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# Carotid calcium burden derived from computed tomography angiography as a predictor of all-cause mortality after carotid endarterectomy

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## ABSTRACT

**Objective:** Carotid endarterectomy (CEA) aims to reduce the risk of stroke in patients with atherosclerotic carotid disease. Preoperative risk assessments that predict complications are needed to optimize the care in this patient group. The current approach, namely relying solely on symptomatology and degree of stenosis, is outdated and calls for innovation. The Agatston calcium score was applied in several vascular specialties to assess cardiovascular risk profile but has been little studied in carotid surgery. It is hypothesized that a higher calcium burden at initial presentation equates to a worse prognosis attributable to an increased cerebrovascular and cardiovascular risk profile. The aim was to investigate the association between preoperative ipsilateral calcium score and postoperative all-cause mortality in patients undergoing CEA.

**Methods:** This single-center retrospective cohort study included 89 patients who underwent CEA at a tertiary referral center between 2010 and 2018. Preoperative calcium scores were measured on contrast-enhanced computed tomography images with patient-specific Hounsfield thresholds at the level of the carotid bifurcation. The association between these calcium scores and all-cause mortality was analyzed using multivariable adjusted Cox proportional hazard analysis.

**Results:** Cox proportional hazard analysis demonstrated a significant association between preoperative ipsilateral carotid calcium score and all-cause mortality (hazard ratio, 1.10; 95% confidence interval, 1.03-1.16;  $P = .003$ ). After adjusting for age, preoperative estimated glomerular filtration rate, and diabetes mellitus, a significant association remained (hazard ratio, 1.07; 95% confidence interval, 1.00-1.15;  $P = .05$ ).

**Conclusions:** A higher calcium burden was predictive of worse outcome, which might be explained by an overall poorer health status. These results highlight the potential of calcium measurements in combination with other traditional risk factors, for preoperative risk assessment and thus for improved patient education and care. (*J Vasc Surg* 2023;78:995-1002.)

**Keywords:** Carotid; Carotid stenosis; Endarterectomy; Mortality; Premature; Vascular calcification

In the United States, about 150,000 people die from stroke each year, making it the fifth leading cause of death. Additionally, 795,000 cases of stroke arise each year. The health care system spends \$53 billion annually on stroke treatment attributable to consequent long-

term disabilities.<sup>1</sup> These numbers are likely to increase due to the aging population and improved care for stroke patients.<sup>1-3</sup>

In 10% to 15% of strokes, the underlying etiology is thromboembolism with >50% stenosis of the internal carotid artery (ICA).<sup>4</sup> Although carotid stenosis is usually asymptomatic, the annual risk of stroke with asymptomatic disease is 0.5% to 1.0%.<sup>4</sup> In addition to the best medical treatment, surgical revascularization (ie, carotid endarterectomy [CEA]) is a routinely performed procedure because of its low-risk profile and excellent prognostic outcomes.<sup>5-8</sup>

In the last 20 years, the degree of stenosis was considered the key factor in assessing the severity of carotid disease. Today, this approach is outdated, because the concept of risk assessment seems to be much more complex. It is well-known that various plaque characteristics and morphological features contribute to cardiovascular risk.<sup>9</sup> Imaging offers a variety of ways to

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obtain valuable information about plaque characteristics that allow a better understanding of plaque behavior. Plaque calcifications are among these plaque features.<sup>10</sup> During atherogenesis, the vessel wall undergoes complex changes, of which developing stenoses are by far not the only and most important observable change.<sup>9</sup> The Agatston score, which quantifies calcium burden in coronary arteries, has been widely studied and allows better risk assessment in cardiac patients. It assesses the risk of atherosclerotic cardiovascular disease based on calcium burden in atherosclerotic plaques.<sup>11,12</sup> Given the common vascular pathogenesis of ischemic heart disease and ischemic stroke, it seems plausible to use similar risk assessment tools in both groups of patients.<sup>13</sup> Although the Agatston score has been studied to predict carotid plaque vulnerability and recurrent stenosis after CEA, no study has elucidated the association between the Agatston score and all-cause mortality.<sup>14</sup> Strikingly, this group of patients often presents with chronic carotid disease and advanced plaque development. Severely calcified plaques are observed in advanced atherosclerotic lesions,<sup>15</sup> and although they have protective properties in terms of plaque stability,<sup>16</sup> severely calcified carotid plaques are a marker not only of advanced cerebrovascular disease but also of cardiovascular disease.<sup>17,18</sup>

This study examined the association between the preoperative ipsilateral modified Agatston score (CaScore) and all-cause mortality after CEA. The incorporation of CaScores might be particularly relevant for optimizing the selection of surgical candidates and anticipating the challenges arising in the near future.<sup>1,2,19</sup>

## PATIENTS AND METHODS

**Study design and study population.** This retrospective, observational cohort study included 316 patients who underwent elective CEA for treatment of carotid stenosis at a single tertiary referral center between 2010 and 2018. Only patients treated with CEA were selected to keep the study cohort as homogeneous as possible. All patients were treated according to current guidelines.<sup>2,4</sup> The following inclusion criteria were applied: Patients had to be at least 18 years of age and give informed consent to participate in the hospital research registry. Patients with a history of CEA or carotid artery stenting (CAS) were excluded from the study. Another exclusion criterion was computed tomography angiography (CTA) images taken more than 3 months before surgery. This criterion was applied to obtain measurements that accurately reflected the calcium burden at the time of surgery. In addition, CTA parameters had to be identical to allow direct comparison of CaScores, as specified in the section 'Quantification of carotid calcification.' Extracted data were collected from the vascular aging study (registration number METC 2016/322) and

## ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective observational cohort study
- **Key Findings:** In this study of 89 patients, a significant association was found between preoperative ipsilateral carotid calcium score and all-cause mortality after carotid endarterectomy (hazard ratio, 1.1;  $P = .003$ ).
- **Take Home Message:** Preoperative quantification of carotid calcifications in patients undergoing carotid endarterectomy has the potential to identify patients with a poorer prognosis. In combination with traditional risk factors, the calcium burden may play a role in treatment decision-making.

pseudonymized. Missing variables were supplemented with data retrospectively retrieved from the electronic health record and municipalities' survival/death registry. The Medical Ethical Institutional Review Board granted dispensation for the study from the Medical Research Involving Human Subjects Act (WMO) obligation (registration number METC 2021/00,866). Therefore, informed consent was not obtained from all patients. Patient data were processed and stored electronically in accordance with the Declaration of Helsinki.

**Clinical variables and outcome measures.** The following baseline characteristics were recorded at the time of surgery: age (years), sex (male/female), body mass index ( $\text{kg}/\text{m}^2$ ), smoking status (non/former/current), comorbidities (yes/no), diabetes mellitus (DM) (yes/no), cerebrovascular disease (yes/no), hypertension (yes/no), chronic obstructive pulmonary disease (COPD) (yes/no), history of myocardial infarction (yes/no), and renal impairment (estimated glomerular filtration rate [eGFR]  $<60$   $\text{mmol}/\text{L}$  3 months before surgery) (yes/no). Preoperative parameters included preoperative symptoms of amaurosis fugax (yes/no), transient ischemic attack (TIA) (yes/no), and cerebrovascular accident (CVA) (yes/no). Symptoms were defined as described by the American Heart Association/American Stroke Association.<sup>20</sup> Preoperative ipsilateral and contralateral stenosis degrees were measured according to the European Carotid Surgery Trial guidelines and divided into four groups (0%-50%, 50%-70%, 70%-99%, and 100%).<sup>21,22</sup> Laboratory values at the time of surgery included eGFR ( $\text{mL}/\text{min}$ ), hemoglobin ( $\text{mmol}/\text{L}$ ), C-reactive protein ( $\text{mg}/\text{L}$ ), and leukocyte count ( $10^9/\text{L}$ ). Surgery-related parameters included side of surgery (right/left), type of anesthesia (general/local), and use of a shunt (yes/no).

The primary outcome variable was all-cause mortality. All-cause mortality was defined as death from any cause and was recorded as the variable "total survival" (alive/dead). In addition, the date of death or the date of last

follow-up date was recognized as the terminal event required for survival analysis.

**Quantification of carotid calcifications.** Preoperatively, nonionic contrast-enhanced computed tomography (CT) images of the neck were obtained. Preoperative CTA scanning confirms the findings obtained by duplex ultrasonography regarding severity of stenosis and may further aid surgical planning by revealing anatomical details. To allow direct comparison of quantified calcium, the imaging parameters had to be identical: performed with a dual-source CT scanner and with a 3-mm single-slice thickness. To quantify calcium content, images from CT were uploaded to the Aquarius iNtuition Viewer software package from TeraRecon (TeraRecon). First, individual anatomic features were examined using a semitransparent three-dimensional reconstruction. Second, the carotid workflow was chosen, in which the segment of interest began at the level of the clavicle and extended through the common carotid artery toward the ICA to the base of the skull. The calcium of the external carotid artery extended to the first branch of the superior thyroid artery. This entire trajectory was chosen to achieve a general, comparable area of interest in all patients and to account for differences in individual plaque margins. Because of the attenuation differences between patients, a patient-specific Hounsfield unit threshold (PST) was determined for both carotid arteries. Distal to the origin of the common carotid artery, a region of interest (ROI) without visible calcification was selected. The mean and standard deviation (SD) of the ROI were measured for all patients. The resulting patient-specific threshold was calculated by adding three SDs to the mean of the ROI,<sup>23</sup> and calcium content was quantified using the individual patient-specific threshold for the resulting ipsilateral and contralateral CaScores. Intraobserver reliability of the CaScore was ensured by repeat measurements after 2 months and comparison with previous measurements.

**Statistical analysis.** The variables listed previously were representative of baseline characteristics. Each variable was assessed for normality using the Shapiro-Wilk test. Baseline characteristics were presented as mean (SD) for normally distributed data and median (interquartile range [IQR]) for skewed data. Categorical data were presented as frequencies (%). Differences within groups were tested with the  $\chi^2$  test for categorical data, the independent Student *t* test for normally distributed data, and the Wilcoxon signed-rank test for nonparametric data. The association between ipsilateral and contralateral CaScores was analyzed using the Pearson correlation coefficient. The reverse Kaplan-Meier method, with the date of surgery as the start of follow-up, was used to determine the median (IQR) follow-up time.<sup>24</sup> Univariable and multivariable Cox proportional hazard

regression analyses were performed to analyze the association between CaScore as a continuous variable and all-cause mortality. The age (years), preoperative eGFR (mL/min), and DM (yes/no) were selected based on the existing literature and the result of the univariate analyses with *P*-values  $\leq .25$ .<sup>25</sup> The same *P*-values were chosen for the interaction terms between covariates. Covariables considered significant according to the literature were excluded in case of missing data. The scale of the continuous CaScore was transformed by dividing it by 100 for illustrative purposes and to support the following univariate analyses. Each unit represented a change by 100 points in ipsilateral CaScore. To avoid overfitting the multivariable model with the a priori selected covariables, the results are presented in three models with stepwise addition of variables. Results are presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and *P*-values. Statistical significance was set at *P*  $\leq .05$ . All statistical analyses were performed using SPSS Statistics software (IBM SPSS, version, 27.0).

## RESULTS

**Study cohort.** After exclusion of patients who did not meet the inclusion criteria, 89 patients were included in the study. The two main reasons for exclusion were unavailable or unsuitable CTA images (77%) and multiple revascularization procedures (19%). Baseline characteristics were similar in the excluded and included group.

**Baseline characteristics.** The mean age was  $69.6 \pm 7.9$  years, and 66 of 89 patients (74.2%) were male. Eighty-one of 89 patients (91.0%) were symptomatic. Most patients (62 of 89; 69.6%) had smoked in the past or were still smoking at the time of surgery. Regarding comorbidities, 21 (23.6%) patients had DM, 52 (58.4%) had hypertension, nine (10.1%) had COPD, 10 (12.4%) had a previous myocardial infarction, and 11 (11.2%) had renal impairment. Fifteen of 89 patients (16.9%) had amaurosis fugax, 36 of 89 (40.4%) had TIA, and CVA occurred in 30 of 89 patients (33.7%). The other baseline characteristics are listed in [Table 1](#).

Based on electroencephalography and transcranial Doppler findings recorded during the procedure, 14 of 89 patients (15.7%) required the use of a shunt. Three-quarters of patients had ipsilateral stenosis of 70% to 99%, and the remainder had stenosis of 50% to 70%. Two patients with a stenosis of 50% underwent CEA because of irregular, vulnerable, and symptomatic plaques on duplex ultrasonography. The 30-day postoperative TIA/CVA/death rate was 0%. Preoperative serological abnormalities were not observed ([Table II](#)). At the time of data collection, 26 of the 89 patients (28.1%) had died. The median follow-up time at the time of censoring was 76.0 months (IQR, 45-106.0 months). By this time, 17 of 26 patients (65.4%) had died.

**Table I.** Patients' baseline characteristics

Variables	N	Mean/frequencies	Percentage/standard deviation
Male sex <sup>a</sup>	89	66	(74.2)
Age, years <sup>b</sup>	89	69.6	(±7.9)
BMI, kg/m <sup>2b</sup>	88	27.1	(±4.5)
≤27		49	(55.7)
≥27 <sup>2</sup>		39	(44.3)
Smoking status <sup>a</sup>			
Current smoking	89	29	(32.6)
History of smoking	89	62	(69.6)
No history of smoking	89	27	(30.3)
Comorbidities <sup>a</sup>			
DM	89	21	(23.6)
Hypertension	89	52	(58.4)
COPD	89	9	(10.1)
History of MI	89	11	(12.4)
Renal impairment	89	10	(11.2)
Preoperative parameters			
Asymptomatic <sup>a</sup>	89	8	(9)
Symptomatic <sup>a</sup>	89	81	(91)
Amaurosis fugax		15	(16.9)
TIA		36	(40.4)
CVA		30	(33.7)
Ipsilateral stenosis <sup>a</sup>	89		
0%-50%		2	(2.2)
50%-70%		20	(22.5)
70%-99%		67	(75.3)
100%		0	(0)
Contralateral stenosis <sup>a</sup>	89		
0%-50%		59	(66.3)
50%-70%		12	(13.5)
70%-99%		8	(9)
100%		10	(11.2)
Surgery-related parameters			
Side <sup>a</sup>			
Right	89	44	(49.4)
Anesthesia <sup>a</sup>	88		
General		87	(97.8)
Regional		1	(1.1)
Shunt <sup>a</sup>	89		
Yes		14	(15.7)
No		75	(84.3)

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; MI, myocardial infarction; TIA, transient ischemic attack.

<sup>a</sup>Binary and categorical variable displayed as frequencies (%).

<sup>b</sup>Normally distributed variables displayed as mean (± standard deviation).

**Quantification of the CaScores.** The median ipsilateral (183; IQR, 54.9-449) and contralateral (200; IQR, 46.6-432.5) CaScore did not differ significantly, as demonstrated in Table III. The Pearson correlation coefficient

between the ipsilateral and contralateral CaScore of 0.56 was statistically significant, with a *P*-value < .001. No association was found between ipsilateral or contralateral CaScores and specific preoperative symptoms, including

**Table II.** Preoperative laboratory values

Variables	N (total = 89)		
eGFR, mL/min	89	74.4	(20.5)
Hb, mmol/L	84	9	(8.1-9.7)
CRP, mg/L	63	4	(1-6)
Leucocytes, 10 <sup>9</sup> /L	71	8.5	(2.6)

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin.  
Data are presented as mean (standard deviation), or median (interquartile range).

**Table III.** Ipsilateral and contralateral calcium scores (CaScores) and their correlation

Variables	Median	Interquartile range	P value	Correlation coefficient	P value
Ipsilateral CaScore	183	53.9-499	.07	0.56	<.001
Contralateral CaScore	200	46.6-432.5	.05		

Data presented as median (interquartile range).  
Correlation represented by Pearson correlation coefficient.

amaurosis fugax, TIA, and CVA. Nearly identical scores were obtained after repeated measurements of 10 random samples 2 months later.

**Univariable and multivariable Cox proportional hazard analysis.** Univariable regression analyzes were performed for the known risk factors of atherosclerosis: age, male sex, increased body mass index, and DM (Table IV). The analysis excluded smoking status because of missing pack-year data. Among these determinants, age was significantly associated with all-cause mortality (HR, 1.06; 95% CI, 1.00-1.12;  $P = .04$ ). Other determinants relevant to subsequent multivariable analysis were eGFR with a HR of 0.99 (95% CI, 0.97-1.00) and DM with a HR of 1.94 (95% CI, 0.88-4.30). No significant interaction terms were found. The results of multivariable Cox regression analysis for all-cause mortality and ipsilateral CaScores are shown in Table V. Each unit increase in ipsilateral CaScore was associated with a HR of 1.10 (95% CI, 1.03-1.16;  $P = .003$ ). In Model 1, adjustment was made for the nonmodifiable risk factor “age.” This resulted in a HR of 1.08 (95% CI, 1.02-1.15;  $P = .01$ ). In addition, adjustment for eGFR in Model 2 resulted in a HR of 1.08 (95% CI, 1.02-1.15;  $P = .01$ ). Model 2 plus DM resulted in a HR of 1.07 (95% CI, 1.00-1.15;  $P = .05$ ).

## DISCUSSION

This study demonstrated a significant association between preoperative ipsilateral carotid CaScores and postoperative all-cause mortality in patients undergoing CEA for atherosclerotic carotid disease. After a median follow-up of 76 months, 65.4% of all deaths occurred. With each unit increase in ipsilateral CaScore, the hazard increased by 10%. The ipsilateral CaScore was the variable most strongly associated with all-cause mortality. Other considerable risk factors were age, DM, and increased contralateral CaScores. Female sex was positively

associated with all-cause mortality; however, there is no obvious association between sex and worse short- and long-term outcomes after CEA.<sup>26,27</sup> Sex was not included in the multivariate analysis because it was regarded as less relevant than other confounders, not neglecting its overall relevance. After adjusting for age and preoperative eGFR in the multivariable Cox regression analysis, the increased mortality risk associated with higher CaScores remained significant.

The association between the CaScore and all-cause mortality has also been confirmed in other studies. Sadat et al measured the CaScore of abdominal visceral arteries in patients with peripheral artery disease on CTA images and found that patients in the high calcium group had a significantly increased hazard compared with patients in the low calcium group.<sup>28</sup> In another study, the preoperative CaScore obtained on CTA at the aortic, iliac, femoropopliteal, and infrapopliteal levels was a reliable predictor of postoperative all-cause mortality at 30 days to 6 months.<sup>29</sup> Each of the studies described above used a different methodologic approach to measure CaScore, and consensus on calcium measurement at CTA remains to be established. The challenge in determining CaScore on CTA images is to account for attenuation caused by the contrast agent itself and not confuse it with calcification. This challenge was addressed by using patient-specific thresholds that depend on individual attenuation coefficients. Several studies have applied the methodology introduced by Agatston et al to nonenhanced CT images and found a significant positive association between CaScores and all-cause mortality.<sup>30,31</sup>

Although these results appear promising, it is important to acknowledge other factors that support the made conclusions. Hendriks et al emphasized that the predictive value of CaScores for each vascular bed must

**Table IV.** Univariable Cox analysis of confounders with all-cause mortality

	HR	95% CI		P value
		Lower	Upper	
All-cause mortality				
Age	1.06	1.00	1.12	.04
Sex	0.81	0.35	1.88	.62
BMI	0.78	0.36	1.69	.52
DM	1.94	0.88	4.30	.10
Preoperative eGFR	0.99	0.97	1.00	.06
Ipsilateral CaScore	1.10	1.03	1.16	.003
Contralateral CaScore	1.07	0.99	1.15	.08

BMI, Body mass index; CaScore, calcium score; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio. The reference group for sex was females. The reference group for BMI was BMI  $\leq 27$  kg/m<sup>2</sup>.

**Table V.** Multivariable adjusted Cox analysis of calcium scores (CaScores) with all-cause mortality

	HR	95% CI		P value
		Lower	Upper	
All-cause mortality				
Univariable	1.10	1.03	1.16	<b>.003<sup>a</sup></b>
Model 1	1.08	1.02	1.15	<b>.01<sup>a</sup></b>
Model 2	1.08	1.02	1.15	<b>.01<sup>a</sup></b>
Model 3	1.07	1.00	1.15	<b>.05<sup>a</sup></b>

CI, Confidence interval; HR, hazard ratio.  
Model 1 adjusted for age.  
Model 2 adjusted for Model 1 + preoperative estimated glomerular filtration rate.  
Model 3 adjusted for Model 2 + diabetes mellitus.  
<sup>a</sup>Statistically significant ( $P \leq .05$ ).

be studied separately and in conjunction with traditional cardiovascular risk factors.<sup>32</sup> Carotid atherosclerotic disease is considered a well-established predictor of cardiovascular risk. Sheet-like plaque calcifications are seen in advanced atherosclerotic lesions, reflecting not only on the local atherosclerotic progression but also on overall cardiovascular health. Although iliofemoral atherosclerosis is the most recognized site for systemic atherosclerosis, this site is not as strongly associated with cerebrovascular events as is carotid atherosclerotic disease.<sup>17</sup> In addition to its association with cardiovascular disease, carotid atherosclerotic disease is also an important etiology for cerebrovascular disease. In other words, carotid atherosclerosis can be used as a proxy for systemic atherosclerotic disease. The major advantage is that it is not excessively time-consuming to examine this relatively short segment, which reflects on other vascular beds beyond the carotid arteries.<sup>33</sup> Based on this knowledge, it can be assumed that patients who, at initial presentation, have a higher calcium burden, have a worse prognosis due to their overall higher cerebrovascular and cardiovascular risk profile and thus poorer health status.

For risk prediction of all-cause mortality, only vascular changes related to calcification were considered. Bos et al identified intraplaque hemorrhage as an independent predictor of adverse events such as stroke and coronary heart disease in a healthy study population with subclinical atherosclerosis. The presence of a lipid-rich necrotic core and calcification were negligible in the presence of intraplaque hemorrhage.<sup>34</sup> Thus, plaque behavior depends not only on the calcium content of the atheromatous plaque but also on other components.

The Agatston score is recognized as an independent predictor of adverse cardiovascular events and all-cause mortality in coronary artery disease. It is a better risk assessment tool than the traditional cardiovascular risk factors.<sup>35</sup> Current proposed risk assessment tools to predict outcomes after CEAs focus mainly on periprocedural stroke/death risk,<sup>36-39</sup> and the availability of tools to assess long-term postoperative outcomes are sparse. These risk assessments use clinical variables to predict outcomes, as opposed to vascular calcification. Keyhani et al presented the 4C model, which considers: (1) any cancer in the past 5 years; (2) COPD; (3) congestive heart failure; and (4) chronic kidney disease, and predicts 5-

year mortality risk based on comorbidities.<sup>40</sup> However, this tool, like many others, considers only asymptomatic patients. These risk assessment tools are not used in screening protocols and are generally not recommended.<sup>4,41</sup>

Vascular surgeons follow guidelines to perform CEA in situations where the perioperative risk is less than the annual risk of stroke/death. This implies that: (1) patient selection is a critical factor in weighing the benefits of an intervention<sup>42,43</sup>; (2) the reduction in stroke risk achieved by revascularization must be greater than the natural history of stroke risk<sup>6,8,44</sup>; and (3) reliable preoperative risk assessment tools are needed to help identify surgical candidates most likely to live long enough to benefit from the improved outcomes expected from CEA. The latter was investigated in this study. It is important to emphasize that exclusion criteria established in randomized clinical trials based on comorbidities are often overlooked in routine clinical practice, resulting in inaccurate risk predictions. The consequence could be unnecessarily exposing patients at risk of premature death to surgical risks.<sup>45-47</sup>

In the absence of previous studies recommending specific calcium cutoff values that could be applied, this study implemented a novel approach that provides new reference points for future studies. Over time, implementation of these measurements into preoperative planning could help identify patients with a high cerebrovascular and cardiovascular risk profile reflecting their overall health status at initial presentation. The knowledge gained about the expected prognosis could support individual patient management by clearly articulating patient expectations based on informed estimates of short- and long-term outcomes. In clinical practice, this means that the CaScore, in combination with widely used prognostic factors such as the patient's general fitness and comorbidities, could assist in selecting potential surgical candidates and enhancing postoperative management. This does not imply that a patient with a high CaScore should be rejected for intervention. Rather, special attention should be paid to those with a high CaScore in the postoperative period by closely monitoring, counseling, and implementing rigorous control of risk factors. When favorable prognostic factors are present, patients with a low CaScore are likely to benefit most from surgery. Although vascular calcification being concomitant with the development of advanced atherosclerosis, traditional cardiovascular risk factors must remain an integral part of the treatment plan, and other studies should focus on possible interactions.

This study has some limitations. Many individuals did not experience the event (death) at the end of the study, leading to a lot right-censoring. Although survival status was determined with certainty by relying on the municipalities' definite survival/death registry, excessive censoring may still lead to unreliable results, particularly

with respect to the median follow-up time. Furthermore, the effects of best medical therapy after CEA could not be examined, because the follow-up trajectory was continued in a primary care setting. Owing to the limited number of patients meeting the inclusion criteria, resulting in a relatively small sample size, the selection was limited to the most important confounders, and others, such as specific laboratory markers and comorbidities, were excluded. As recommended by Vittinghoff and McCulloch, five to nine events per predictor variable were chosen.<sup>48</sup> Despite these limitations, the strengths of this study must be highlighted. The methodology was feasible and reproducible, and the cohort was reasonably homogenous. After repeated measurements, the precision was high, and the CaScore was within the same range. However, this novel methodology must be studied in greater depth in both symptomatic and asymptomatic patients, and preferably externally validated before it can be used as a prognostic tool in clinical practice.

## CONCLUSIONS

In conclusion, this study demonstrated an independent association between preoperative ipsilateral carotid CaScore determined by CTA and all-cause mortality after CEA. Patients with higher CaScores had a worse prognosis than patients with lower CaScores. This finding highlights the potential of calcium measurements as part of preoperative risk assessment. Further studies are needed to confirm the applicability of calcium measurements as a preoperative predictive tool for risk assessment in the clinical setting of carotid surgery.

## AUTHOR CONTRIBUTIONS

Conception and design: FR, RB, CZ, RP

Analysis and interpretation: FR, LB, JdV, RS, CZ, RP

Data collection: FR, LB, CZ, RP

Writing the article: FR

Critical revision of the article: FR, LB, RB, JdV, RS, CZ, RP

Final approval of the article: FR, LB, RB, JdV, RS, CZ, RP

Statistical analysis: FR, LB, RP

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Overall responsibility: RP

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