Journal of Cardiovascular Computed Tomography 20 (2026) 140–147

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research Paper

Carotid perivascular adipose tissue attenuation predicts stroke and TIA in symptomatic carotid artery disease patients

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ARTICLE INFO

Keywords:
Ischemic stroke
Perivascular adipose tissue
Carotid artery disease
Computed tomography angiography
Intraplaque hemorrhage

ABSTRACT

Background: Vascular inflammation is a key aspect of plaque vulnerability. Cross-sectional studies suggest that increased carotid perivascular adipose tissue (PVAT) attenuation on CTA, which is thought to reflect vascular inflammation, is associated with stroke.
Objectives: We investigated the predictive value of carotid PVAT attenuation for ischemic stroke and TIA in a longitudinal study of symptomatic patients with carotid plaque.
Methods: We included patients with recent TIA or stroke and a ≥2 mm carotid plaque with <70 % stenosis who underwent CTA and MRI and were clinically followed-up for 5 years. Mean PVAT attenuation (−190 to −30 Hounsfield Units (HU)) was quantified within a radial distance from the outer vessel wall equal to the vessel diameter on the CTA slice containing the thickest plaque. Cox proportional hazards models assessed associations with ipsilateral stroke and TIA risk. Predictive value was compared with intraplaque hemorrhage (IPH) and the European Carotid Surgery Trial (ECST) score using the C-index.
Results: Among 159 patients (74 % men; 69 (63–73) years), 11 ischemic strokes and 10 TIAs occurred over 5.1 (3.1–5.6) years. Increased PVAT attenuation was independently associated with ischemic stroke or TIA (HR: 3.21 per 10 HU increase, 95%CI:1.70–6.05) and ischemic stroke alone (HR: 5.60, 95%CI:1.93–16.31). PVAT attenuation alone predicted ischemic stroke or TIA (C-index: 0.71, 95%CI:0.70–0.73) and ischemic stroke alone (C-index: 0.78, 95%CI:0.63–0.93). Adding PVAT attenuation improved prediction beyond IPH (C-index: 0.66–0.68 to 0.81–0.84) and the ECST score (0.64–0.75 to 0.75–0.86, respectively).
Conclusion: In symptomatic patients, PVAT attenuation is an independent marker for ischemic stroke and TIA risk.

Abbreviations: CTA, computed tomography angiography; ECST, European Carotid Surgery Trial; HR, hazard ratio; HU, Hounsfield unit; IPH, intraplaque hemorrhage; MRI, magnetic resonance imaging; PVAT, perivascular adipose tissue; TIA, transient ischemic attack.

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https://doi.org/10.1016/j.jcct.2025.12.009
Received 29 September 2025; Received in revised form 12 November 2025; Accepted 22 December 2025
Available online 9 January 2026

1. Introduction

Stroke constitutes a major cause of mortality and long-term disability worldwide.[1] Extracranial carotid artery disease is an important cause of ischemic stroke through atherosclerotic plaque rupture, subsequent thrombus formation, and embolization. The risk of ischemic stroke associated with carotid artery disease is largely dependent on plaque vulnerability.[2] Vascular inflammation is a key process in atherosclerosis and is associated with increased plaque vulnerability and the likelihood of plaque rupture.[2]

Carotid endarterectomy (CEA) can reduce recurrent stroke risk in high-risk symptomatic patients with carotid stenosis.[3] Nevertheless, current patient stratification, predominantly based on the degree of carotid stenosis, is suboptimal. The number-needed-to-treat is 6 for 70–99 % stenosis and 15 for 50–69 % stenosis, suggesting only a marginal benefit in the 50–69 % stenosis group.[4] Furthermore, patients with carotid plaque and <50 % stenosis are not considered for CEA, but still face a substantial risk of 2.6–3.0 recurrent ipsilateral strokes per 100 person-years.[5] Clinical risk modeling has the potential to improve clinical decision-making. However, the European Carotid Surgery Trial (ECST) risk score,[6] the most widely used clinical prediction model, exhibits limited predictive performance (C-index = 0.67) in patients with a carotid plaque with <70 % stenosis.[7] Improving patient stratification based on plaque vulnerability in this population could enable more targeted use of invasive therapies. For instance, intraplaque hemorrhage (IPH) has emerged as a novel, very strong predictor of recurrent stroke.[7,8]

Magnetic resonance imaging (MRI) is preferred for identification of IPH due to its superior soft-tissue contrast.[2,9] However, computed tomography angiography (CTA) and ultrasonography are more commonly used to assess carotid stenosis in daily clinical practice.

[2]. Identifying features on CTA or ultrasonography associated with stroke risk could improve the identification of high-risk patients, without requiring MRI.

Previous research in the coronary arteries indicated that increased perivascular adipose tissue (PVAT) attenuation on computed tomography angiography (CTA) may be a marker of vascular inflammation.[10] Increased PVAT attenuation around coronary arteries has been linked to major adverse cardiac events (MACE) incidence and recurrence.[11,12] Around carotid arteries, elevated PVAT attenuation has been associated with cerebrovascular events and vulnerable plaque components, such as IPH, in cross-sectional studies.[13–17] However, the relationship between carotid PVAT attenuation and ipsilateral ischemic stroke or transient ischemic attack (TIA) recurrence remains unknown.

This longitudinal study investigates the association between carotid PVAT attenuation on CTA and ipsilateral ischemic stroke or TIA during follow-up in symptomatic patients with carotid disease. Additionally, it evaluates whether carotid PVAT attenuation provides predictive value beyond IPH and the ECST risk score.

2. Methods

2.1. Study population

Data were collected from the PARISK study (Plaque at RISK; NCT01208025), a prospective multicentre cohort including patients with recent (<3 months) TIA or minor ischemic stroke, carotid plaque ≥2 mm with <70 % stenosis, who were not scheduled for CEA.[18] Carotid stenosis was evaluated through CTA, using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Patients with a probable cardiac source of embolism, clotting disorder or severe comorbidity were excluded from the PARISK study. Patients with a renal clearance <60 ml/min/1.73 m^2 or documented allergies to iodine contrast agents did not undergo CTA and were excluded from the present sub-study. The PARISK study was approved by the Medical Ethics Committee azM/UM, (NL29116.068.09/MEC:09-2-082). All patients gave written informed consent.

2.2. Assessment of PVAT and plaque on CTA

Carotid CTA images were acquired using a multi-detector row CT system, with a standardized contrast-enhanced carotid CTA protocol (150–180 mAs, collimation 16 × 0.75 mm or 64 × 2 × 0.6 mm, pitch<1). At three centers, images were acquired at 120 kVp, while one center reconstructed 120 kVp images from 100 kVp/140 SnkVp images obtained with dual-energy CTA. The scanning range encompassed the region from the ascending aorta to the intracranial circulation. Each patient was administered 80–85 ml of iodinated contrast agent (concentration 300–320 mg/ml), followed by a 45 ml saline bolus, both delivered at an injection rate of 4–5 ml/s. Real-time bolus tracking was performed at the level of the ascending aorta. Images were reconstructed with a field of view of 120–160 mm, a matrix size of 512 × 512, a slice thickness of 1.0 mm, an increment of 0.6–0.7 mm, and intermediate reconstruction kernels (Philips: B; Siemens: B31f).

PVAT was defined as adipose tissue (attenuation range: -190 HU to −30 HU) located within a region of interest (ROI) of one radial distance from the outer vessel wall equal to the carotid artery diameter, as described and validated previously.[10,11,14–16,19] Mean PVAT attenuation was quantified semi-automatically following delineation of the vessel wall using FIJI (Fig. 1). Measurements were performed on the axial slice corresponding to the thickest carotid plaque, in order to capture PVAT attenuation surrounding the most advanced atherosclerotic lesion. PVAT attenuation measurements were performed exclusively when the PVAT area was ≥2.5 mm^3 to mitigate partial volume effects associated with diminutive PVAT regions.

Plaque ulcerations were assessed in the PARISK study as previously described.[7] Ulceration was defined as an extension of contrast material of >1 mm into the atherosclerotic plaque on at least two orthogonal planes.[7] Plaque volume was semi-automatically determined using dedicated software (vascuCAP Research Edition, Elucid Bioimaging).

2.3. Assessment of IPH on MRI

Carotid MRI was performed on 3T systems (Achieva; Philips Healthcare, Best, The Netherlands, or Discovery MR750; GE Healthcare, Milwaukee, Wisconsin, USA) using dedicated four-channel or eight-channel coils. IPH was visualized using dedicated 3D hyper T1-weighted sequences (3D T1w inversion recovery turbo field echo (IR-TFE) or 3D spoiled gradient echo (SPGR)). The repetition times were 9.0 ms and 9.1 ms, the echo times were 1.3 ms and 5.5 ms, and the flip angles were 30° and 15° for the IR-TFE and SPGR sequences, respectively. Fat suppression was applied, and IR-TFE included an inversion pre-pulse (inversion time: 304 ms, shot interval: 550 ms). Fifteen contiguous 2-mm axial slices were acquired, with in-plane acquisition and reconstruction resolutions ranging from 0.62 to 1 mm × 0.63–1.25 mm and 0.30–0.63 mm × 0.24–0.63 mm, respectively.

The presence of IPH was previously assessed by trained observers, who demonstrated good interobserver agreement with expert readers (>7 and > 10 years of experience, respectively).[20] MR images were analyzed using VesselMass (Leiden UMC, Leiden, the Netherlands), while being blinded to CTA and clinical data. IPH was identified as a hyperintense region in the bulk of the plaque compared to the surrounding muscle, as previously described.[20]

2.4. Follow-up of clinical endpoints

The primary endpoint was recurrent ipsilateral ischemic stroke or TIA, during ≥5 years of follow-up. The secondary endpoint was ipsilateral ischemic stroke only. Events were identified through structured interviews at three months and annually for up to five years. If patients were unreachable, general practitioners were consulted. All diagnoses of recurring ischemic cerebrovascular events were confirmed through medical records from the hospital and/or the general practitioner. Two experienced vascular neurologists, who were blinded to imaging data, assessed and validated the clinical endpoints.

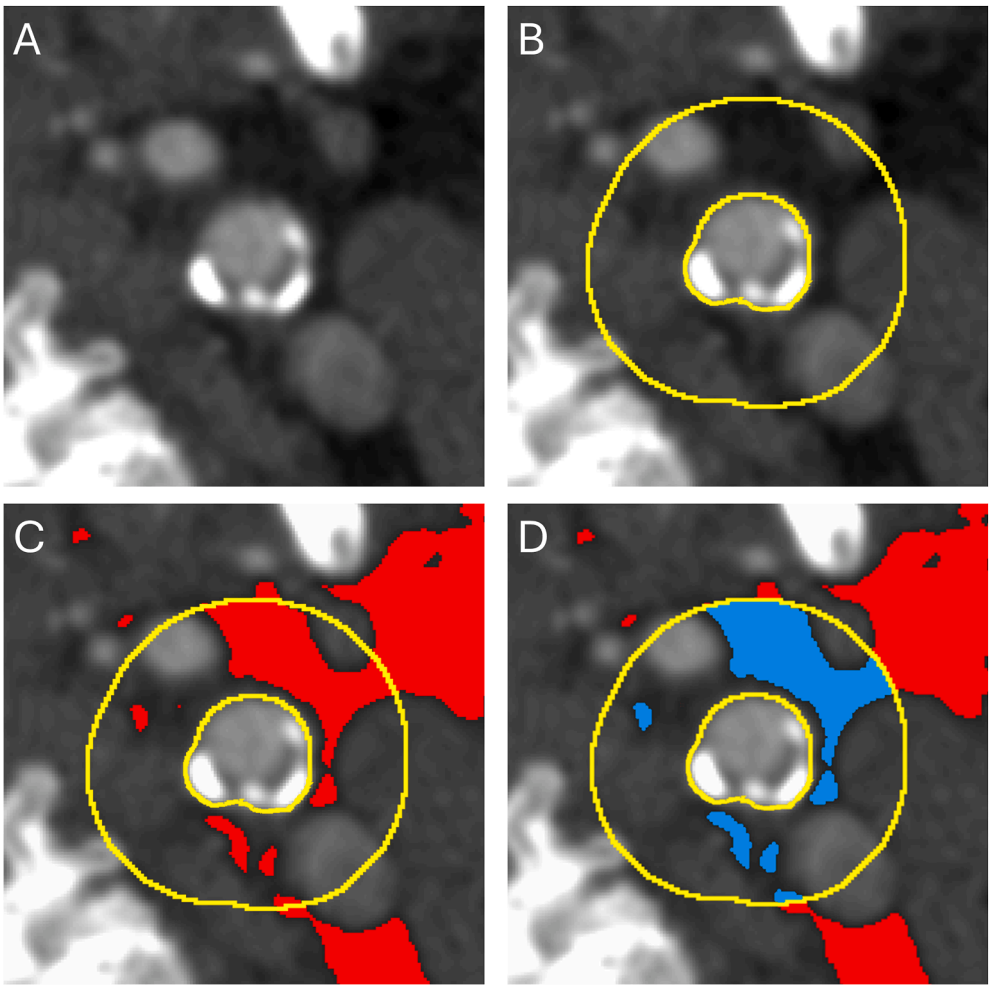

Fig. 1. Example of PVAT measurement
A) CTA of the internal carotid artery. B) ROI with a radial distance from the outer vessel wall equal to the vessel diameter. C) Selection of adipose tissue through thresholding from −190 to −30 HU (red). D) PVAT within the ROI (blue).

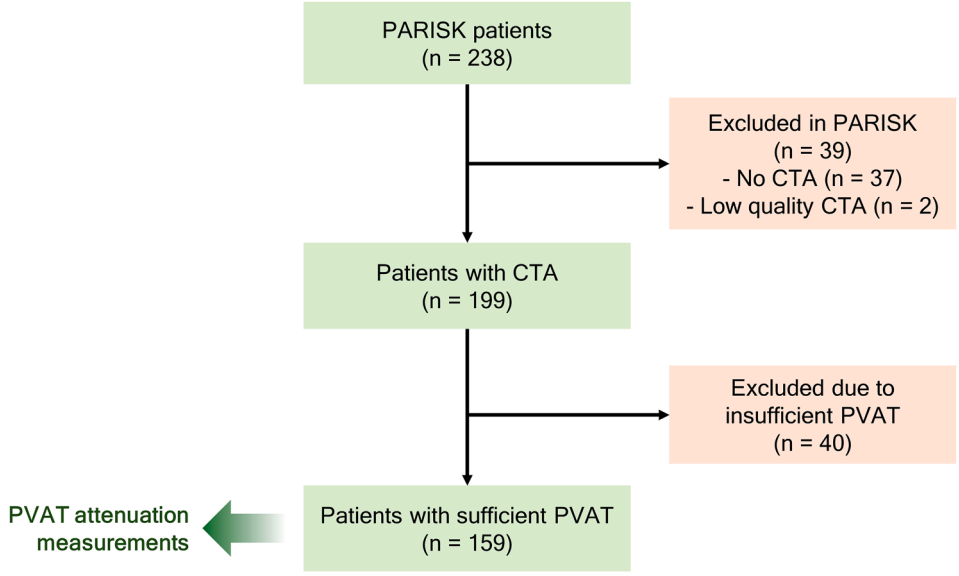

Fig. 2. Flowchart of the study.

2.5. Statistical analysis

Analyses were performed using SPSS 28.0.0.1 (IBM Corp, Armonk, NY, USA) and R 4.3.2 (R Foundation for Statistical Computing). *P*-values of <0.05 were considered significant. Differences in PVAT attenuation across scanner types were assessed using the Kruskal-Wallis test. Differences in clinical characteristics across PVAT attenuation quartiles were assessed using the Kruskal-Wallis test or the Chi-square test. Cox proportional hazard models assessed the association between PVAT attenuation and recurrent ipsilateral ischemic stroke or TIA. We performed unadjusted analyses and analyses that adjusted for age, sex, degree of stenosis, presence of IPH, and plaque volume. For visualization, patients were grouped by quartiles of PVAT attenuation. Kaplan-Meier curves were drawn for visualization and tested using the Log-rank test. To assess incremental prognostic value of PVAT beyond IPH, Kaplan-Meier curves stratified by IPH presence and PVAT category were plotted.

Additionally, we investigated whether PVAT attenuation improves risk prediction in addition to the ECST risk score and IPH. The discriminative performance of the models was assessed using the C-index and compared using the Likelihood-ratio test (LRT). Finally, we calculated the continuous net reclassification improvement (NRI) using 500 bootstrap samples.

3. Results

3.1. Baseline characteristics

In the PARISK study, 238 patients underwent multimodality carotid imaging. A CTA scan was not performed in 37 of these patients due to an impaired renal clearance or a documented allergy against iodine contrast agent. Two additional patients were excluded as their CTA scans were of insufficient quality due to imaging artifacts. During CTA analysis, 40 additional patients were excluded due to insufficient amount of PVAT and PVAT attenuation was thus measured in 159 patients (Fig. 2). The baseline clinical and imaging characteristics of these patients are presented in Table 1. The average age of the included patients was 69 years (IQR: 63–73) and 133 (75 %) participants were male. The median PVAT attenuation was −58 HU (IQR: -65 to −52). PVAT attenuation was not significantly different across the different scanner types: -60 HU (IQR: -77 to −53) for 64-slice, −58 HU (IQR: -63 to −53) for 128-slice, and −57 HU (IQR: -65 to −50) for 256-slice scanners (p = 0.38). No significant differences in clinical characteristics were observed across patients stratified by PVAT attenuation quartiles (Table 2). Additionally, PVAT attenuation did not differ significantly between patients with and without IPH on MRI (−58 vs −58 HU, p = 0.37) or between those with and without ulceration on CTA (−58 vs −58 HU, p = 0.45).

3.2. Relation between PVAT attenuation and clinical endpoints

Median follow-up time was 5.1 (IQR: 3.1–5.6) years. During follow-up, recurrent cerebrovascular events were observed in 21 (13.1 %) patients, comprising ischemic stroke (n = 11) and TIA (n = 10). Among the 40 patients excluded due to insufficient PVAT area for accurate quantification, five individuals (12.5 %) experienced an event, a similar percentage as the included cohort.

Table 3 shows that increased mean PVAT attenuation was associated with the risk for ipsilateral ischemic stroke or TIA (HR: 2.14 per 10 HU increase, 95%CI: 1.32–3.49). This association persisted after adjustments for age and sex, degree of stenosis, presence of IPH, and plaque volume (HR: 3.21 per 10 HU increase, 95%CI: 1.79–6.05). For the secondary endpoint, ipsilateral ischemic stroke, the association was even

Table 1
Baseline clinical and imaging characteristics.

Clinical characteristics at index event (n = 159)	
Age, y	69 (63–73)
Male sex	118 (74)
Current smoking	34 (21)
BMI, kg/m^2	26 (24–29)
Hypertension	112 (70)
Hypercholesterolemia	130 (82)
Diabetes Mellitus	41 (26)
History of ischemic cardiovascular disease	81 (51)
Medication use before index event	
Statins	80 (50)
Antihypertensives	96 (60)
Antiplatelets	73 (46)
Anticoagulants	2 (1)
Medication use during follow-up	
Statins	143 (90)
Antihypertensives	107 (67)
Antiplatelets	158 (99)
Anticoagulants	4 (2)
Classification event	
Cerebral stroke	78 (49)
Cerebral TIA	68 (43)
Monocular stroke or TIA	13 (8)
Imaging characteristics of symptomatic carotid artery	
Time between index event and CTA, d	47 (29–68)
Time between CTA and MRI, d	1 (1–27)
NASCET degree of stenosis on CTA, %	13 (0–33)
PVAT attenuation on CTA, HU	−58 (−65–−52)

The values are presented as median (IQR) or n (%). BMI, Body Mass Index; CTA, computed tomography angiography; HU, Hounsfield Unit; MRI; magnetic resonance imaging; NASCET, North American Symptomatic Carotid Endarterectomy Trial; TIA, transient ischemic attack.

Table 2
Clinical characteristics across quartiles of PVAT attenuation.

	Q1: < −65 HU	Q2: 65 to −58 HU	Q3: -58 to −52 HU	Q4: > −52 HU	*P*-value
Age, y	68 (63–73)	70 (64–73)	66 (60–73)	69 (66–72)	0.38
Male sex	35 (87)	31 (74)	27 (67)	26 (68)	0.15
Current smoking	5 (13)	9 (21)	11 (28)	9 (24)	0.41
BMI, kg/m^2	27 (25–30)	27 (25–31)	26 (24–28)	25 (23–28)	0.06
Hypertension	30 (75)	30 (71)	31 (77)	22 (58)	0.24
Hypercholesterolemia	29 (35)	37 (26)	32 (25)	32 (16)	0.31
Diabetes Mellitus	14 (72)	11 (88)	10 (74)	6 (74)	0.29
History of ischemic cardiovascular disease	19 (48)	23 (55)	18 (45)	21 (55)	0.74
Medication use before index event					
Statins	22 (55)	22 (52)	21 (53)	15 (39)	0.52
Antihypertensives	28 (70)	21 (50)	27 (67)	20 (53)	0.16
Antithrombotics	17 (43)	23 (55)	15 (37)	20 (53)	0.35

The values are presented as median (IQR) or n (%). Antithrombotics contains both antiplatelets and anticoagulants. BMI, Body Mass Index; CTA, computed tomography angiography; HU, Hounsfield Unit; MRI; magnetic resonance imaging; NASCET, North American Symptomatic Carotid Endarterectomy Trial; TIA, transient ischemic attack.

Table 3
Adjusted Cox proportional hazard models of PVAT attenuation per 10 HU Increase.

Cox Proportional Hazard Models	Ipsilateral TIA and ischemic stroke		Ipsilateral ischemic stroke	
	HR per 10 HU increase	p-value	HR per 10 HU increase	p-value
Model 1[a]	2.14 (1.32–3.46)	0.002	3.02 (1.49–6.13)	0.002
Model 2[b]	2.16 (1.38–3.41)	<0.001	3.49 (1.66–7.37)	0.001
Model 3[c]	2.21 (1.38–3.53)	<0.001	3.57 (1.65–7.73)	0.001
Model 4[d]	3.21 (1.70–6.05)	<0.001	5.60 (1.93–16.31)	0.002

IPH, intraplaque hemorrhage; HR, Hazard ratio; HU, Hounsfield Unit.
[a] unadjusted.
[b] adjusted for age and sex.
[c] adjusted for age, sex, and degree of stenosis.
[d] adjusted for age, sex, degree of stenosis, presence of IPH, and plaque volume.

stronger (HR: 3.02 per 10 HU increase, 95%CI: 1.49–6.13; adjusted HR: 5.60, 95%CI: 1.93–16.31).

For illustrative purposes, the event-free survival curves of patients across quartiles of PVAT attenuation were visualized (Fig. 3A and B). To illustrate the incremental predictive value of PVAT attenuation in addition to the presence of IPH, event-free survival was analyzed for patients stratified by low or high PVAT attenuation and presence or absence of IPH (Fig. 3C and D). Fig. 3C and D reveal that patients with low PVAT attenuation and no IPH have a low risk of recurrent ipsilateral TIA or ischemic stroke. Conversely, patients with either low PVAT attenuation and IPH or high PVAT attenuation without IPH exhibited a similar intermediate risk. Patients with both high PVAT attenuation and IPH demonstrated the largest risk of recurrent events.

In a separate analysis, associations were adjusted for the ECST score to reduce model dimensionality. This adjustment did not lead to a relevant change of the associations (HR stroke or TIA: 2.17, 95%CI: 1.31–3.61; HR stroke only: 3.23, 95%CI: 1.51–6.91). Lastly, exploratory adjustment for statin therapy before the index event strengthened the associations slightly (HR stroke or TIA: 2.35, 95%CI: 1.40–3.93; HR stroke only: 4.00, 95%CI: 1.76–9.12).

3.3. Predictive performance of PVAT attenuation

PVAT attenuation (C-index: 0.71, 95%CI: 0.60–0.82) demonstrated predictive performance comparable to IPH (C-index: 0.68, 95%CI: 0.58–0.78) for predicting ischemic stroke or TIA recurrence. Combining PVAT attenuation and IPH significantly improved discrimination (C-index: 0.81, 95%CI: 0.73–0.88; P < 0.001) (Fig. 4).

Adding PVAT attenuation to the ECST risk score increased the C-index from 0.64 (95%CI: 0.50–0.79) to 0.75 (95%CI: 0.65–0.85; P = 0.002). Similarly, adding IPH increased the C-index to 0.73 (95%CI:

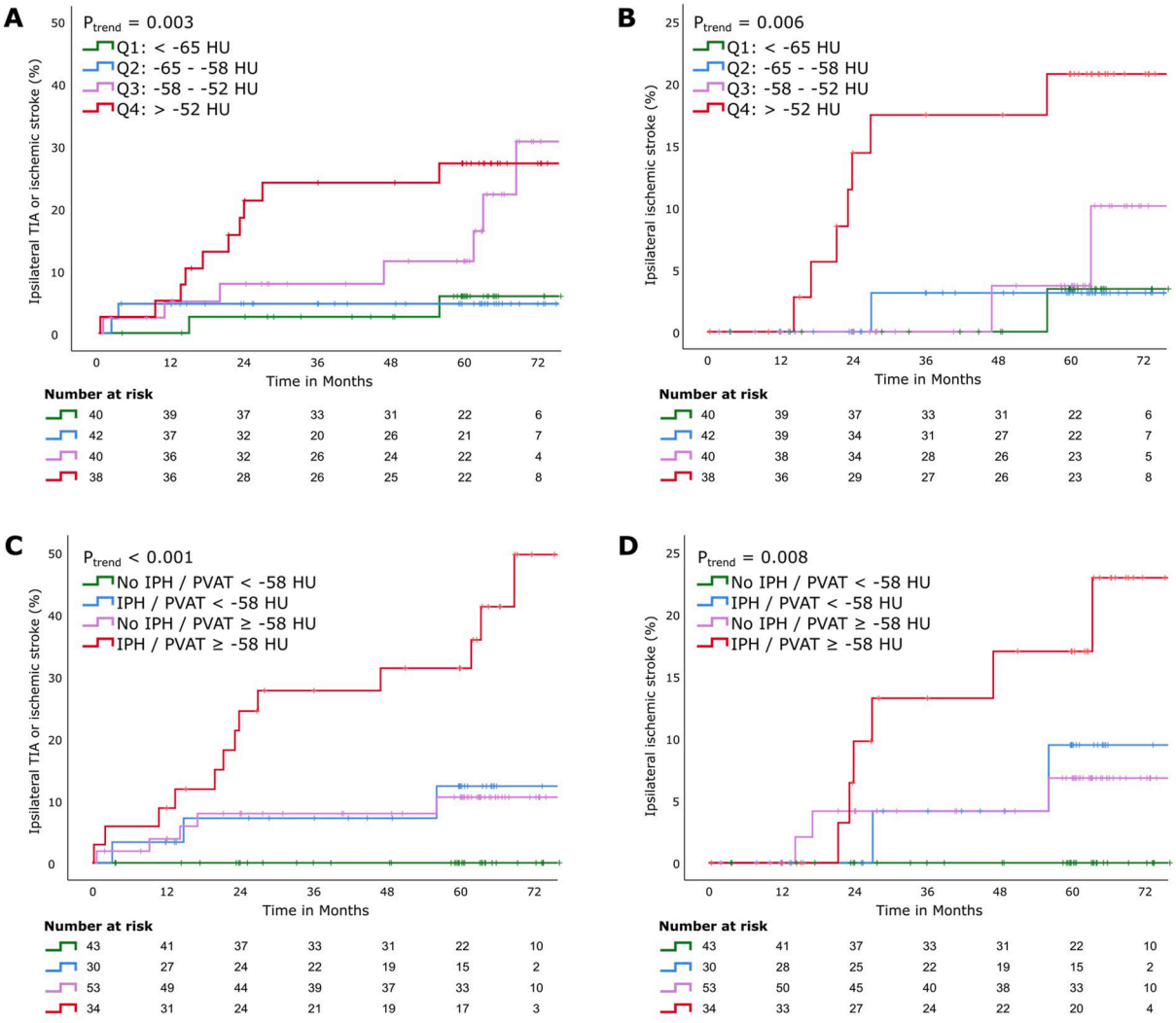

Fig. 3. Kaplan-Meier curves illustrating ipsilateral TIA or ischemic stroke incidence (A and C); or ipsilateral ischemic stroke incidence (B and D). Patients were stratified based on quartiles of PVAT attenuation (A and B) and a combination of median PVAT attenuation and the presence of IPH (C and D).

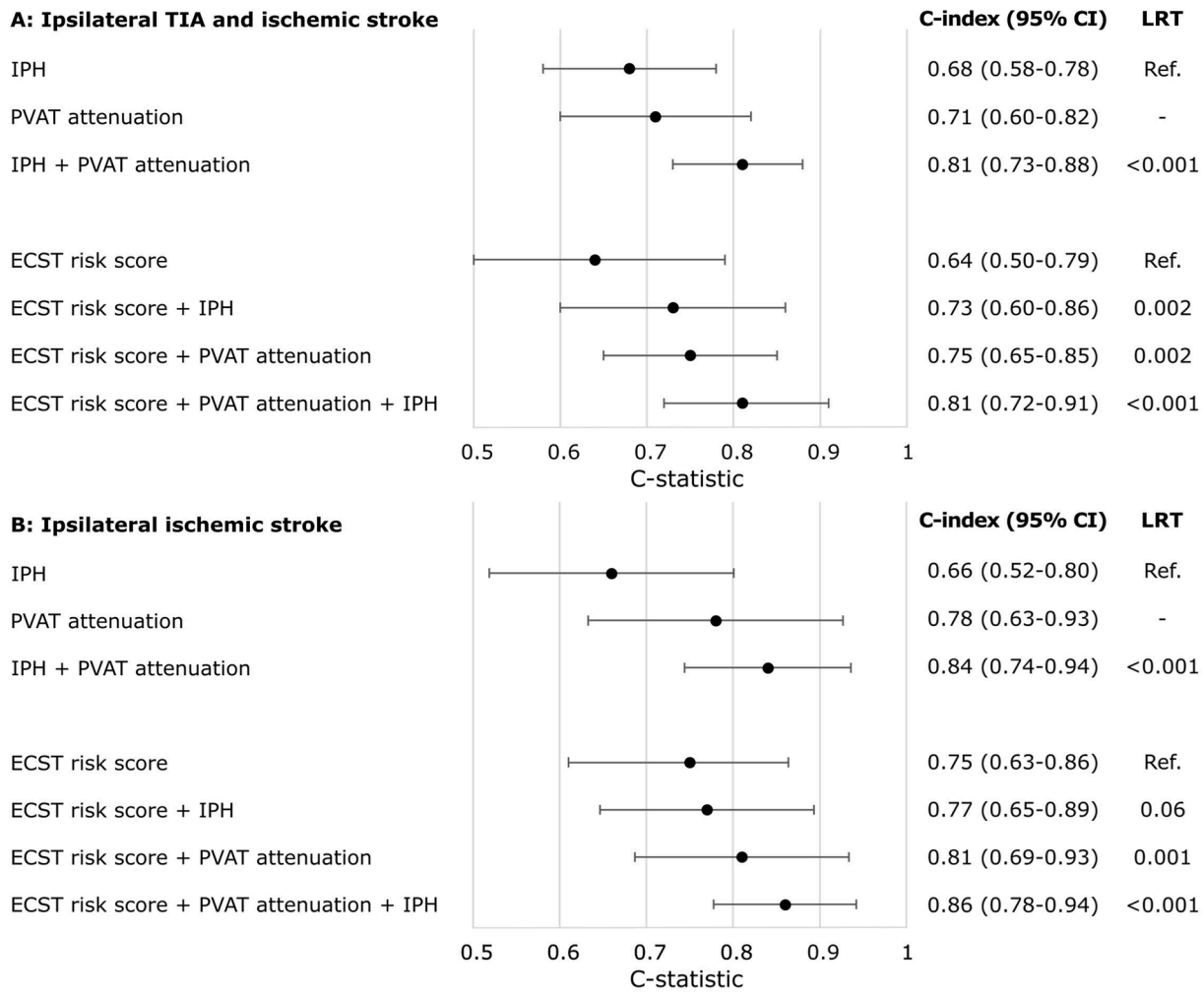

Fig. 4. Prognostic performance of IPH and PVAT attenuation for the prediction of ipsilateral TIA and ischemic stroke (A) or ipsilateral ischemic stroke (B). LRT = likelihood ratio test; Ref. = reference

0.60–0.86; P = 0.002), while including both markers achieved the highest performance (C-index: 0.81, 95%CI: 0.72–0.91; P < 0.001).

For ischemic stroke alone, predictive performance was stronger: PVAT attenuation alone reached a C-index of 0.78 (95%CI: 0.63–0.93), and its combination with IPH further improved discrimination (C-index: 0.84, 95%CI: 0.74–0.94; P < 0.001). Integrating PVAT attenuation into the ECST risk score increased the C-index from 0.75 (95%CI: 0.63–0.86) to 0.81 (95%CI: 0.69–0.93; P = 0.001), and the full model combining PVAT attenuation, IPH, and ECST risk score achieved the highest predictive accuracy (C-index: 0.86, 95%CI: 0.78–0.94; P < 0.001).

The continuous NRI for ischemic stroke or TIA of the extended ECST models with PVAT attenuation, IPH, or the combination of IPH and PVAT attenuation was 0.87 (95 % CI: 0.18–1.27), 0.74 (95 % CI: 0.23–1.28), and 0.83 (95 % CI: 0.25–1.36), respectively. The net proportions of individuals with a recurrent event who were correctly reclassified into a higher predicted risk category were 52.7 %, 44.2 %, and 28.7 %, respectively. The net proportions of individuals without a recurrent event who were correctly reclassified into a lower predicted risk category were 34.3 %, 30.2 %, and 53.9 %, respectively.

4. Discussion

This study indicates that PVAT attenuation on carotid CTA is significantly associated with the ipsilateral TIA or ischemic stroke risk in patients with symptomatic carotid disease, independent of clinical risk factors, stenosis, and IPH. Importantly, adding PVAT attenuation to the ECST model or IPH improves risk prediction. Notably, the associations and predictive performance were even stronger when considering ipsilateral ischemic stroke alone as endpoint.

To our knowledge, this is the first longitudinal investigation examining the association between carotid PVAT attenuation and ipsilateral ischemic stroke or TIA recurrence. In coronary disease, PVAT attenuation a recognized predictor of MACE risk.[11,12,19] It was plausible that carotid PVAT attenuation serves as a stroke predictor in a similar manner. Our findings build on prior cross-sectional carotid studies, which reported elevated PVAT attenuation around vulnerable or symptomatic plaques.[13–17]

Previous cross-sectional studies identified a positive association between IPH and carotid PVAT attenuation, suggesting PVAT attenuation as a surrogate marker of IPH.[15,16] However, our study demonstrated that PVAT attenuation contributes additional predictive value beyond IPH, indicating its utility as a complementary marker of stroke risk rather than a surrogate.

The PARISK study previously demonstrated that adding IPH to the ECST risk score improved risk prediction.[7] However, IPH detection requires MRI, which may be less accessible than CTA in routine stroke care.[2,9] Therefore, PVAT attenuation, could serve as a more accessible imaging marker. Notably, PVAT attenuation showed predictive value comparable to IPH, and integrating it into the ECST risk score achieved a C-index comparable to the integration of IPH to the ECST risk score. Therefore, PVAT attenuation may offer an alternative risk prediction marker when MRI is unavailable. Nevertheless, the best risk prediction was achieved by combining IPH and PVAT attenuation.

While IPH is a robust and well-validated stroke predictor, supported by extensive evidence,[7,8,21] this study is the first to demonstrate the potential of carotid PVAT attenuation as a predictor of ipsilateral ischemic stroke or TIA recurrence. Further validation is necessary before PVAT attenuation can be considered a viable alternative to IPH.

While the pathophysiological role of inflamed PVAT in atherosclerosis is not fully understood, its role as a marker of vascular inflammation has been documented.[10,19,22–24] PVAT adipocytes are influenced by vascular inflammatory mediators released from atherosclerotic plaques via an inside-out signaling pathway.[10,19,24] Specifically, exposure to inflammatory cytokines has been linked to a reduction in adipocyte size.[10] This adipocyte "cachexia" results in diminished lipid content and an increased water-to-lipid ratio, leading to higher HU values on CT due to changes in radiodensity.[10,19]

Alternatively, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) can directly assess plaque inflammation and has shown predictive value for recurrent stroke.[25] However, PET is limited in clinical settings due to limited spatial resolution, additional ionizing radiation exposure, and high costs.[13] Utilizing CTA to evaluate plaque inflammation could enhance clinical applicability while reducing patient burden. Recent research has demonstrated positive correlation between PVAT attenuation and coronary inflammation on PET (68Ga-DOTATATE uptake)).[26] Although PVAT attenuation does not directly quantify inflammation, it likely reflects plaque inflammation.

Other studies investigated the extra-media thickness (EMT), which includes arterial adventitia and PVAT, using ultrasound. Carotid EMT was associated with coronary artery disease,[27] carotid stiffness,[28] the presence of carotid plaques and recently symptomatic plaques.[29] No studies have yet investigated the association between EMT and recurrent cardiovascular events.

Our study has several strengths. First, it is the first prospective, multicenter cohort study to assess the predictive value of carotid PVAT attenuation for ipsilateral ischemic stroke or TIA recurrence. The median follow-up period of 5.1 years allowed for robust assessment of long-term outcomes. The stronger associations observed for ischemic stroke alone further reinforce the clinical relevance of our findings. Second, we adjusted for key risk factors (age, sex, stenosis degree, and IPH), showing that the association is independent of these risk factors. Third, the multimodal design enabled direct comparison with IPH on MRI, and PVAT attenuation on CTA, providing insight into their complementary predictive value.

4.1. Limitations

One limitation is the inclusion of TIA as primary endpoint to enhance statistical power. Nevertheless, our secondary analysis restricted to ipsilateral ischemic stroke demonstrated even stronger associations and predictive value, remaining statistically significant despite the reduced number of events. These findings highlight the potential of PVAT attenuation as a robust marker for stroke risk and underscore the need for future studies with larger cohorts to validate these results using stroke-only endpoints. Additionally, 20 % of patients were excluded due to a small PVAT area ($<2.5\ mm^2$, consistent with other studies), to avoid partial volume effects. Previous carotid PVAT studies have not reported exclusion rates due to small PVAT regions.[13–17] Lastly, although prior research reported dose-dependent effects of statins on periaortic PVAT attenuation,[30] information on statin dose was unavailable in the PARISK study, limiting adjustment for dose effects.

4.2. Conclusion

In symptomatic patients, carotid PVAT attenuation is an independent predictive imaging marker for ipsilateral ischemic stroke or TIA recurrence. PVAT attenuation improves risk prediction independent of IPH and traditional risk factors, with the combined use demonstrating the highest predictive value. PVAT attenuation may represent an alternative to IPH for stroke risk assessment when carotid MRI is unavailable, however, external validation is needed first.

Funding

The PARISK study was supported by the Dutch Heart Foundation (grant number DHF2008-T094) and was performed within the framework of the Center for Translational Molecular Medicine, project PARISK (Plaque At RISK; grant number 01C-202). The authors have reported that they have no relevant conflict of interest to disclose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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