

Bulky Carotid Calcification on Preoperative Computed Tomography Angiography as a Predictor of Adverse Outcomes Following Carotid Revascularization

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Research Article

Keywords: carotid artery stenosis, carotid artery stenting, carotid endarterectomy, calcification, computed tomography angiography, calcified nodule

Posted Date: September 28th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10809747/v1>

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Additional Declarations: No competing interests reported.

Abstract

Carotid calcification can complicate carotid artery stenting (CAS), but its clinical impact may depend on calcification morphology rather than calcification burden alone. We retrospectively evaluated 92 patients who underwent carotid revascularization with either carotid endarterectomy (CEA) or CAS and classified preoperative computed tomography angiography (CTA) findings as no/spotty calcification (Group 1), outer calcification (Group 2), or bulky calcification directly abutting the contrast-enhanced lumen (Group 3). The primary composite endpoint comprised procedural failure, ischemic complications, or restenosis. The endpoint occurred in four of 83 patients (4.8%) in Groups 1/2 and five of nine patients (55.6%) in Group 3 (unadjusted odds ratio [OR], 24.69; 95% confidence interval [CI], 4.72–129.14; $p < 0.001$). In a parsimonious multivariable model including treatment modality and calcification pattern, Group 3 remained associated with the composite endpoint (adjusted OR, 49.05; 95% CI, 4.82–498.94; $p = 0.001$), whereas CEA was associated with lower odds of reaching the endpoint (adjusted OR, 0.045; 95% CI, 0.003–0.664; $p = 0.024$). Among patients who underwent CAS, the endpoint occurred in three of 38 patients (7.9%) in Groups 1/2 and all five patients (100%) in Group 3 ($p < 0.001$). CTA-defined bulky calcification may identify lesions at particularly high risk for CAS-related technical failure or restenosis and may support consideration of CEA when surgically feasible.

Introduction

Carotid artery stenosis is a major cause of ischemic stroke, and carotid revascularization reduces the risk of first or recurrent stroke in appropriately selected patients. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are established revascularization procedures for carotid stenosis. However, the safety and efficacy of CAS are influenced by vascular anatomy, lesion morphology, and plaque characteristics [2, 3].

Severely calcified carotid lesions have been associated with technical difficulties during CAS, including difficulty with device passage and inadequate balloon or stent expansion, as well as perioperative ischemic complications and postprocedural restenosis [5, 7, 9, 10]. However, calcified carotid plaques are heterogeneous, and their impact on CAS may depend not only on the extent of calcification but also on its distribution, morphology, and relationship to the vascular lumen [1, 9].

A calcified nodule (CN) is a distinct pathological entity characterized by nodular calcification protruding from the plaque surface into the vascular lumen. In the coronary circulation, CNs have been associated with acute coronary syndromes and restenosis after treatment. In the carotid artery, nodular calcification protruding into the lumen has been identified on preoperative computed tomography angiography (CTA), with CNs subsequently confirmed by pathological examination of plaques removed during CEA [8]. Such protruding calcific lesions may have a greater impact on the technical feasibility and outcomes of CAS than conventional calcified plaques.

In this study, we classified carotid calcification morphology into three patterns on preoperative CTA and examined their associations with procedural failure, ischemic complications, and restenosis after carotid

revascularization. We aimed to identify preoperative CTA features that may aid in risk stratification and treatment selection between CEA and CAS.

Materials and Methods

Study population

We retrospectively reviewed patients who underwent revascularization for atherosclerotic carotid artery stenosis at our institution between January 2022 and April 2024. Patients who underwent emergency CAS for acute ischemic stroke and those who underwent revascularization for non-atherosclerotic lesions, including arterial dissection and carotid web, were excluded. Ninety-two patients were included in the final analysis.

Baseline variables included age, sex, symptomatic status, presence of severe stenosis, treatment modality (CEA or CAS), and calcification pattern on preoperative CTA.

The study was approved by the Institutional Review Board (approval no. 2023-0118-03) and conducted in accordance with the principles of the Declaration of Helsinki.

CTA classification of calcification patterns

Calcification at the site of carotid stenosis was classified on axial images from preoperative contrast-enhanced CTA into three groups (Fig. 1).

Group 1 was defined as no/spotty calcification. No definite calcification within the atherosclerotic plaque or only localized spotty calcification were present.

Group 2 was defined as outer calcification. Calcification was distributed predominantly along the periphery of the plaque and did not directly abut the contrast-enhanced vascular lumen. Even when calcification was circumferential, lesions were classified as Group 2 if a non-calcified component remained between the calcification and the lumen.

Group 3 was defined as bulky calcification. Nodular or mass-like calcification extended toward and directly abutted the contrast-enhanced vascular lumen. This pattern was considered a CTA morphology suggestive of a CN protruding toward the lumen.

Outcome measures

The primary outcome was a composite endpoint of procedural failure, ischemic complications, or restenosis.

Procedural failure was defined as the inability to complete CEA or CAS. Ischemic complications were defined as symptomatic ischemic events occurring within 30 days after the procedure. Restenosis was defined as recurrent stenosis of $\geq 70\%$ on postoperative magnetic resonance imaging or ultrasonography. The mean follow-up duration was 24 months (range, 10–38 months). Imaging follow-up was generally performed every 6 months during the first postoperative year and annually thereafter, with shorter intervals when recurrent stenosis was suspected or detected.

Clinical and imaging factors associated with the composite endpoint were analyzed.

Statistical analysis

Continuous variables are presented as medians with ranges, and categorical variables as numbers and percentages. Baseline characteristics among the three calcification groups were compared using the Kruskal–Wallis test for continuous variables and the Fisher–Freeman–Halton exact test for categorical variables.

For analyses of factors associated with the composite endpoint, continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher’s exact test. For the analysis of calcification morphology, Groups 1 and 2 were combined and compared with Group 3 because the primary hypothesis was that bulky calcification directly abutting the vascular lumen represents a distinct high-risk phenotype rather than a stepwise increase in risk across the three calcification patterns.

Given the limited number of composite endpoint events, the multivariable logistic regression model was restricted to two clinically relevant variables directly related to the study hypothesis: treatment modality (CEA vs. CAS) and calcification pattern (Group 3 vs. Groups 1/2). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. As a secondary analysis, the association between Group 3 calcification and the composite endpoint was evaluated among patients who underwent CAS alone using Fisher’s exact test. A two-sided p value < 0.05 was considered statistically significant.

Statistical analyses were performed using Python version 3.10.12 with SciPy version 1.15.0 and statsmodels version 0.14.4 in Google Colaboratory.

Results

Patient characteristics

Among the 92 patients, 49 underwent CEA and 43 underwent CAS. The mean age was 73 years (range, 53–89 years); 83 patients were men and nine were women. Fifty-seven patients (62.0%) had symptomatic lesions, and 83 (89.2%) had severe stenosis (Table 1). Preoperative CTA classified 40 patients as Group 1, 43 as Group 2, and nine as Group 3.

Patient characteristics according to calcification pattern are summarized in Table 2. Group 3 had a higher proportion of women (33.3%) and symptomatic lesions (77.8%) than Groups 1 and 2. However, no statistically significant differences were observed among the three groups in age, sex, symptomatic status, degree of stenosis, or treatment modality, although the difference in sex distribution approached statistical significance ($p = 0.060$).

Clinical outcomes

Nine of the 92 patients (9.8%) reached the primary composite endpoint (Table 3).

One ischemic complication occurred in a Group 2 patient who underwent CAS.

Restenosis occurred in six patients: one after CEA in Group 1, two after CAS in Group 2, and three after CAS in Group 3.

Procedural failure occurred in two patients, both of whom were in Group 3 and underwent CAS. In both cases, the lesion could not be crossed, and the planned CAS procedure could not be completed.

All five Group 3 patients who underwent attempted CAS reached the composite endpoint: two because of procedural failure and three because of restenosis after successful CAS.

Factors associated with the composite endpoint

Factors associated with the composite endpoint are summarized in Table 4.

In the univariate analysis, male sex was less frequent among patients who reached the composite endpoint than among those who did not (66.7% vs. 92.8%, $p = 0.041$), whereas CAS was more frequently performed among patients who reached the endpoint (88.9% vs. 42.2%, $p = 0.011$).

When calcification patterns were dichotomized into Groups 1/2 and Group 3, the composite endpoint occurred in four of 83 patients (4.8%) in Groups 1/2 and five of nine patients (55.6%) in Group 3. Group 3 calcification was strongly associated with the composite endpoint (unadjusted OR, 24.69; 95% CI, 4.72–129.14; $p < 0.001$). Because only nine composite endpoint events occurred, the multivariable logistic regression model was restricted to treatment modality and calcification pattern to reduce the risk of overfitting. In this model, CEA was associated with lower odds of reaching the composite endpoint (adjusted OR, 0.045; 95% CI, 0.003–0.664; $p = 0.024$), whereas Group 3 calcification was independently associated with higher odds of reaching the composite endpoint (adjusted OR, 49.05; 95% CI, 4.82–498.94; $p = 0.001$).

In a secondary analysis restricted to patients who underwent CAS, the composite endpoint occurred in three of 38 patients (7.9%) in Groups 1/2 and all five patients (100%) in Group 3 ($p < 0.001$, Fisher's exact

test). Among the five Group 3 patients who underwent attempted CAS, two experienced procedural failure because the lesion could not be crossed, and three developed restenosis during follow-up.

Discussion

Key findings

We classified carotid artery calcification on preoperative CTA into three morphological patterns and identified bulky calcification directly abutting the vascular lumen as a distinct high-risk phenotype. Patients with Group 3 calcification had a substantially higher incidence of the composite endpoint than those with Group 1/2 calcification (55.6% vs. 4.8%). This association remained significant after adjustment for treatment modality.

Importantly, adverse outcomes in Group 3 were predominantly associated with CAS. Among patients who underwent attempted CAS, all five patients with Group 3 calcification reached the composite endpoint, including two procedural failures because the lesion could not be crossed and three cases of restenosis after successful CAS. In contrast, only three of 38 patients with Group 1/2 calcification who underwent CAS reached the composite endpoint. Although the number of Group 3 patients who underwent attempted CAS was small, these findings suggest that the spatial relationship between calcification and the vascular lumen, rather than the presence or overall extent of calcification alone, may be particularly relevant to the technical feasibility and durability of CAS.

Carotid calcification and CAS

CEA and CAS are established revascularization procedures for carotid artery stenosis. In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the composite primary endpoint did not differ significantly between CEA and CAS; however, perioperative stroke was more frequent after CAS, whereas myocardial infarction was more frequent after CEA [3]. Accordingly, selection between the two approaches should consider not only patient characteristics but also vascular anatomy and lesion morphology [2, 3].

Calcification is an important lesion-related factor that may influence CAS outcomes. Lv et al. reported that a greater circumferential degree of carotid calcification was associated with a higher incidence of new ischemic lesions on postoperative diffusion-weighted imaging [7]. Calcified plaques have also been associated with residual stenosis after CAS [10]. More recently, Li et al. quantitatively assessed calcification on preoperative CTA and found that a higher calcified plaque volume fraction and circumferential calcification score were independently associated with residual stenosis after CAS [6]. Together, these findings suggest that both the extent and morphology of calcification on CTA may be relevant to CAS risk stratification.

Kim et al. evaluated 235 lesions with long-term CTA follow-up after CAS and reported that severe calcification involving more than 50% of the vessel circumference was independently associated with

restenosis [5]. In contrast, Katano et al. found no clear association between calcium score and restenosis after CAS [4]. These discrepant findings suggest that calcification burden alone may not fully predict outcomes after CAS and support the evaluation of calcification distribution and morphology.

Calcification morphology and intraluminal protrusion

A large registry study supports the importance of calcification morphology. Mota et al. analyzed 21,860 CAS procedures in the Vascular Quality Initiative and reported that lesions with 51–99% calcification and those with 100% circumferential calcification or intraluminal protrusion were associated with an increased risk of in-hospital stroke or death compared with non-calcified lesions [9]. Lesions with 100% circumferential calcification or intraluminal protrusion were also associated with a higher risk of ipsilateral stroke or death at 1 year.

These findings suggest that intraluminal protrusion, in addition to calcification burden, may be relevant to the risk associated with CAS. Group 3 in the present study was defined by mass-like calcification directly abutting the contrast-enhanced lumen and may include lesions analogous to the highly calcified or protruding lesions described in previous studies.

In contrast, no CAS procedural failures occurred in Group 2, even among patients with relatively extensive calcification, when the calcification remained peripheral and a non-calcified component separated it from the lumen. Thus, the spatial relationship between calcification and the residual lumen may influence the technical feasibility of CAS beyond the circumferential extent of calcification alone.

Outer calcification and the rim sign

Carotid plaque calcification does not uniformly indicate plaque stability, as different calcification morphologies may reflect different pathological substrates. The CTA “rim sign” has been described as thin peripheral calcification surrounding a non-calcified plaque component. However, histopathological studies have shown that the relationship between the rim sign and features of plaque vulnerability, including intraplaque hemorrhage, is complex [1].

Group 2 may include lesions with imaging features resembling the previously described rim sign; however, because pathological validation was not performed, the two entities cannot be considered equivalent. The absence of procedural failure during CAS in Group 2 suggests that peripheral calcification alone does not necessarily preclude technically successful CAS.

Bulky calcification and calcified nodules

A distinctive finding of this study was the Group 3 pattern of bulky calcification, characterized by nodular or mass-like calcification extended toward and directly abutted the contrast-enhanced lumen.

Morisue et al. reported two patients with carotid stenosis in whom preoperative CTA demonstrated bulky calcification protruding into the vascular lumen; pathological examination of plaques removed during

CEA confirmed CNs [8]. Thus, the CTA morphology observed in Group 3 may reflect CNs in at least a subset of patients.

Because pathological confirmation was not available for all Group 3 lesions, CTA-defined bulky calcification should not be considered synonymous with CN. Rather, Group 3 may represent a CTA phenotype suggestive of CN.

When a hard CN protrudes toward the lumen, guidewire or device passage during CAS may be difficult. Even when stent placement is technically successful, the rigid calcified component may resist compression, resulting in incomplete stent expansion or residual stenosis and potentially contributing to subsequent restenosis. The occurrence of procedural failure and restenosis among patients with Group 3 calcification who underwent CAS is consistent with this proposed mechanism.

In contrast, CEA permits direct removal of the calcified plaque. Therefore, when a surgical approach is feasible and the perioperative risk of CEA is acceptable, CEA may be preferable to CAS for lesions with bulky calcification abutting or protruding into the vascular lumen.

Clinical implications

Advances in endovascular devices and access techniques have expanded the feasibility of CAS in anatomically challenging lesions. CAS can be successfully performed in selected patients with heavily calcified lesions [11]; therefore, calcification alone should not be regarded as an absolute contraindication to CAS.

The clinically relevant question may therefore be whether specific calcification morphologies predict technical or clinical difficulties with CAS. In the present cohort, the composite endpoint occurred in only three of 38 patients (7.9%) with Group 1/2 calcification who underwent CAS, compared with all five patients (100%) with Group 3 calcification who underwent CAS. Although the number of Group 3 patients treated with CAS was small, this marked difference suggests that bulky calcification directly abutting the lumen may identify lesions for which CAS is particularly challenging. Because this CTA phenotype can be identified preoperatively, it may serve as a useful imaging marker when selecting between CEA and CAS.

In patients with bulky calcification suggestive of CN on CTA, CEA should be considered when surgically feasible, given the potential risks of technical failure and restenosis associated with CAS. However, these findings should be considered hypothesis-generating because of the small number of Group 3 lesions and outcome events.

Limitations

This study has several limitations. First, it was a single-center retrospective study with a limited sample size. Group 3 included only nine patients, and the total number of composite endpoint events was nine. Accordingly, the multivariable model was intentionally restricted to treatment modality and the prespecified calcification comparison to reduce the risk of overfitting. Nevertheless, the wide CIs indicate substantial statistical uncertainty, and the effect estimates should be interpreted cautiously.

Second, treatment allocation was not randomized and was based on operator judgment, patient characteristics, vascular anatomy, and plaque morphology. Therefore, selection bias and confounding by indication cannot be excluded.

Third, the CTA classification used in this study was study-specific, and its inter-observer reproducibility has not yet been established.

Fourth, the relationship between Group 3 CTA findings and pathological CN was not confirmed in all patients; therefore, not all lesions classified as bulky calcification can be assumed to represent CN.

Fifth, the composite endpoint included events with different mechanisms and time horizons, including procedural failure, perioperative ischemic complications, and restenosis. In addition, ascertainment of restenosis may have been influenced by differences in follow-up duration.

Future multicenter studies with larger cohorts should assess the reproducibility of this CTA classification, evaluate long-term outcomes, and correlate CTA morphology with pathological findings from CEA specimens.

Conclusion

Preoperative CTA identified three patterns of carotid calcification with potentially different implications for carotid revascularization. Bulky calcification directly abutting the vascular lumen was associated with a markedly higher incidence of the composite endpoint than Group 1/2 calcification and was particularly associated with adverse outcomes among patients undergoing CAS.

Bulky calcification may represent a CTA phenotype suggestive of CN and may aid in risk stratification and treatment selection. In the present cohort, this morphology was associated with technical failure and restenosis after CAS. When bulky calcification directly abutting or protruding into the vascular lumen is identified preoperatively, CEA should be considered as an alternative revascularization strategy when surgically feasible.

Declarations

Acknowledgments

None

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: H.U., R.T., A.K. and H.S collected data. All authors reviewed the manuscript.

Ethics approval: This study was approved by the Institutional Review Board (approval no. 2023-0118-03) and was conducted in accordance with the principles of the Declaration of Helsinki.

Consent to participate: The requirement for individual informed consent was waived by the Institutional Review Board because of the retrospective nature of the study. The study was approved by the Institutional Review Board (approval no. 2023-0118-03).

Consent to publish: Not applicable

Data, material, and/or code availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Clinical trial number: Not applicable

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Tables

Tables are available in the Supplementary Files section.

Figures

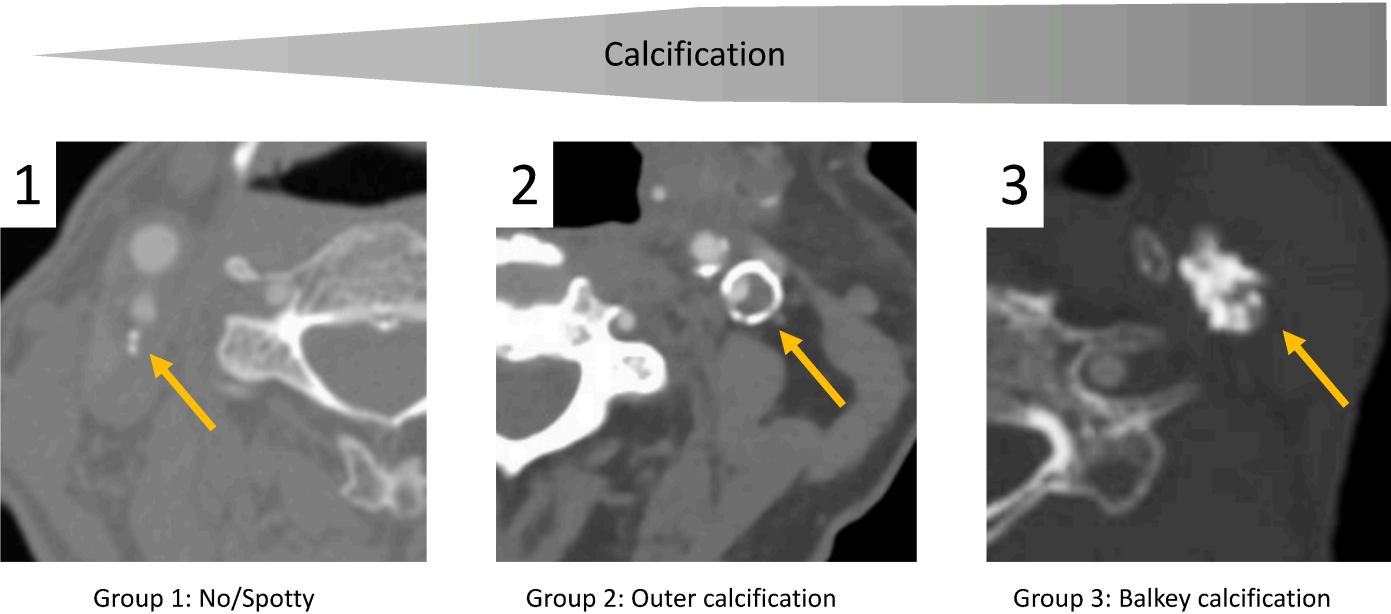


Figure 1

Representative CTA images of the three carotid calcification patterns. Representative axial CTA images showing the three calcification patterns used in this study. (1) Group 1, no/spotty calcification, showing no calcification or only focal spotty calcification within the plaque. (2) Group 2, outer calcification, showing calcification predominantly located at the periphery of the plaque without direct contact with the contrast-enhanced lumen. (3) Group 3, bulky calcification, showing nodular or mass-like calcification directly abutting the contrast-enhanced lumen. Arrows indicate the calcified lesions.

Supplementary Files

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