Reviewer's report

**Title:** Observational Dutch Young Symptomatic StrokE studY (ODYSSEY): study rationale and protocol of a multicentre prospective cohort study.

**Version:** 2  
**Date:** 20 December 2013

**Reviewer:** Jukka Putaala

**Reviewer's report:**

This manuscript presents a multicenter observational study protocol, aiming at characterizing risk factors, etiology, transient triggers, future risk of vascular events and epilepsy in patients with first-ever TIA, or ischemic/hemorrhagic stroke at age 18 to 49. In addition, a neuropsychological test pattern will be performed at baseline and 1-year follow-up visits. This field is understudied and the current knowledge comes mostly from retrospective single-center data. There is thus a clear rationale for this study.

To further improve the protocol and manuscript, please consider the following recommendations and address the concerns:

**Major Compulsory Revisions**

1. **Objectives:** Considering the relative rarity of the stroke event in this age group, extensive baseline data collection, and efforts being invested, the study could not only aim at estimating the risks for the endpoints, but also try to identify baseline factors associated with these endpoints. There are very scarce prospective data in this field.

2. **Sample size:** The aim is to recruit 1500 patients. Please present rationale. Is this based on assumptions on the risk of the primary endpoint, all-cause mortality? Please provide power and sample size calculations and refer to publications on which these estimates may be based on.

3. **Healthy control subjects (pages 7-8):** Why 250 subjects? Give rationale. How is the verification of stroke-free status planned to be done?

4. **Related to objectives,** is the planned sample size and minimum follow-up sufficient to detect meaningful number of endpoint events (primary and secondary) with respect to covariates that can be entered in a Cox regression model? I would suggest doing power calculations separately for all endpoints stratified at least by primary event subtype, even by subtypes of ischemic and hemorrhagic events.

5. **Related again to sample size,** but also to generalizability of the results: Consider leaving the protocol open for an international collaboration. I believe there is a lot of interest in this type of study and international collaboration would allow a substantially higher number of subjects recruited in a shorter time.
6. Physical examination and additional investigations (page 10): “Additional DNA will be stored for future genetic analysis.” Will an investigational blood sample obtained for genetic analysis? There is no mention about this elsewhere in the manuscript. Must the patient consent on this or is the sample taken as part of routine care?

7. Endpoint events (page 11) and their validation (page 13): Consider using harmonized definitions for each event and at least two blinded reviewers. Particularly, in case of ischemic events, reports on recurrent events may be heterogeneous and careful assessment is warranted to judge an event as TIA or ischemic stroke.

8. Endpoint events (page 11): Is information on medication at the time/prior to event being obtained?

9. Neuropsychological assessment (table 2): Despite very comprehensive set of tests, consider adding serial Color-Word Test to assess adaptation capacity to stressful situations (André-Petersson L et al. Stroke 2001;32:1712-1720). This may be relevant especially in the young working-aged individuals.

Minor Essential Revisions

1. Medical history (page 8-9): Given that migraine frequency among young stroke cohorts is relatively high and there is a rationale to hypothesize migraine may play a role in a substantial number of young stroke, please consider screening and classifying migraine with a structured questionnaire.

2. Potential trigger factors (page 9): Infections preceding stroke in the young are common. Considering screening also infections, not only fever. What is the criterion for significant fever and how it is verified?

3. Hazard and control periods for triggers (page 9): It is not clear whether hazard and control periods can be uniformly applied to all triggers in stroke, related to very heterogeneous underlying pathology. Therefore, consider using several hazard periods, e.g. hours 1 and 2 for physical triggers, and several control periods, e.g. hours 25 and 26 preceding the stroke, same day 1 week ago, in addition to the usual frequency. Furthermore, accuracy and timing of asking about triggers is crucial for data reliability. Aphasic patients, those with poor memory around the stroke or cognitive deficits most likely cannot provide trigger information.

4. Etiologic classification (page 10): Regarding the shortcomings of the original TOAST classification, would consider using CCS or ASCO to better characterize patient phenotype.

5. Classification of ICH (page 10): According to Boston criteria, amyloid angiopathy is nonexistent in patients aged <55. What criteria are then used? Some sporadic reports exist that amyloid pathology might lead to ICH also in younger patients. There are also recent attempts to create a classification system.

6. Course of the disease (page 11): modified Rankin Scale during admission does not likely provide meaningful information. Consider leaving just admission NIHSS score to depict symptom severity. mRS prior to index event in those with disabilities, in turn, is meaningful.

7. Discussion (page 15, 4th paragraph): There is an ongoing study (NCT01934725) investigating potential triggering factors among young adults with cryptogenic ischemic stroke. A better statement would read e.g.: “In addition, this study is the first investigating potential acute trigger factors preceding a stroke or TIA in nonselected young patient population.”

8. Discussion (page 15): Many trials had minimum age criterion of >18 years, so perhaps you should state that “...stroke trials in which young adult patients have been underrepresented or excluded.”

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing financial or non-financial interests.