PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Statin and dual antiplatelet therapy for the prevention of early neurological deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) : protocol for a prospective single-arm study using a historical control for comparison
AUTHORS	Huang, Yen-Chu; Lee, Jiann-Der; Weng, Hsu-Huei; Lin, Leng-Chieh; Tsai, Yuan-Hsiung; Yang, Jen-Tsung

VERSION 1 – REVIEW

REVIEWER	Seners, Pierre Universite Paris Descartes, Sainte-Anne Hospital, Neurology
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	I read with interest the study protocol by Huang et al. To sum up, the authors will prospectively include acute (<24h) stroke patients with branch atheromatous disease (ie, small subcortical infarcts expected to be due to perforator occlusion in front of a non stenotic atheromatous plaque), treated with Aspirine + clopidogrel for 21 days then Aspirin or clopidogrel alone associated with high dose statin therapy ; and compare their clinical outcome with historical controls (same type of patients yet treated with aspirin or clopidogrel alone and no intensive statins therapy). The overall manuscript is very well written and very interesting. The study protocol is well described and sounds methodologically correct. In particular, the authors well justify why they do not perform a randomized controlled trial of Aspirin alone vs Asp + clopidogrel in this population (not ethically feasible, considering the current recommandations). The outcomes are well described and well chosen. I only have the two following comments: 1) I do not really understand the BAD definition : “have BAD, defined by a visible lesion in three or more axial MRI cuts in the lenticulostriate territory or infarcts that extend from the basal surface of the pons ». Was does « lesion » mean ? Ischemic lesion on DWI ? I understand that this criteria differs lacunar infarcts due to « lipohyanilosis » and BAD ? Please clarify. 2) Statistical methodology: Considering the design (comparison with historical controls), which is –as well acknowledged by the authors- prone to several limitations, I think that using a propensity-score weighting or matching methodology would be

	more appropriate. Indeed, this type of methodology is more appropriate to reduce the between group differences.

REVIEWER	Berberich, Anne Heidelberg University Hospital
REVIEW RETURNED	22-Sep-2021

GENERAL COMMENTS	Treatment strategies to reduce early neurological deterioration in patients with BAD are important to improve functional outcome for these patients. This prospective study aims to compare early dual antiplatelet treatment and high-intensity statin treatment with a historical control group of patients treated with single antiplatelet therapy without high-intensity statin treatment. The authors discussed the need for a historical control group. Two treatments are changed simultaneously (DAPT and high-intensity statin treatment) in the treatment group compared to the control group. Therefore, drawing conclusions of the effects of each treatment will not be possible. In order to improve the therapy for these patients it is important to know the effect of each individual treatment. Please comment on this and discuss it in the limitations of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. **I do not really understand the BAD definition: "have BAD, defined by a visible lesion in three or more axial MRI cuts in the lenticulostriate territory or infarcts that extend from the basal surface of the pons ». Was does « lesion » mean? Ischemic lesion on DWI?**
   I understand that this criteria differs lacunar infarcts due to « lipohyanilosis » and BAD?
   Please clarify.

Response:

The lesion means acute infarction on diffusion weighted imaging (DWI) and we have changed the term of MRI to DWI to make it clear in the revised manuscript (Page 5, lines 21–23; page 13, table 1).

The radiological diagnosis of BAD is currently based on vascular territory, dimensions and/or shape of the acute ischemic lesion [1]. Even though high-field and high-resolution MRI techniques may allow for the direct exploration of the atheromatous changes of parent vessels that support the diagnosis of BAD, they cannot be used to directly observe the plaque morphologies inner to the penetrating arteries [2]. For clinical practice, we used the radiological diagnostic criteria of a lesion of ≥ 3 consecutive slices on transversal plane slices in the anterior circulation or a lesion extending to the ventral pontine surface in the posterior circulation [1].

[1] Petrone L, Nannoni S, Del Bene A, Palumbo V, Inzitari D. Branch Atheromatous Disease: A Clinically Meaningful, Yet Unproven Concept. Cerebrovasc Dis 2016;41:87–95.

[2] Miyazawa H, Natori T, Kameda H, Sasaki M, Ohba H, Narumi S, et al. Detecting lenticulostriate artery lesions in patients with acute ischemic stroke using high-resolution MRA at 7 T. Int J Stroke 2019;14:290–7.

2. **Statistical methodology: Considering the design (comparison with historical controls),**

which is –as well acknowledged by the authors- prone to several limitations, I think that using a propensity-score weighting or matching methodology would be more appropriate. Indeed, this type of methodology is more appropriate to reduce the between group differences.

Response:

Thank you for the critical comment and helpful suggestion. A propensity score matching analysis will be used to measure and balance pre-determined covariates between two groups (page 8, lines 3–4).

Reviewer #2

Treatment strategies to reduce early neurological deterioration in patients with BAD are important to improve functional outcome for these patients.

This prospective study aims to compare early dual antiplatelet treatment and high-intensity statin treatment with a historical control group of patients treated with single antiplatelet therapy without high-intensity statin treatment.

The authors discussed the need for a historical control group.

Two treatments are changed simultaneously (DAPT and high-intensity statin treatment) in the treatment group compared to the control group. Therefore, drawing conclusions of the effects of each treatment will not be possible. In order to improve the therapy for these patients it is important to know the effect of each individual treatment. Please comment on this and discuss it in the limitations of the study.

Response:

Because DAPT and high-intensity statin treatment are changed simultaneously, it's indeed unable to know each treatment effect according to this study. However, DAPT and high-intensity statins are the mainstay treatments for intracranial atherosclerosis (ICAS). As BAD and ICAS share the same pathology as atherosclerosis, it's a reasonable strategy to administer these two treatments together. If the study results are positive, further studies focusing on high-intensity statin or DAPT alone will be warranted to evaluate the separate effect of each one. The limitation has been addressed in the revised manuscript (page 3, line 19–20).

VERSION 2 – REVIEW

REVIEWER	Seners, Pierre Universite Paris Descartes, Sainte-Anne Hospital, Neurology
REVIEW RETURNED	25-Oct-2021

GENERAL COMMENTS	Thanks for the clarification. I have no further comments.

REVIEWER	Berberich, Anne Heidelberg University Hospital
REVIEW RETURNED	01-Nov-2021

GENERAL COMMENTS	My comments were addressed. I recommend to accept the manuscript for publication.