Author’s response to reviews

Title: Transcranial Doppler ultrasonography predicts cardiovascular events after transient ischemic attack

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Author’s response to reviews:

Dear Dr. Alam,

I am sending you the revised manuscript “Transcranial Doppler ultrasonography predicts cardiovascular events after transient ischemic attack” (MS: 1082776614251964). I am glad that you reconsider it for publication.

The authors made the following changes according to the referees’ comments:

1. In the abstract, “these abnormal ECD and TCD findings” are described in more detail.

2. Assessment of outcome is described in more detail on page 6 now. Moreover, assessment of outcome by telephone or mail interview at a late point of time is mentioned as limitation of the study on page 13.

3. All patients were contacted by an experienced neurologist who was blinded to the patients’ ultrasonographic findings. This information is given on page 7 now.

4. Tackling of uncertain events is characterized on page 7.

5. ECD and TCD classification did not distinguish symptomatic and asymptomatic vessel disease. This is mentioned on page 6 and in the limitation section now.

6. All patients were admitted to the Stroke Unit within the first 72 hours after symptom onset. This information is added on page 4 now. As suggested by reviewer 1, optimized TIA care isn’t discussed as explanation for the lack of association between prolonged symptom duration and risk of recurrent cerebral ischemic events any more.

7. As suggested by reviewer 1, the study of van Wijk et al. is cited in the background section.
8. The phrase "be simply by" is replaced by "be simply explained by" on page 12.
9. Baseline characteristics of patients with and without abnormal TCD are provided as additional file.
10. Only patients with cerebral TIA were included in the present study, as data suggest that there are pathogenic and prognostic differences between transient eye and brain ischemic syndromes [1, 2]. The sentence “Amaurosis fugax was not considered as TIA.” may have been unclear and is rephrased now.
11. Cardiac insufficiency was used as a synonym for cardiac failure. As suggested to by reviewer 2, the term “cardiac failure” is used in the manuscript now.
12. Tandem lesions of the cervical internal carotid and ipsilateral intracranial artery were detectable in 3 patients. This information is inserted on page 9.
13. Intracranial vertebral arteries and basilar artery were examined systematically by TCD in the present study, too. Although TCD findings of the intracranial vertebral arteries and basilar artery were documented separately from ECD findings in each patient, vertebrobasilar ECD and TCD findings unfortunately were mixed in the manuscript. We are sorry for that!

For answering this review, we therefore reassessed all ultrasonographic documents. 8 patients showed stenoocclusive disease of the vertebrobasilar arteries as detected by ECD and TCD:

- Vertebrobasilar ECD detected stenosis of cervical vertebral arteries in 4 patients and occlusion of cervical vertebral arteries in 3 patients. These findings were stratified correctly according to the ECD classification.
- Vertebrobasilar TCD detected stenosis of the basilar artery in one patient. This patient also suffered from an occlusion of the left cICA leading to collateral flow through the circle of Willis.

Basilar artery stenosis was wrongly stratified according to the ECD classification in the present study. However, ECD classification of this patient still remains “stenosis” due to his cICA stenosis. TCD classification has to be changed from “reactive collateral flow patterns” to “stenosis”.

The ultrasonographic classification and the ultrasonographic findings are corrected in the abstract, methods and results section now. There are no changes affecting statistical analyses or study results.
14. Insonation protocol of PCA is added in the methods section.
15. As suggested by reviewer 3, recent studies regarding the ABCD2 score are cited in the background section.
16. The manuscript is adjusted to journal style once more.
17. The research protocol was approved by the local ethical committee. This has been included in the manuscript.

The authors also would like to try to explain some issues:
1. In the present study, we analyzed the prognostic value of ECD and TCD findings in TIA patients. We did not try to evaluate the prognostic value of extracranial versus intracranial stenoocclusive disease in TIA patients as for this question angiographic methods would have been the gold standard. However, ECD and TCD are accepted as accurate, safe, cost-effective and widely accessible diagnostic methods for the detection of extracranial and intracranial stenoocclusive disease [4-6]. The definition of abnormal TCD findings in the present study referred to both reactive collateral blood flow secondary to extracranial lesions and intracranial lesions. 12 of 20 (60.0%) patients with abnormal TCD findings showed at least one #50% stenosis or an occlusion in ECD. Abnormal TCD findings thus probably characterized those TIA patients with the highest risk of generalized atherosclerosis and consequently cardiovascular ischemic events. The results of the present study support the routine use of TCD in addition to ECD in TIA patients.

2. Angiographic validation of ECD and TCD findings surely would have been worthwhile. However, the lack of angiographic validation was mentioned as limitation of the study already. Both ECD and TCD have been shown to be accurate diagnostic tools for the detection of extracranial and intracranial stenoocclusive disease [4-6]. TCD diagnosis of intracranial stenosis was defined not only by cut-off peak flow velocities in our study, but also side-to-side differences >20% and disturbed flow patterns.

3. ECD and TCD, of course, are not limited to detection of stenoocclusive disease. However, this was the point on interest of the present study. Although measurement of intima-media-thickness as well as plaque characterization is routinely done in most TIA patients in our academic center, these features were not documented systematically for the present study. Standardized detection of cerebral microemboli by TCD and measurement of vasomotor reactivity were done in selected patients only.

4. Of course, we did not consider collateral flow patterns equivalent to intracranial stenosis. Findings were pooled, because we tried to analyse the prognostic value of TCD as an ultrasonographic method. Unfortunately, a larger patient cohort would have been necessary to improve the statistical power of the study and allow further subgroup analyses (e.g. differentiating between detection of collateral flow patterns and intracranial stenoocclusive disease by TCD).

5. We could not provide upper 95% CI intervals in figure 1, because data are descriptive. Figure 1 shows the frequency of events we observed in the study.

With kind regards,

Dr. Katrin Holzer

2. Mead GE, Lewis SC, Wardlaw JM, Dennis MS: Comparison of risk factors in


