCS Lyon, France)-positive patients. The data have been reconfirmed by our database as not being a reporting error.

Our study reflects a real-life scenario of replacing an existing laboratory test within the emergency department with another POC assay (AQT90 FLEX POC D-dimer analyzer; radiometer medical ApS, Åkandevej, Denmark). This involves conducting a bioequivalence study between the two assays to rule out the risk of missed positive results–the outcome by which clinicians would be guided.

Raising the cut-off values, including age-appropriate cut-offs has been suggested in the literature as a measure to improve the specificity of D-dimer assay and reduce the implications of radiological investigations for various subsets of patients [2-7]. Furthermore, a separate study on the sensitivity and specificity of D-dimer test in venous thromboembolism is in progress. As pointed out in the results of our study, the POC D-dimer assay demonstrated better specificity than the VIDAS assay; however, our study was neither designed nor powered to investigate this question as the primary outcome measure. If statistically proven in a larger cohort of patients, the improved specificity of POC D-dimer assay may reduce the risk of unnecessary radiation or other interventions for a subset of patients, which could be considered as a significant strength of the assay.

As pointed out by Sukhu et al. [8], discordant values are increasingly obtained near the cut-off levels leading to mismatched results between the two assays, therefore, a larger study would be required before implementing a new methodology in a clinical setting. A study on bioequivalence between the two assays was not enough to make an informed decision to replace one test with the other, a conclusion also supported by Sukhu et al. [8] in their study.

The criteria for bioequivalence studies and cut-offs for drugs are well established [9, 10], but the question can be raised whether the same standards can be applied for bioequivalence of diagnostic assays, especially in diseases of low prevalence [11].

Our study results show that the 8 patients who were tested positive by the VIDAS assay demonstrated negative POC D-di-

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mer results, and these results together with the wide Bland-Altman limits of agreement (0.24-2.13) led to a conclusion that the two assays were not bioequivalent. This conclusion does not refer to the performance of the POC assay, but only to the comparison with the VIDAS method.

It was reassuring to see that amongst the 40 patients evaluated using the 'gold standard' imaging test, all of the 12 POC D-dimer-negative patients also had negative imaging results as, for that matter, did the 6 patients with negative VIDAS results. Much larger studies on comparison of both methods to the 'gold standard' imaging test are required before significant differences in sensitivity or specificity between these tests can be claimed.

A review of the manuscript, data files, clinical details of the participants' medical records, and discussions with the data collectors has revealed that contrary to the reported results, only 6 of the 8 patients who were positive by the VIDAS but negative by POC testing had imaging during their stay in the emergency department. For cases 3 and 8 in Table 2 of the original manuscript, the imaging procedure was deferred at their admission to the emergency room. Although in both cases the imaging results were negative, they were obtained after the patients discharge from the emergency department.

These 2 cases were not included in the sensitivity and specificity calculations reported in Tables 4 and 5 of the manuscript because of a significant time delay (over 24 hr) between the D-dimer data collection and the imaging. The authors would like to apologize for not having disclosed it in the original manuscript.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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