PEER REVIEW HISTORY

This paper was submitted to the JNNP but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and Long Term Clinical Significance of Intracranial Atherosclerosis after Ischemic Stroke or Transient Ischemic Attack
AUTHORS	Ovesen, Christian; Abild, Annemette; Christensen, Anders; Rosenbaum, Sverre; Krarup, Christine; Havsteen, Inger; Nielsen, Jens; Christensen, Hanne

VERSION 1 - REVIEW

REVIEWER	Prabhakaran, Shyam Northwestern University, Neurology
REVIEW RETURNED	15-Apr-2013

GENERAL COMMENTS	This is an interesting paper. The authors are to be commended for their rigorous methodology, longitudinal approach, and thoughtful presentation. However, while the finding of higher prevalence of IAS/IAC in the cohort is noteworthy, the main thrust of the paper rests on the finding of increased hazard of recurrent events in patients with >30% IAS. In that regard, I have several concerns: 1. Why were the co-variates in the multivariate hazard model selected? Why weren't other factors such as large artery atherosclerosis by TOAST criteria (which IAS may be a subset and surrogate for), medical conditions like hypertension, diabetes, coronary artery disease/congestive heart failure, laboratory results such as glucose and cholesterol, and treatments such as anticoagulation and statin therapy included in the model? It would seem that a fully adjusted model is warranted here since the relationship between IAS and events may be confounded by many of these factors. 2. The low rate of symptomatic ICAD in this cohort (< 1%) is surprising even for a predominant Caucasian cohort. While it may be due to early imaging and underestimation due to superimposed thrombus, the authors should better attempt to classify mechanism/subtype in their cohort by established criteria (TOAST or CCS schemes) and present this in Table 1. 3. Given 1 and 2 (possibility of confounding with other atherosclerotic risk factors and low rate of symptomatic ICAD), it would seem that their finding of association with IAS and recurrent events is further evidence that it is a surrogate marker of risk rather than direct mechanism of stroke or TIA (and certainly not IHD). Therefore, I would again suggest that the authors carefully explore potential confounders.

	4. There are several minor typos such as "angioplasticity".

- The manuscript received three reviews at The JNNP but the other reviewers have declined to make the reviews public. Please contact BMJ Open editorial office for any further information.

VERSION 1 – AUTHOR RESPONSE

Comments to the Author
This is an interesting paper. The authors are to be commended for their rigorous methodology, longitudinal approach, and thoughtful presentation. However, while the finding of higher prevalence of IAS/IAC in the cohort is noteworthy, the main thrust of the paper rests on the finding of increased hazard of recurrent events in patients with >30% IAS. In that regard, I have several concerns:

Again, we would like to emphasise that the aim of this paper was to investigate stenosis and calcifications as makers of increased risk. It is true that our findings indicate that atherosclerosis giving rise to lumen reductions of more than 30% is a risk-factor of recurrent ischemic event. In addition, we find that an increasing burden of intracranial artery calcifications increases the risk of recurrent ischemic event.

1. Why were the co-variates in the multivariate hazard model selected? Why weren't other factors such as large artery atherosclerosis by TOAST criteria (which IAS may be a subset and surrogate for), medical conditions like hypertension, diabetes, coronary artery disease/congestive heart failure, laboratory results such as glucose and cholesterol, and treatments such as anticoagulation and statin therapy included in the model? It would seem that a fully adjusted model is warranted here since the relationship between IAS and events may be confounded by many of these factors.

We recognise this potential issue and have changed the method of analysis accordingly as previously described.

2. The low rate of symptomatic ICAD in this cohort (< 1%) is surprising even for a predominant Caucasian cohort. While it may be due to early imaging and underestimation due to superimposed thrombus, the authors should better attempt to classify mechanism/subtype in their cohort by established criteria (TOAST or CCS schemes) and present this in Table 1.

We agree that the rate of symptomatic stenosis was low which is probably due to a more strict definition of which stenosis were symptomatic compared to the one employed in other studies. We did not find the use of these classifications useful in our hyperacute population.

3. Given 1 and 2 (possibility of confounding with other atherosclerotic risk factors and low rate of symptomatic ICAD), it would seem that their finding of association with IAS and recurrent events is further evidence that it is a surrogate marker of risk rather than direct mechanism of stroke or TIA

(and certainly not IHD). Therefore, I would again suggest that the authors carefully explore potential confounders.

Please see above.

4. There are several minor typos such as "angioplasticity".

Has been corrected.

VERSION 2 – REVIEW

REVIEWER	Shyam Prabhakaran, MD, MS Associate Professor of Neurology Northwestern University Chicago, IL, USA
REVIEW RETURNED	26-Aug-2013

- The reviewer completed the checklist but made no further comments.