Author’s response to reviews

Title: Characteristics of patients initiated on edoxaban in Europe: baseline data from Edoxaban Treatment in routiNe clinical prActice for patients with atrial fibrillation (AF) in Europe (ETNA-AF-Europe)

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Reviewers’ comments

Peter Brønnum Nielsen (Reviewer 1)

The manuscript by Prof De Caterina et al. reports on the baseline characteristics from the ETNA-Europe prospective registry including data on atrial fibrillation patients using edoxaban for stroke prevention.

The manuscript includes clinically relevant and scientifically interesting insight into the use of the most recent approved NOAC agent. The results are clearly presented and selected subgroup analysis provide meaningful clinically insight. The manuscript is generally well-written, but some overall changes could likely improve the disposition of the text. I have the following suggestions:

Response: We thank the reviewer for their feedback.

Major comments:

The structure of the Methods section could be improved: reading a sub-headline with "Objectives" as the last paragraph before the results was confusing. I suggest the following:

1) Remove the last sentence in the Introduction section ("Here, we report…"); page 6, line 1-3.

Response: The last sentence in the introduction section has been removed and instead, a statement on objectives of the study has been included.

2) The last sentence from the Objectives section ("The objective of this analysis…"); page 7, line 25-26 and page 8, line 1-2 - this sentence should end the Introduction section.

Response: As detailed above, the last sentence from the objectives (methods section) has been moved to the end of the background section.

3) The first paragraph of the Objectives section ("The primary objective…"); page 7, line 20-24 could be moved to page 7, line 9 preceding the sentence starting "Details of the design".

Response: This adjustment has been made (Page 7, lines 9 to 14).
These structural changes to the text would allow the reader to understand the author's purpose of the conducted analysis, and maintain the provided (and necessary) insight in the ETNA-AF registry description.

Response: We thank the reviewer for their feedback.

While the readers are referred to an earlier publication on the design and rationale of the ETNA registry (ref #21), it would be helpful to provide additional information in this manuscript. E.g. expected number of patients in the registry; how AF was determined; types of previous AF-related therapy collected; assessment/calculation of the CHA2DS2-VASc and HAS-BLED score (rather than providing this additional information in the Results section); and information on number of follow-up visits. Also, specification on subgroup analyses could be described in the Methods section to prime the reader of the Results section.

Response: Information on all these points has been added in the Methods section, page 7, from lines 21 to 27 and page 8 at lines 1 to 4.

The Discussion section could preferably begin with a summary of the obtained results, and how these compare with the ENGAGE AF-TIMI 48 trial baseline data. Additionally, in the discussion of limitations of RCTs and the benefits of prospective registries to inform on a use in routine care, it would be fair to also mention the limitations of a prospective registry: That is, patients opt in for enrolment, which causes a selection bias that is difficult to examine, and therefore may hamper the generalizability of the observed results.

Response: We have added a summary of the obtained results at the beginning of the discussion (Page 12, lines 2 to 7).

A comment on the limitations of the prospective registries was added and the whole paragraph on RCTs and Prospective registries benefits and limitations was moved further down in the Discussion section to page 16 from lines 4 to 13.

Minor comments:

Page 9, line 22: Please avoid using the arbitrary classification of patients as low, intermediate, and high stroke risk based on the CHA2DS2-VASc score; the score level itself is sufficient.

Response: This change has been applied (Page 9, lines 22 to 24)
Page 10, line 12: I disagree with the adjective of SmPC adherence of 83.8% is "good". Suggest to report the number as is and avoid interpretation of this result in this section.

Response: This change has been applied (Page 10, lines 12 and 13)

Page 10, line 25: A "]" (bracket) typo.

Response: Bracket has been deleted.

Page 12, line 13-17: Suggest to move this paragraph to the Methods section.

Response: This paragraph has been moved to the last paragraph of the Methods session, page 8, lines 7 to 11.

Page 14, line 4: The statement of "commonly observed that NOACs are frequently prescribed at a lower dose" requires a reference.

Response: References have been included (Page 14, line 8).


Response: The sentence has been rephrased (Page 16, lines 23 to 25).

İhsan Alur, MD (Reviewer 2)

First of all I want to thank the writers of this article for their planning and performed such an important 'Descriptive' study. I have read this study and here are my ideas and thoughts about it:

The methodology of the study is well-designed. The results are consistent with the literature.

I think this paper can be accepted.

Response: We thank the reviewer for their feedback.
Andrea Bezzeccheri (Reviewer 3)

The manuscript is well written. Data were analysed well and the conclusion is adequate to the data analysed.

Agree for submission.

Response: We thank the reviewer for their feedback.