**Peer Review File**

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**Reviewer A**

In this MS, a total of 196 patients with moderate-to-severe proximal internal carotid artery (ICA) stenosis associated with calcification thickness were assessed using non-contrast and contrast-enhanced computed tomography angiography (CTA). A significant association between arterial positive remodeling and plaque calcification thickness was reported.

The results of this study seemingly supported that the remodeling ratio (RR) helps predict ischemic symptoms and arterial remodeling can serve as a novel measure to help ascertain the risk stratification of ischemic events in carotid atherosclerotic disease.

The manuscript has been properly organized, but is intrinsically lacking uniformity and standardization in the approaches of deriving the outcomes related with the association of calcium and the carotid arteries. The following concerns and issues should be addressed before being considered for publication.

**Comment 1:**

Most of the included studies are retrospective, which may lead to a less accurate relationship between the calcium amount and morphologies with ischemic stroke.

• Adoption of carotid calcification measures in clinical decision making will require additional studies which assess the imaging strategies in prospective studies.

• Also needed is expanding of a small sample size or reducing methodologic variability among included studies, which may lead to the false results in the outcomes related with association.

**Reply 1:** Thank you for your precious comments and suggestions. The accurate association between the calcium amount and morphologies in carotid plaques and ischemic stroke remains to be elucidated in detail. Although most literature about this topic is retrospective cross-sectional design, which may weaken the predictive power for future ischemic events, these data can provide applicable parameters for subsequent prospective studies to determine the association between carotid calcium and the risk of cerebrovascular events.

Because our patients are from a single institution, and one of the inclusion criteria is moderate-to-severe carotid artery stenosis, only 196 patients were included in the final analysis. These limitations provide a useful platform for future endeavors, which could include multicenter prospective studies on the efficacy of carotid calcification measures in clinical decision-making.

**Comment 2:**

The differences in association outcomes (i.e., ICA and calcification thickness) within patients whose carotid plaques caused significant stenosis from those caused non-stenotic plaques should be provided. In other words, future investigation into calcifications in non-stenotic carotid arteries is needed to develop a better understanding of the role of calcifications in carotid atherosclerotic disease.

**Reply 2:** We appreciate your recommendations; this is a fascinating study component. According to our study protocol, the patients with an internal carotid artery stenosis degree <50% were excluded. We will investigate the pathogenesis and clinical outcome of calcified plaques in different degrees of carotid artery stenosis in the future.

**Comment 3:**

As the association between carotid calcification and ischemic stroke involves complex pathophysiological mechanisms, some distributing variability or the proximity of the calcified component may result in mechanical stress, weakening the cap and the enhanced risk of rupture. Thus, the effects of distal calcifications at varying cites on the risk ischemic stroke should be further provided.

**Reply 3:** Thank you for your suggestions. The effect on the stress distribution in the fibrous plaque tissue at the calcification interface may serve as a potential source of plaque rupture in carotid arteries and clinical cerebrovascular events. At present, the common and internal carotid artery or carotid bifurcation is defined as a target in study of biomechanics. We will investigate the pathogenesis of carotid calcification at varying sites on the risk of ischemic stroke in the future.

**Comment 4:**

A major drawback of this study is the lack of uniformity and standardization in calcium burden characterization in the carotid arteries.

• The levels of heterogeneity among all analyses, which could have stemmed from

differences in calcification metric quantification, variability in defining plaque morphological features, differences in the rigor of adjudication of stroke should be investigated using more reproducible and standardized methods of calcium characterization.

• Total calcium volume calculations do not distinguish between bulky calcified plaques and smaller calcified plaques, which may lead to false outcomes in association of calcium and increased stroke risk.

**Reply 4:** Thank you for your comments. Several plaque components are often simultaneously present in the carotid plaque. Hydroxyapatite and calcium oxalate are 2 distinct types of physiological calcification in humans. The capability of differentiating between calcium subtypes may further improve our understanding of the unique roles played by each type of calcium in predicting stroke risk. Manual measurement and visual assessment of these calcification variables are used in most studies at present. The distinction between the two types of calcium is challenging for the operator due to the different calcium densities. The automatic assessment software and more new and advanced imaging technologies, such as dual-energy CT scanners, can promote a paradigm shift in the characterization and spatial analysis of in vivo carotid artery plaques, which are helpful for the formation of reproducible and standardized methods in calcium burden characterization.

We are especially grateful for the precious comments and suggestions you provided, which have allowed us to delve deeper into the implications of our future research.

**Reviewer B**

This study explores the relationship between vascular remodeling and plaque calcification patterns in the carotid artery and their impact on ischemic symptoms using CT angiography. The statistical analysis reveals a notable association between arterial positive remodeling and plaque calcification thickness. This finding introduces a potential novel metric for assessing the risk stratification of ischemic events. In terms of the writing, the manuscript is well-organized with no logistical gaps, and comprehensive quantitative analyses are presented and discussed.

However, a few questions require attention before acceptance. The detailed comments are as follows:

**Comment 1:**

Line 150: Change "sizeof" to "size of."

**Reply 1:** We apologize for the careless mistake. It has been corrected as “size of”.

Changes in the text: in line 151.

**Comment 2:**

Results: The study comprises 196 patients, with 81% men and 19% women. Clarify whether the sample selection was random or deliberate. Additionally, discuss the potential impact of gender on the study results.

**Reply 2:** We apologize for any confusion. The subject selection of this study was random. We added the data on gender in Table 2. There was no statistical difference in subsequent analysis.

Changes in the text: In Table 2.

**Comment 3:**

Results: The statement, "On binary logistic regression analysis, calcification thickness remained significantly associated with positive remodeling of carotid arteries," should be expanded. Positive remodeling is clinically linked to various factors such as lumen diameter, plaque calcification types, calcium scores, and calcification thickness. Consider developing a multiple logistic regression model to accurately depict their relationships.

**Reply 3:** Thank you for your comments and suggestions. There are a few mistakes in my expression. Actually, the variables, such as plaque calcification types, calcium scores, calcification thickness and the positive remodeling of the carotid arteries were confirmed using both univariable and multivariable logistic regression analysis (Table 4). Descriptions of logistic regression analysis in the Statistical analysis and Result section were modified. We consider that it is improper to analyze the correlation between positive remodeling and lumen diameter because arterial remodeling was estimated using the carotid artery’s lumen diameter.

Changes in the text: We modified the Statistical analysis and Result section in lines 175, 195 and 219.

**Comment 4:**

Model Establishment: Emphasize the importance of accurately quantifying the various parameters involved in model establishment.

**Reply 4:** Thank you for your insightful comments. We have emphasized the importance of the calcification parameters involved in the multivariable logistic regression model, especially the calcification thickness.

**Comment 5:**

Discussion: The statement, "This manuscript demonstrates a significant correlation between calcification thickness and positive remodeling," is supported by a similar conclusion in a previous study (Pugliese L. et al., Atherosclerosis 311, 2020). Acknowledge this previous work and discuss its relevance to the current findings.

**Reply 5:** We appreciate your comments. Pugliese et al. reported that large calcifications, especially those ≥3 mm in size, have been frequently associated with positive remodeling in the coronary artery. Our study found that there is a significant correlation between calcification thickness and positive remodeling in the carotid artery. Despite the differences in study subjects, there may be similarities in mechanisms underlying the relationship between calcification thickness and arterial positive remodeling. We added the corresponding content in the Discussion section.

Changes in the text:

We added the Discussion section in lines 271-282.

**Comment 6:**

Discussion: Given the current data's conclusion on the significant role of calcification thickness in positive remodeling, provide a commentary from a pathogenesis perspective. Elaborate on the potential mechanisms underlying this association and its implications for understanding the disease process.

**Reply 6:** Thank you for your insightful comments. Biomechanical and hemodynamics changes can help to elucidate the potential mechanisms of the association between calcification and vascular remodeling. Atherosclerotic plaque may result in the variation of biomechanical and hemodynamics of the artery. Plaque tissue components have different biomechanical properties. Wide-spread macro-calcification might result in advantageous stress redistribution. Positive remodeling is thought to be the consequence of altered local hemodynamics due to increased stress at sites of

luminal narrowing in response to plaque growth. We added the corresponding contents in text, as detailed in the Discussion and References section of the revised version.

Changes in the text: In lines 271-282 and 388-394.

Thank you again for your precious comments. Your suggestions for revisions and additional analyses have made the discussion of this paper clearer and more informative.