

Peer Review File

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Reviewer Comments

The author summarized the evidence assessing the optimal timing of anticoagulation in patients with acute ischemic stroke and atrial fibrillation.

Overall, this editorial would benefit from improved logical flow in the first (large) paragraph instead of, going from one topic to another, and one article to another. Another thing puzzles me is that the content of this commentary does not seem to be relevant to the readership of a journal focused on palliative medicine. Please find below my detailed comments:

Reply: Regarding the structure of the text the author included subheadings to better organize the text in the manuscript. The manuscript was invited by the journal in regards to the comment of the reviewer regarding the chosen journal for the editorial.

Major:

Comment 1: The author raised concern regarding the safety of anticoagulation very early on after a stroke given the results of the RAF-NOACs study showing worst outcomes when anticoagulation initiated within 2 days of stroke event. However, the author failed to mention that RAF-NOACs study had an observational design for the overall timing of hemorrhagic events after starting of anticoagulant, and patients may receive LMWH before NOAC.

Reply 1: We thank the reviewer for pointing out that it is important to emphasize the shortcomings of the cited study in the context of the studies advocating the early start of anticoagulation in patients with stroke and atrial fibrillation. Thus, we did include this part at the beginning of the editorial.

Changes in the text: The blue marked text is now featured in lines 32-41 page 1 with:

“The early start of anticoagulation is not without reported risk as an study could show that patients who were started on direct oral anticoagulants (DOACs) within 2 days after acute stroke had a composite rate of recurrence and major bleeding of 12.4% and composite rates were 2.1% for those who initiated DOACs between 3 and 14 days further, 9.1% for those who initiated DOACs >14 days after acute stroke (3). Thus, it still remains to elucidate when the best time to initiate treatment in patients with acute stroke is directly following the event or at different time in the first 4 days. However, these data have limitations as the study was observational and further patients were allowed to receive low molecular weight heparin before DOAC. In addition, the study had multiple selection bias to only include patients which were deemed at a low risk for hemorrhage or with mild stroke regarding impairment or small size (4).”

2. A few messages seem out of place and do not contribute to the logical flow of the text.

Examples include:

a. Lines 64 to 69: The author mentions that NIHSS is a poor surrogate to estimating size of infarct and is not used in major studies because location of infarct also affects NIHSS. This statement, although likely true, is out of place in this text and should either be moved elsewhere or omitted altogether.

Reply 2a: The reviewer is correct regarding the not appropriate text regarding the NIHSS in the featured paragraph in the first version of the manuscript. Thus, the authors did rearrange the text in the way that the NIHSS and in this context imaging-based severity grading of stroke is featured before the main body of the editorial.

Changes in the text:

The text is now shown in lines 42-48 pages 1-2:

“Grading stroke severity in the context of functional impairment and imaging-based grading
The most often variable to grade stroke severity is the National Institutes of Health Stroke Scale (NIHSS) which increases due to the documented impairment with an increase of the score (5, 6). In the recent years investigators did collect data in a multicenter approach to predict infarct size and location as the implications are important for decision-making and to establish prognosis in patients with acute stroke (7, 8). As of current due to progressive establishment of neural networks in research and science prediction of the final infarct size can be established with the baseline scan (7, 8).”

Comment 2b. Lines 73 to 81: Given that the TIMING study is similar to ELAN study, it might flow better if it is cited next to the ELAN study instead of mentioning it near the end of the text.

Reply 2b: The comment of the reviewer is correct regarding this aspect. Thus, the author chose to include the aspects of the other studies related to this study with TIMING and OPTIMAS in the same text and show common aspects and differences in the text.

Changes in the text: The author did change and overwork the main body of the text to show results of the other studies as well. Please refer to line 49 and following.

3. A few important points were missing such as:

Comment 3a. The natural history of recurrent stroke and hemorrhagic transformation after an acute ischemic stroke in patients with atrial fibrillation should be explored in the introduction.

Reply 3a: The author did include the topic of recurrent stroke and hemorrhagic transformation into the introduction of the editorial lines 27-30 on page 1

Changes to the text:

“In patients with acute ischemic stroke and atrial fibrillation, early start of anticoagulation is associated with less recurrent stroke but with the risk of hemorrhagic transformation of the infarcted area (3). In the literature a later onset of 12 days is described in patients with hemorrhagic transformation following ischemic stroke in AF patients (3).”

Comment 3b. ELAN study: No mention of the rate of sICH in each group (early vs late)

Reply 3b: The author did include the numbers regarding spontaneous intracerebral hemorrhage

into the manuscript text. Lines 82-85 page 2

Changes in the text:

“However, in contrast the data published previously in an observational trial (4) the results of ELAN suggest that the incidence of symptomatic intracranial hemorrhage is low with 2 patients (0,2%) each in the early and late treatment arm at 30 and 90 days (11) and in TIMING even no cases of intracranial hemorrhage were reported (12). “

Minor:

Comment 1. A few grammatical and stylistic errors:

a. Line 30: In “an important questions”, “questions” should be in singular form.

General author comment: The authors thanks the reviewer for correcting typos and grammatical issues in the text.

Reply 1a: Done. Line 25

Change in the text: “an important question”

b. Line 31: In “in the patients”, “the” should be omitted.

Reply 1b: Done. Line 26

Change in the text: “in patients”

Comment 2. Lines 44 to 46: The author should clarify that “anticoagulation was started in the first 48 hours in minor and moderate stroke and on day 6 to 7 in a major stroke” refers to ELAN trial early anticoagulation approach.

Reply Comment 2: The author did highlight that the mentioned anticoagulation scheme was used in the ELAN study. Lines 63-64 page 2.

Changes in the text: According to this imaging-based definition of stroke size the anticoagulation was started in the ELAN study in the first 48 hours in minor and moderate stroke and on day 6 to 7 in a major stroke (11).