Author’s response to reviews

Title: Carotid Plaque Rather than Intima-media Thickness As A Predictor of Recurrent Vascular Events in Patients with Acute Ischemic Stroke

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Responses to the comments from the reviewers

Reviewer #1: Major Revisions:

1. Methods, carotid ultrasound examination: I would suggest to make this section clearer. Moreover, more details regarding the IMT evaluation should be reported: which is the length of the site were the measurement was performed? Which kind of semiautomatic measurement was adopted? Which is the robustness (i.e. repeatability) of this measurement?
Ans) Thanks for important comments. The methodology regarding carotid IMT measurements were described in detail in method section. As mentioned by the reviewer, AutoIMT® of GE Healthcare were used as semiautomatic measurement software for carotid IMT, and this program was licensed from FDA, it’s reference of validation was also added in the method section.

2. Methods: therapy of patients should be reported.

Ans) According to the comments from the reviewer, the prescribed medications between the groups were compared and added as table 3. There were no differences in the prescribed medications.

3. Results: I would suggest to analyze also VEs predictive value of IMT in patients without plaque.

Ans) We performed subgroup analysis for stroke patients without carotid plaque and demonstrated that carotid IMT was also not an independent predictor of future VEs. This analysis was added in the result section.

4. Discussions: from this section I would expect more evidence regarding the "additive" clinical value of the reported data with respect to other classical risk factor.

Ans) Thanks for important comments. Despite of high prevalence of classic risk factors such as hypertension and dyslipidemia in patients with recurrent stroke, hypertension and dyslipidemia were not predictors of stroke recurrence in the present study. These findings suggested that other risk factors or predictors for stroke recurrence are needed to improve clinical outcomes and these points would be the additive value with respect to classic risk factor. We addressed and discussed the reported data regarding clinical and imaging predictors including carotid plaque for VEs in the discussion. Considering the results that diabetes was an independent risk factor for VEs and the risk of future VEs was greatest in patients with both carotid plaque and diabetes, the presence of carotid plaque may have a complimentary role in predicting future VEs in addition to classic risk factors.
Reviewer #2

This retrospective study confirms that in a Korean group of individual with ischemic stroke that common carotid plaque, but not IMT, is associated with recurrent stroke. Though interesting and clinically relevant, the results are rather confirmatory. We recommend to deal with the following issues:

Abstract: method section in the abstract should be rewritten: number of events is part of the results.

Ans) Abstracts were revised according to the comment from the reviewer.

Background: - page 4, line 27 please change "a recent metaanalysis" instead of "the current metaanalysis"

Ans) It has been corrected in the text. Thanks.

Methods: - page 5, line 57-59: in the composite endpoint considered, it is not clear how coronary events and peripheral arterial disease occurrence were defined; furthermore, it is debatable to consider total mortality in a composite endpoint labeled as "vascular events": only cardiovascular mortality should be included. Are recurrent TIA considered as endpoints too? The authors should also specify how the clinical follow-up was performed and how information about events was retrieved

Ans) Thanks for important comments. Definitions for each component of VEs were described in the method section, and only CV death was included in VEs in this study. As shown in exclusion criteria and the definition of VEs, TIA was excluded in this study. According to the comment from the reviewer, in the method section, we added the detailed descriptions regarding clinical follow up and information about events. As a retrospective study, the authors analyzed only the study subjects who were able to clinical follow up at our institution.

- page 6 : which kind of semi-automated vessel-wall detection software was used?

Ans) AutoIMT® of GE Healthcare was used as semiautomatic measurement software for carotid IMT, and this issue is addressed in the method section. Thanks.
- The rationale of comparing echocardiographic measurements is not entirely clear, please explain or remove the data. This might probably allow the authors to exclude less patients from the analysis.

Ans) The authors agreed the opinion of the reviewer regarding the comparisons of the echocardiography data. The reason why the authors showed echocardiographic data is that cardiac functions or abnormalities were not different between the groups because cardiac abnormalities including LV dysfunction would affect recurrent stroke. Therefore, if the reviewer allows us to remain echocardiographic data, we would like to keep the echocardiographic data. However, if the reviewer does not allow, we will remove the echocardiographic data. Thanks.

- Please specify methods regarding blood samples.

Ans) Methods regarding samples were added in the method section as a separate paragraph.

- Statistical analysis: how did the authors choose variable included in the multivariate analysis?

Ans) As described in the statistical analysis of method section, multivariate analysis was applied to the significant variables in univariate analysis. Thanks.

Results:

- Please specify ethnicity of the participants

Ans) According to the comment form the reviewer, the authors described that study subjects of this study were Korean in the text. Thanks.

- lower LDL-chol levels in the VE group is somewhat surprising, is statin use more prevalent in this group? Please provide some information about treatment at enrollment. It seems appropriate to include LDL levels or statin use in the model

Ans) Thanks for important comments. According to the reviewer`s comments, we added table 3 to show and compare the prescribed medications between the groups. The use of statin or other drugs were not different between groups. Also LDL levels were also shown in the table.
- It seems that only plaques in common carotid artery were considered in the results, whereas the bulb and internal carotid are more common sites of atherosclerosis. If yes, please specify throughout the text CCA plaque instead of carotid plaque. Did previous literature cited in the article analyze CCA, ICA or global plaques? This issue should be discussed in the discussion section. Are plaques in bulb/ICA predictive of VE in the present population? Are there any patients with ICA stenosis >50%? Did they have a higher risk of recurrent stroke? Did any of them undergo carotid revascularization or where they excluded?

Ans) Thanks for good comments. Regardless of locations, the presence of any plaque in CCA or bulb or ICA was considered as the presence of carotid plaque (plaque, any site) in the present study. As indicated by the reviewer, carotid plaque was also most commonly identified in carotid bulb in the present study (Table 5). According to the reviewer’s comments, we addressed the issues regarding the location of carotid plaques (CCA, ICA, or global) in the discussion section. The data regarding the impacts of CCA, bulb, or ICA plaques on VEs were also addressed in Table 5. In the present study population, regardless of location, the presence of CCA, bulb, or ICA plaque was associated with VEs in univariate analysis (Table 5). ICA stenosis > 50% was not different between VE (9 patients = 6.3%) and no VE group (11 patients = 3.2%) (Table 5). Carotid revascularization was performed only in 2 patients of VE group and 2 patients of no VE group (p=ns), and they were not excluded in the present study.

Discussion

- Please underline in the discussion the elements of novelty of this article in comparison to previous literature.

Ans) Thanks for good comments. According to the reviewer’s comment, we underlined the novelty of this article in the head of discussion as main findings. And each of main findings was also discussed in comparison to previous literature.

- Prevalence of carotid plaques in the study population appears to be around ¼ of individuals with first stroke. Is this in line with epidemiological data in this ethnic group?

Ans) According to the reviewer’s comments, the authors introduced and discussed the previous studies regarding the prevalence of carotid plaque in comparison to this study. The prevalence of carotid plaque was 5.7% in general population, and 24.6~42.1% in patients with atherosclerotic CVD such as coronary artery disease in Korean population. In the present study population, regardless of location, the plaques of CCA, bulb, or ICA were found in 37.8 % cases with index
stroke, and the result of the present study also showed quite similar to those of the previous studies. This issue was described in the discussion part. Thanks.

- Page 11, line 16: please correct "marker" instead of "maker"

Ans) Thanks. It has been corrected in the text.

- How do the author comment of lack of predictive value of plaque size and echogenicity?

Ans) Thanks for good comments. The reason why the characteristics of plaque were not associated with VEs in the present study is unclear, and selection bias from the retrospective nature of this study or ethnic differences might be possible explanations. This issue was addressed in the discussion part.