Peer Review File

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Reviewer Comments

Li et al. Performed a work to develop a risk score scale of multiparameter ultrasound for the identification of patients at high risk of
stroke, including plaque stiffness, surface
morphology and carotid stenosis degree at the same time they want to investigate the discrimination performance of the scale.

As already commented by the author the main utility of this scale would be to use in the setting of moderate carotid stenosis (50-69%) Based on Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack written by Kenran et al. Three major randomized trials have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with a high-grade (>70% angiographic stenosis) atherosclerotic carotid stenosis. The role of CEA is less clear with symptomatic stenoses in the 50% to 69% range and stenoses <50%, surgical intervention did not offer benefit in terms of stroke risk reduction.

So, I recommend to focus the paper on the population that may potentially benefit of ultrasound advance screening techniques, patients with moderate carotid stenosis (50 to 69%), and search for predictors of inestable plaque rupture.

Reply: Thank you for your good advice. As the reviewer said, RCT trials had confirmed that CEA plus medical therapy was superior to medical therapy alone for symptomatic patients with severe atherosclerotic carotid stenosis. However, the evidence of CEA for symptomatic patients with mild and moderate atherosclerotic carotid stenosis was not sufficient. As the reviewer recommended, we have added the

utility of our USR score in moderate carotid stenosis.
Changes in the text: Page 13, Line 2-12

As the author mention “Patients who had already experienced ipsilateral ischaemic events within the past 30
days (acute stroke, transient ischaemic attack, or amaurosis fugax) before study inclusion were categorized in the symptomatic group”

I would recommend to exclude patients with definite cardioembolic sources such as Atrial Fibrillation to be sure that stroke is related to ipsilateral atherosclerotic disease and not caused by other embolic diseases.
Please calculate multivariable logistic regression analysis Among moderate (50% to 69%) carotid stenosis subgroup.

Reply: Thank you for your well-meaning suggestion. In our study, according to the TOAST standard (Adams HP Jr, et al. Stroke 1993), all the stroke subtypes were large artery atherosclerosis stroke (LAA). We are sorry for not declaring that in our article, we have added it in the exclusion criteria. According to the reviewer’s advice, we have added the utility of our USR score in the subgroup of moderate carotid stenosis.
Changes in the text: Page 6, Line 8-9 and 20, and Page 13, Line 2-12

As the author mention, there were 45 patients with moderate carotid stenosis, with 14 ischaemic events, I would like to know if any of these carotids were treated with surgical endarterectomy or endovascular stenting and I would like to know if there were any stroke recurrence during follow up of any of the asymptomatic or symptomatic carotid stenosis and if any of the ultrasound parameters was a predictor of inestable plaque.

Reply: Thank you for your kind advice. Actually, we did have a long-term follow-up of all included patients, and we have made a preliminary statistical analysis of the

follow-up outcomes, and nowadays we are busy writing the thesis, and we hope the follow up studies will also be published at ATM soon.

I assumed there were patients studied in the acute phase of stroke, were there any difference in ultrasound measures between early (in hospital patients) and late (around 30 days) studies?

Reply: Thank you for your careful review. This is an interesting question about the time interval between the stroke onset and the ultrasound assessment. Some studies (Amarenco P, et al. Circulation. 2020; Tawakol A, et al. J Am Coll Cardiol. 2013) have showed that medical therapy (for example, statins) can change plaque characteristics, and even cause regression of carotid atherosclerosis, however, the follow-up time of these studies is usually longer than 3 months. In addition, there is no evidence for the impact of short-term drug use on plaque characteristics. In such a short time interval, we think there was no difference in ultrasound assessment between early and late studies.