Received: 8 April 2024 | Accepted: 17 April 2024

https://doi.org/10.1016/j.rpth.2024.102429

LETTER TO THE EDITOR

Reply to "Letter to Dobesh et al. on lower mortality with andexanet alfa in factor Xa inhibitor–related major bleeding"

To the Editor,

We would like to thank Lucarelli et al. [1] for their interest in our manuscript [2] and for highlighting the methodological challenges prone to nonrandomized study designs. While a high risk of bias has been noted in previous observational studies on the current topic [3], our study employed multiple strategies to mitigate this risk. For this large sample of patients from >350 hospitals across the United States over a 4-year time span [2], we captured several laboratory and clinical variables that are not commonly available in other observational data sources and applied multiple analytical approaches to understand and reduce the risk of residual confounding. These approaches included regression analyses with adjustment for confounders, propensity score-weighted analyses in which missing data on key confounders were imputed, and sensitivity analyses. Findings across all of these analytical approaches consistently showed lower mortality in patients treated with andexanet alfa compared with 4-factor prothrombin complex concentrate (4F-PCC).

Contrary to the assumption by Lucarelli et al. [1], the current study did not exclude the sickest patients; rather, no eligibility criteria on severity markers were applied in order to reflect patients who received either andexanet alfa or 4F-PCC in routine clinical practice. Of the patients with intracranial hemorrhage (ICH) and an available Glasgow Coma Scale (GCS) score, approximately one-third had a GCS score of ≤8 (ie, severe). While the mean door-to-needle time was 7 to 8 hours (due to extreme outliers), the median door-to-needle time of 2.3 to 2.5 hours suggests a population that required prompt anticoagulation reversal. Further, we excluded patients who received both andexanet alfa and 4F-PCC in alignment with prescribing information advising against combination use [4]. Less than 1% of patients met this exclusion criterion; thus, it is unlikely to impact study findings or generalizability.

The ANNEXA-I (Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor) trial referenced by Lucarelli et al. [1] was designed to assess hemostatic efficacy, and the imaging component of limiting hematoma expansion was achieved in 77% of patients treated with andexanet alfa vs 65% of patients treated per usual care, the majority of whom received 4F-PCC [5]. The observed 35% hematoma expansion with usual care in ANNEXA-I may suggest little to no benefit with PCC in factor Xa (FXa) inhibitor–related bleeds based on its inability to effectively lower FXa levels, in alignment with findings from other studies [6]. Hematoma expansion is associated with poor functional outcomes and an increased risk of death after ICH. However, the ANNEXA-I trial was not designed or powered to evaluate these endpoints. Extrapolation of the results of ANNEXA-I to the study by Dobesh et al. [2] is hampered by key differences between the studies, including eligibility criteria (type of bleed and severity), choice of primary endpoint (hemostatic efficacy vs mortality), and baseline risk profiles. Of note, patients in ANNEXA-I were nearly 15 years older than those in the study by Dobesh et al. [2] and thus had an inherently higher risk of death, potentially irrespective of treatment [5].

Noting a challenge inherent to observational, nonrandomized study designs, Lucarelli et al. [1] brought up the point that clinicians may have selected which treatment to use with consideration given to the patient's risk profile and predicted outcomes. To address this risk of confounding by severity, our analyses controlled for many of the critical confounding variables highlighted by Lucarelli et al., including impaired mental status, spontaneous vs traumatic bleed cause, and GCS score. Hematoma volume and thickness were underreported (captured from medical charts for only 6% and 15% of ICH patients, respectively) and therefore not adjusted for. Further, in alignment with recommendations from the American Statistical Association [7] and contrary to the suggestion from Lucarelli et al., potential confounding covariates were identified based on their clinical relevance and completeness of data rather than by statistical comparison.

Finally, Lucarelli et al. [1] highlight the absolute difference of 4.4% in the proportion of ICH patients with a severe GCS score, erroneously linking this to the overall absolute mortality difference rather than the 10.7% absolute mortality difference observed among patients with ICH. We agree with Lucarelli et al. [1] on the importance of the GCS score as a key severity marker and confounder, especially in the absence of complete data on hematoma volume. Accordingly, we performed an

adjusted sensitivity analysis restricted to ICH patients with an available GCS score as well as propensity score-weighted analyses in which the GCS score was balanced between groups, both of which yielded results consistent with the primary analysis, showing lower mortality in patients treated with andexanet alfa compared with 4F-PCC. This emphasizes the robustness of findings in this largest-to-date, most comprehensive observational study of patients treated with andexanet alfa or 4F-PCC while hospitalized for FXa inhibitor–related major bleeding. Contrary to the final remarks from Lucarelli et al. [1], our findings, along with those of other recent observational as well as randomized trials [5,6,8], do help inform clinical practice.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing, reviewing, and editing of the Letter to the Editor, and read and approved the final version for submission.

RELATIONSHIP DISCLOSURE

P.P.D. has served as a consultant for the Pfizer/Bristol Myers Squibb Alliance and Janssen Pharmaceuticals. G.J.F. has served on a speakers bureau for Janssen Pharmaceuticals and AstraZeneca, has served as a consultant for Milestone Pharmaceuticals, and has received research funding from Siemens, PCORI, and NIH. B.K., E.L., H.C., and T.D. are employees of AstraZeneca. M.J.C. and B.L. are previous employees of AstraZeneca. M.D., J.U., and S.D. are employees of Outcomes Insights, which has received research funding related to cardiovascular disease from Amgen and Boston Scientific. C.I.C. has received research funding and/or consulting honoraria from Janssen Pharmaceuticals, Bayer AG, and AstraZeneca.

FUNDING INFORMATION

This work was supported by Alexion, AstraZeneca Rare Disease, and AstraZeneca AB.

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