



Title	A Risk Score Including Carotid Plaque Inflammation and Stenosis Severity Improves Identification of Recurrent Stroke
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Original Contribution

Risk Score Including Carotid Plaque Inflammation and Stenosis Severity Improves Identification of Recurrent Stroke

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Background and Purpose—In randomized trials of symptomatic carotid endarterectomy, only modest benefit occurred in patients with moderate stenosis and important subgroups experienced no benefit. Carotid plaque ¹⁸F-fluorodeoxyglucose uptake on positron emission tomography, reflecting inflammation, independently predicts recurrent stroke. We investigated if a risk score combining stenosis and plaque ¹⁸F-fluorodeoxyglucose would improve the identification of early recurrent stroke.

Methods—We derived the score in a prospective cohort study of recent (<30 days) nonsevere (Rankin ≤3) stroke/transient ischemic attack. We derived the symptomatic carotid atheroma inflammation lumen-stenosis (SCAIL) score (range, 0–5) including ¹⁸F-fluorodeoxyglucose standardized uptake values (SUV_{max} <2 g/mL, 0 points; SUV_{max} 2–2.99 g/mL, 1 point; SUV_{max} 3–3.99 g/mL, 2 points; SUV_{max} ≥4 g/mL, 3 points) and stenosis (<50%, 0 points; 50%–69%, 1 point; ≥70%, 2 points). We validated the score in an independent pooled cohort of 2 studies. In the pooled cohorts, we investigated the SCAIL score to discriminate recurrent stroke after the index stroke/transient ischemic attack, after positron emission tomography-imaging, and in mild or moderate stenosis.

Results—In the derivation cohort (109 patients), recurrent stroke risk increased with increasing SCAIL score ($P=0.002$, C statistic 0.71 [95% CI, 0.56–0.86]). The adjusted (age, sex, smoking, hypertension, diabetes mellitus, antiplatelets, and statins) hazard ratio per 1-point SCAIL increase was 2.4 (95% CI, 1.2–4.5, $P=0.01$). Findings were confirmed in the validation cohort (87 patients, adjusted hazard ratio, 2.9 [95% CI, 1.9–5], $P<0.001$; C statistic 0.77 [95% CI, 0.67–0.87]). The SCAIL score independently predicted recurrent stroke after positron emission tomography-imaging (adjusted hazard ratio, 4.52 [95% CI, 1.58–12.93], $P=0.005$). Compared with stenosis severity (C statistic, 0.63 [95% CI, 0.46–0.80]), prediction of post-positron emission tomography stroke recurrence was improved with the SCAIL score (C statistic, 0.82 [95% CI, 0.66–0.97], $P=0.04$). Findings were confirmed in mild or moderate stenosis (adjusted hazard ratio, 2.74 [95% CI, 1.39–5.39], $P=0.004$).

Conclusions—The SCAIL score improved the identification of early recurrent stroke. Randomized trials are needed to test if a combined stenosis-inflammation strategy improves selection for carotid revascularization where benefit is currently uncertain. (*Stroke*. 2020;51:00-00. DOI: 10.1161/STROKEAHA.119.027268.)

Key Words: diabetes mellitus ■ endarterectomy ■ hypertension ■ inflammation ■ positron emission tomography

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Despite modern prevention therapy, the 5-year risk of recurrent stroke and coronary events in stroke survivors is 25% to 30%, about 10% of which are fatal.¹ Improved approaches to secondary prevention are urgently needed. Atherosclerotic carotid stenosis occurs in 15% to 20% of patients with transient ischemic attack (TIA) and stroke in population studies and hospital registries. Carotid stenosis is associated with a 3-fold increase in recurrent stroke risk and is an important risk marker for subclinical coronary disease and future cardiac events in stroke survivors.^{2,3}

In pooled analysis of randomized trials of carotid endarterectomy (CEA) for symptomatic carotid stenosis, the greatest benefit occurred in patients with severe stenosis (70%–99% lumen narrowing). The absolute risk reduction for recurrent stroke or death by 5 years was 16%.^{4,5} By contrast, patients with moderate stenosis (50%–69% narrowing) had less overall benefit from surgery (absolute risk reduction 4.6%), and no benefit was observed in important subgroups with moderate stenosis, including women, those who had surgery >2 weeks after randomization, younger patients (<65 years), and those with ocular events.^{4,5} Consequently, guidelines recommend careful selection of patients with moderate stenosis for surgery based on a favorable risk-benefit assessment.⁶

Improved methods to identify patients at the highest risk of stroke may refine selection for CEA, allowing surgery to be targeted towards patients most likely to benefit. Inflammation is important in the pathophysiology of atherosclerotic plaque development and rupture, leading to thromboembolism and stroke.⁷ Uptake of radiolabelled ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) on positron emission tomography (PET) is a validated marker for plaque metabolism caused by inflammation.^{8,9} Experimental and clinical studies indicate that radiolabelled ¹⁸F-FDG is specifically localized to plaque inflammatory cells, mainly macrophages, and is associated with markers of plaque instability and late clinical events. We recently demonstrated that ¹⁸F-FDG uptake in carotid plaque predicted early recurrent stroke in symptomatic patients with carotid stenosis independently of stenosis severity and other risk factors.¹⁰ In this study, we aimed to investigate: (1) if a simple risk score including both plaque inflammation-related ¹⁸F-FDG uptake and lumen stenosis would improve identification of patients with carotid stenosis and recurrent stroke after symptom onset; (2) if the score would predict future stroke recurrence after PET imaging; and (3) if the score identified recurrent stroke in the subset of patients with mild or moderate stenosis, the group for whom improved risk stratification may be of greatest use for clinical decision-making when considering CEA.

Methods

Derivation Cohort

To derive the risk score, we analyzed patients in the BIOVASC study (Biomarkers and Imaging of Vulnerable Atherosclerosis in Symptomatic Carotid Artery Disease). Patient eligibility and study procedures for BIOVASC have previously been reported.¹⁰ Briefly, BIOVASC is a multicenter prospective cohort study at 10 centers in Ireland, Barcelona, Paris, Calgary, and Singapore.

Inclusion criteria were (1) age ≥50 years, (2) recent (<30 days before study entry) nonsevere ischemic stroke (modified Rankin scale

score ≤3) or TIA affecting speech, motor function, or vision, (3) ipsilateral internal carotid artery stenosis (≥50% lumen narrowing) based on reports of admission carotid imaging by radiologists for clinical care, (4) combined PET/computed tomography angiography (CTA) imaging completed. Exclusion criteria were (1) probable hemodynamic stroke/TIA because of carotid near-occlusion, (2) renal impairment (glomerular filtration rate <60 mL/min) or other contraindication to contrast-enhanced CT or magnetic resonance imaging (eg, known contrast allergy), (3) prior neck irradiation, ipsilateral carotid surgery, or stenting, (4) pregnancy, and (5) dementia, malignancy, or other comorbid conditions precluding study participation.

All patients had a detailed baseline assessment by trained study personnel. Treating clinicians were advised to prescribe antiplatelet agents, statins, and other prevention treatments according to guidelines. Decisions relating to choice and doses of medical treatments were at the discretion of the treating clinician.

BIOVASC was approved by Ethics Committees of participating centers and all patients gave informed consent.

Ascertainment of Recurrent Stroke

The primary outcome was recurrent stroke. To avoid misclassification bias of recurrent stroke before hospital presentation, each patient was carefully questioned about episodes of persistent (>24 hours) or transient focal neurological disturbance consistent with TIA or stroke within the 30 days before hospital presentation. All suspected earlier TIA or stroke events were confirmed by in-person assessment of the patient by a senior stroke clinician and independently centrally adjudicated by a study investigator blinded to PET data (Dr Kelly). Only unequivocal focal motor, speech, or monocular vision loss were classified as prehospital TIA, and vague nonfocal, sensory, or visual symptoms were excluded.

After study entry, standardized follow-up assessments were performed in-person or by telephone interview at 7, 30, and 90 days. Patients were carefully questioned to assess for recurrent stroke. Suspected stroke recurrences were confirmed in duplicate, by in-person evaluation by the site lead investigator and by independent central adjudication by another investigator (Dr Kelly) blinded to imaging data.

The first stroke or TIA within the 30-day prehospital presentation interval was classified as the index event, with subsequent ipsilateral new strokes following the index event (prehospital or within 90-day follow-up) classified as recurrent strokes. For the primary analysis, only recurrent strokes unrelated to a revascularization procedure (defined as before or later than 24 hours of carotid revascularization) were defined as outcomes. A sensitivity analysis was performed when recurrent stroke following revascularization was excluded.

PET-CT Imaging

¹⁸F-FDG PET-CT was performed within 7 days after a minimum 6-hour fast (online-only Data Supplement). 320 MBq of ¹⁸F-FDG was administered 2 hours before image acquisition. The uptake phase was standardized with the patient resting. PET images were acquired in 3-dimensional mode in 2-bed positions for 10 minutes each. A low-dose CT for attenuation correction was then done using the same scanner, followed by aortic arch to skull-base carotid CTA using contrast-bolus tracking.

Image Analysis

Following co-registration of PET and CT images using a semi-automated algorithm with manual correction, carotid ¹⁸F-FDG activity in 10 regions of interest was quantified by a single reader (Dr Giannotti) blinded to clinical outcomes. Each region of interest was defined relative to the slice of maximal stenosis on the co-registered CTA, corresponding to a 1 mm axial plaque slice. ¹⁸F-FDG was quantified using standardized uptake values (SUV g/mL, defined as measured uptake [MBq/mL]/injected dose [MBq] per patient weight [g]). We defined the single hottest slice as the axial slice with maximal SUV uptake (SUV_{max}).¹¹ We calculated tissue-to-background ratios (TBRs) as the

AQ8 ratio of ICA SUV_{max} /internal jugular vein SUV_{mean} . All images were centrally analyzed by a single trained reader (Dr Giannotti) using OsiriX MD version 6.5.2 (Pixmeo SARL, Geneva). Intrarater reliability assessment showed excellent agreement (intraclass correlation $\alpha=0.814$, $P<0.001$).

For inclusion into BIOVASC, all patients without near-occlusion with ICA stenosis $\geq 50\%$ on the admission ultrasound, magnetic resonance angiography, CTA, or angiogram reported by radiologists for clinical care were eligible. Subsequently, all CTAs done for combined PET/CT imaging were centrally remeasured by a single reader blinded to clinical outcomes (Dr Giannotti) and degree of stenosis classified by the NASCET (North American Symptomatic Carotid Surgery Trial) method (online-only Data Supplement). Eleven patients originally categorized as moderate stenosis were reclassified as mild (30%–49%) stenosis on central re-measurement. Using an intention-to-treat principle, all patients were included for derivation of the risk score.

Validation Cohort

We investigated the external validity of the risk score by analyzing the association of the score with recurrent stroke in an independent cohort comprising pooled data from the DUCASS (Dublin Carotid Atherosclerosis Study) and Barcelona Plaque Study. Both studies used eligibility criteria, outcome ascertainment, and imaging methodologies, which were highly similar to BIOVASC.

DUCASS was an earlier study (conducted between 2008 and 2011) by members of the BIOVASC study group.¹² The protocol subsequently used in BIOVASC is almost identical to the earlier DUCASS methods (online-only Data Supplement).

The Barcelona Plaque Study was conducted between October 2015 and March 2018, also using methods based on the earlier DUCASS study. Consequently, study eligibility criteria, stroke recurrence ascertainment, and imaging methods were also highly similar to BIOVASC, except that the Barcelona study was done at a single-center, the interval between qualifying stroke/TIA and study inclusion was 7 days, and CTA was usually done before PET-CT (online-only Data Supplement).

All PET and CTA images in DUCASS and Barcelona patients were reviewed by the same reader (Dr Giannotti), who reviewed the BIOVASC images using identical methodology for image analysis.

Statistical Analysis:

Comparison of baseline clinical variables in patients with and without recurrent stroke was compared using *t* tests, Mann-Whitney tests, or χ^2 tests as appropriate. In the derivation cohort, we performed bivariate Cox regression analysis to determine factors associated with recurrent stroke at 90 days, expressed as hazard ratio (HR) with 95% CI. Patients were censored at the time of recurrent stroke, or last follow-up visit (if lost to follow-up). The proportional hazard assumption was tested by visual examination of survival curves and by the Schoenfeld test. Forward step-wise multivariable Cox regression modeling was performed with time to recurrent stroke as the dependent variable. Independent variables were included in the model based on a $P \leq 0.05$ on bivariate analysis or a known clinical rationale for association with stroke recurrence.

Based on the observed HRs on multivariable Cox regression, we derived the symptomatic carotid atheroma inflammation lumen-stenosis (SCAIL) score by assigning points based on ^{18}F -FDG uptake¹³ ($SUV_{max} < 2$ g/mL, 0 points; $SUV_{max} 2$ – 2.99 g/mL, 1 point; $SUV_{max} 3$ – 3.99 g/mL, 2 points; $SUV_{max} \geq 4$ g/mL, 3 points) and stenosis severity (<50% stenosis, 0 points; 50%–69% stenosis, 1 point; $\geq 70\%$ stenosis, 2 points). The derived SCAIL score consisted of 2 items, ranging from 0 to 5 points. In the derivation cohort, we investigated the relationship of the score to the risk of early recurrent stroke by analyzing the distribution of recurrent stroke across increasing levels of the score and by calculating the C statistic (area under the curve) on receiver-operating characteristic analysis. To examine the influence of other prognostic factors on the relationship of the SCAIL score with recurrent stroke, we did multivariable Cox regression

analysis with inclusion of the SCAIL score, age, sex, and other risk factors as covariates. To assess the external validity of the score, we then repeated these analyses in the independent validation cohort.

We tested for heterogeneity of the 3 included studies by calculating the Mantel-Haenszel χ^2 and I^2 statistics and by visual examination of forest plots. As no evidence of heterogeneity was identified, individual-patient data from all 3 cohorts were pooled. In the pooled data set, we explored threshold levels of the score associated with optimal sensitivity and specificity for association with recurrent stroke. We further investigated the prognostic relationship of the SCAIL score with future recurrent stroke (ie, recurrent stroke which occurred after PET imaging) by repeating our analyses after exclusion of recurrent strokes which occurred before PET. To examine the score in patients with mild or moderate stenosis, where improved risk prediction might be most clinically useful, we repeated our analyses after exclusion of patients with severe stenosis, with outcome defined first as any recurrent stroke (pre- or post-PET imaging) and then as recurrent stroke post-PET imaging only. In sensitivity analyses, we repeated our analyses for patients censored at the time of carotid revascularization (to eliminate potential residual confounding associated with CEA or stenting) and when plaque inflammation was defined as TBR_{max} in single hottest slice from each patient (online-only Data Supplement).

All analyses were done in Stata version 14. All significance testing was 2-sided, with a $P < 0.05$ considered significant.

Results

Derivation Cohort

One hundred and nine patients were included in the BIOVASC derivation cohort. Clinical characteristics are described in Table 1 in the online-only Data Supplement. Briefly, mean age of included patients was 69.7 years and 71% were men. Overall, 45% had severe, 45% moderate, and 10% mild stenosis on central imaging re-measurement. Carotid revascularization was done in 63% (69 patients, CEA in 65, stenting in 4, median 10 days postadmission [interquartile range, 8–17.5 days]). Early recurrent stroke occurred in 12.8% (14 patients, 9 prehospital stroke recurrences, 1 recurrence after CEA).

Multivariable Cox regression analysis of factors associated with recurrent stroke has been previously reported.¹⁰ After adjustment for age, sex, stenosis severity, hypertension, diabetes mellitus, smoking, antiplatelets, and statin treatment, the HR for recurrent stroke per 1 g/mL SUV_{max} was 2.2 (95% CI, 1.1–4.48, $P=0.025$). The HR associated with increasing stenosis severity was 2.45 (95% CI, 0.9–6.5, $P=0.07$, unadjusted, referent group mild stenosis). No other variable was associated with recurrent stroke on bivariate or multivariable analysis.

Based on the observed HRs per unit increase in SUV_{max} and stenosis category, points of 0–3 were assigned according to ^{18}F -FDG uptake and points of 0–2 assigned to stenosis severity (Figure 1). The resulting 2-item SCAIL score ranged from 0 to 5 points (Table 1). Twenty-one (19.3%) patients had a score of 4 or more, and 4 patients (3.7%) had a score of 5. The risk of early recurrent stroke increased with increasing SCAIL score ($P=0.002$ for trend; Table 2 and online-only Data Supplement). No patients with a score of 0 or 1 had recurrent stroke, whereas all 4 patients with a score of 5 had recurrent stroke (2 patients) or recurrent TIA (2 patients).

On multivariable Cox regression analysis, after adjusting for age, sex, hypertension, diabetes mellitus, smoking, antiplatelet, and statin treatment, a 1-point increase in SCAIL

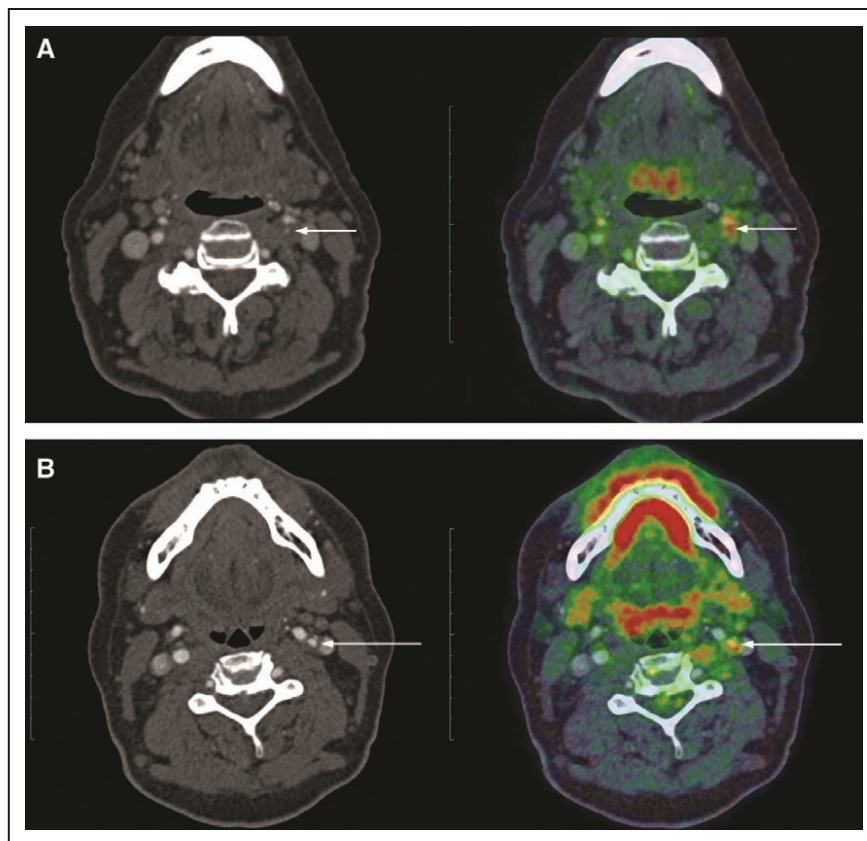


Figure 1. **A**, Patient with severe left ICA stenosis and plaque maximal SUV uptake (SUV_{max}) 4.9 g/mL (symptomatic carotid atheroma inflammation lumen [SCAIL] score 5). **B**, Patient with moderate left ICA stenosis and plaque SUV_{max} 4.4 g/mL (SCAIL score 4).

AQ9

AQ10

score was associated with recurrent stroke (adjusted HR, 2.4 [95% CI, 1.2–4.5], $P=0.01$). On receiver-operating characteristic analysis, the C statistic for discrimination of recurrent stroke postindex event was 0.71 (95% CI, 0.56–0.86).

Validation Cohort

Eighty-seven patients were included in the independent validation cohort. Clinical characteristics are described in the [online-only Data Supplement](#). Thirty-three percent (29 patients) had severe stenosis, 59% moderate (51 patients), and 8% mild stenosis (7 patients) on central re-measurement. Carotid revascularization was done in 44%. Recurrent stroke occurred in 23 patients (26.4%), 13 of which occurred before hospital presentation. In the validation cohort, the risk of recurrent stroke increased across SCAIL categories ($P<0.001$). After adjustment for age, sex, hypertension, diabetes mellitus, smoking, antiplatelet, and statin treatment, the adjusted HR for each 1-point SCAIL increase was 2.9 (95% CI, 1.9–5, $P<0.001$). The C statistic for discrimination of early recurrent stroke postindex event was 0.77 (95% CI, 0.67–0.87).

Pooled Cohorts

As no evidence of significant heterogeneity was apparent among all 3 studies (I^2 0%, Mantel-Haenszel χ^2 0.9), we pooled the derivation and validation cohorts to further explore the characteristics of the score and to provide additional statistical power for subgroup analyses. The pooled data set included 196 patients, with 37 recurrent strokes (22 prehospital, 15 postadmission, 8 of which were post-PET stroke recurrences).

In the pooled data set, discrimination of any recurrent stroke following the index event was improved by the SCAIL score (C statistic 0.74 [95% CI, 0.66–0.82]) compared to stenosis alone (C statistic 0.65 [95% CI, 0.56–0.73], $P=0.016$ for comparison; Figure 2A). When the score was collapsed into low (0–1), medium (2–3), and high (4–5) categories, a linear increase in stroke recurrence risk was observed ($P<0.001$ for trend; Table 3; Figure 3A). The recurrent stroke risk was 0% (0/18 patients) in the low category, 18% (23/128 patients) in the medium category, and 52% (14/27 patients) in the highest SCAIL category. On threshold analysis, a score of 3 or more had 81% sensitivity and 54% specificity for discrimination of recurrent stroke. A score of 4 or more had 38% sensitivity but 90% specificity for recurrent stroke. Plaque FDG uptake did not correlate with stenosis severity ($P=0.8$).

In a sensitivity analysis, our results were unchanged when ^{18}F -FDG uptake was quantified as TBR_{max} and the SCAIL score redefined by integrating TBR_{max} with stenosis severity ($SCAIL_{TBR}$; [online-only Data Supplement](#)). In this analysis, the adjusted HR of any recurrent stroke was 1.67 (95% CI, 1.22–2.29) for each 1-point increase in $SCAIL_{TBR}$ ($P=0.001$). Stroke risk increased with progressive increases in $SCAIL_{TBR}$ strata ($P<0.0001$ for trend).

Prediction of Recurrent Stroke After PET

To investigate if the SCAIL score predicted future stroke after PET imaging, we repeated our analyses in the pooled data set after exclusion of all recurrent strokes before PET. In this analysis, after excluding the 29 patients with recurrent stroke before PET imaging, 167 patients were included, with 8 recurrent stroke outcomes post-PET imaging.

Table 1. SCAIL Item Measures and Points, Based on Multivariable Cox Regression Model in Derivation Cohort¹³

SCAIL Item	Measure	SCAIL Points
Plaque SUV _{max} , g/mL	<2	0
	2–2.99	1
	3–3.99	2
	≥4	3
Lumen stenosis, %	<50	0
	50–69	1
	≥70	2
Total		0–5

SCAIL indicates symptomatic carotid atheroma inflammation lumen; and SUV, standardized uptake value.

The risk of post-PET recurrent stroke across low, medium, and high SCAIL categories also increased ($P_{\text{trend}} < 0.001$; Figure 3B). On multivariable Cox regression, after adjustment for age, sex, hypertension, diabetes mellitus, smoking, antiplatelet, and statin treatment, the HR for post-PET recurrent stroke per 1-point SCAIL increase was 4.52 (95% CI, 1.58–12.93, $P=0.005$). Compared with stenosis severity alone (C statistic 0.63 [95% CI, 0.46–0.80]), discrimination of recurrent stroke after PET was improved with the SCAIL score (C statistic 0.82 [95% CI, 0.66–0.97], $P=0.04$ for comparison; Figure 2B).

In a sensitivity analysis, when ¹⁸F-FDG uptake was expressed as TBR, the adjusted HR for recurrent stroke after PET was 3.14 (95% CI, 1.25–7.91, $P=0.015$) per 1-unit increase in SCAIL_{TBR}, with increased stroke risk across SCAIL_{TBR} strata ($P=0.02$; online-only Data Supplement).

SCAIL Score and Recurrent Stroke in Mild and Moderate Stenosis

To explore the relationship of the SCAIL score with recurrent stroke in patients where additional information to stenosis severity might be most useful for clinical decisions relating to carotid surgery, we repeated our analyses after exclusion of patients with severe stenosis. By definition, in such patients, the SCAIL stenosis item was scored as zero or one. The subgroup with mild or moderate stenosis comprised 118 patients (18 mild and 100 moderate stenoses), with 17 recurrent strokes (4 of which occurred following PET imaging).

On Cox regression analysis, after adjustment for age, sex, antiplatelet and statin treatment, and other risk factors, the HR of any recurrent stroke (pre- or post-PET) in patients with mild or moderate stenosis per 1-point increase in SCAIL score was 2.74 (95% CI, 1.39–5.39, $P=0.004$). The C statistic for discrimination of any recurrent stroke was 0.71 (95% CI, 0.59–0.83).

When the analysis was restricted to patients with mild or moderate stenosis who had stroke recurrence after PET imaging, the HR per 1-point SCAIL score increase was 10.89 (95% CI, 1.93–61.16, $P=0.007$). The C statistic for discrimination of post-PET recurrent stroke in patients with mild or moderate stenosis was 0.82 (95% CI, 0.57–1).

Table 2. Risk of Nonprocedural Stroke Recurrence Stratified by SCAIL Score in Derivation Cohort (P for Trend 0.002, $n=95$, 14 Patients With Recurrent TIA Excluded)

SCAIL Score	Recurrent Stroke (No. of Patients)	Total (No. of Patients)	Risk, %	95% CI	P (Trend)
0	0	0	0		0.002
1	0	12	0	0–26.5	
2	4	34	11.8	3.3–27.5	
3	4	34	11.8	3.3–27.5	
4	4	13	30.8	9.1–61.4	
5	2	2	100	15.8–100	
Total	14	95			

SCAIL indicates symptomatic carotid atheroma inflammation lumen; and TIA, transient ischemic attack.

Recurrent Stroke Before Carotid Revascularization

To further test the robustness of our findings, we excluded patients whose stroke recurrence occurred after carotid revascularization (CEA or stenting). In this analysis, patients were censored at the time of stroke recurrence, carotid revascularization, or 90 days (online-only Data Supplement). Only one patient had recurrent stroke after CEA, leaving 196 patients with 36 recurrent strokes after the index event. Our results were unchanged—the adjusted HR of any recurrent stroke per 1-point SCAIL increase was 2.0 (95% CI, 1.38–2.86, $P < 0.001$) and that for post-PET recurrent stroke was 4.53 (95% CI, 1.6–12.77, $P=0.004$). Our results were consistent in patients with mild or moderate carotid stenosis and when the metric of ¹⁸F-FDG uptake was quantified as TBR_{max} (online-only Data Supplement).

Discussion

We describe a simple risk score including plaque inflammation and arterial lumen narrowing in recently symptomatic patients with carotid stenosis. Our study provides new information in several ways. First, we show for the first time that incorporating information relating to plaque inflammation-related metabolism and lumen stenosis in a single measure identifies patients at highest risk of early recurrent stroke. In the derivation cohort, the risk of early stroke recurrence increased in a step-wise manner across increasing SCAIL score strata. No patients in the lowest SCAIL categories (0 or 1) had recurrent stroke, while all patients with a SCAIL score of 5 had recurrent stroke or TIA.

Second, the relationship of the SCAIL score with early stroke recurrence was replicated in an independent validation cohort. In the validation data set, each 1-point increase in the score was associated with a 3-fold increase in the hazard of early stroke recurrence after adjustment for potential confounding variables. A SCAIL score of 4 or 5 had 90% specificity for identification of recurrent stroke, with 79% of patients correctly classified based on presence or absence of stroke recurrence.

Third, on multivariable analysis, the SCAIL score independently predicted recurrent stroke after PET imaging, in addition to its association with all recurrent stroke events before or after PET. This suggests that early ¹⁸F-FDG-PET after

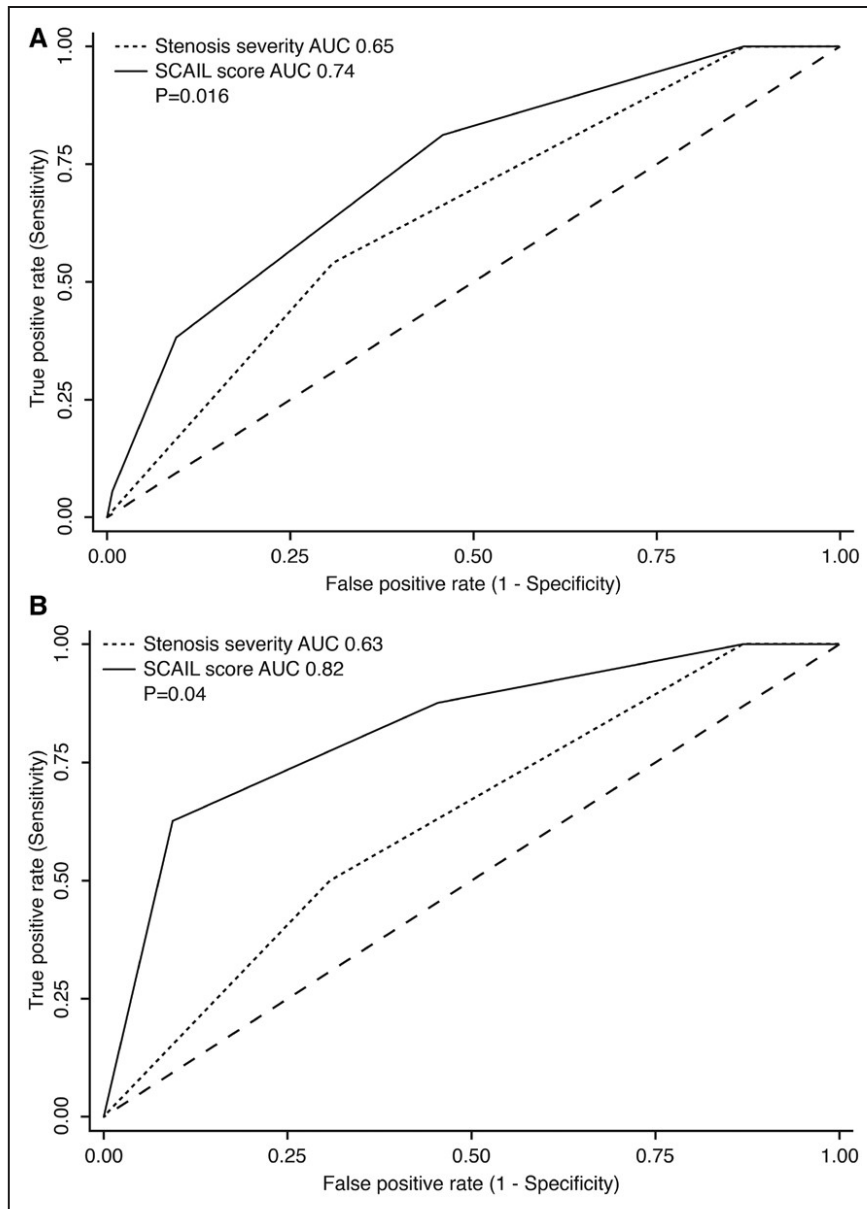


Figure 2. A, Receiver-operating characteristic curves for all recurrent stroke after index event by stenosis severity alone compared with symptomatic carotid atheroma inflammation lumen (SCAIL) score in pooled cohorts (area under the curve [AUC] for stenosis severity alone 0.65 [95% CI, 0.56–0.73], AUC for SCAIL score 0.74 [95% CI, 0.66–0.82]; $P=0.016$). **B,** Receiver-operating characteristic curve for discrimination of post-positron emission tomography [PET] recurrent stroke by stenosis severity alone compared with SCAIL score in pooled cohorts (AUC for stenosis severity alone 0.63 [95% CI, 0.46–0.80], AUC for SCAIL score 0.82 [95% CI, 0.66–0.97]; $P=0.04$).

hospital presentation may have prognostic utility to identify high-risk patients with carotid stenosis, thus guiding treatment decisions. For any stroke recurrence (pre- and post-PET), the C statistic improved from 0.65 to 0.74, a modest improvement, although statistically significant. By contrast, the C statistic for discrimination of post-PET stroke recurrence improved

from 0.63 to 0.82, suggesting that the SCAIL score might have better discrimination for recurrent stroke in the days immediately following PET imaging, when PET may be most useful to guide clinical practice. However, this finding must be interpreted with caution as the CIs were wide, reflecting the low number of post-PET stroke outcomes.

Fourth, our findings were consistent in analyses restricted to patients with mild or moderate stenosis, the group for whom improved identification of high-risk patients is most likely to be clinically useful when considering selection for surgery. Fifth, our results were consistent when only recurrent stroke before carotid revascularization were considered, indicating that they are not confounded by periprocedural stroke events.

Inflammation is an important contributor to the development and rupture of atherosclerotic plaque. Studies of blood inflammation markers, such as C-reactive protein and genetic epidemiological studies of functional polymorphisms in inflammatory proteins, have shown consistent associations with myocardial infarction and ischemic stroke. In the

Table 3. Risk of Nonprocedural Stroke Recurrence Stratified by SCAIL Risk Category (Low=0, 1; Medium=2, 3; and High=4, 5) in Pooled Cohorts (P for Trend <0.001, $n=173$, 23 Patients With Recurrent TIA Excluded)

SCAIL Risk Category	Recurrent Stroke (No. of Patients)	Total (No. of Patients)	Risk, %	95% CI	P (Trend)
Low (0, 1)	0	18	0	0–18.5	<0.001
Medium (2, 3)	23	128	18	11.7–25.7	
High (4, 5)	14	27	51.9	32–71.3	
Total	37	173			

SCAIL indicates symptomatic carotid atheroma inflammation lumen; and TIA, transient ischemic attack.

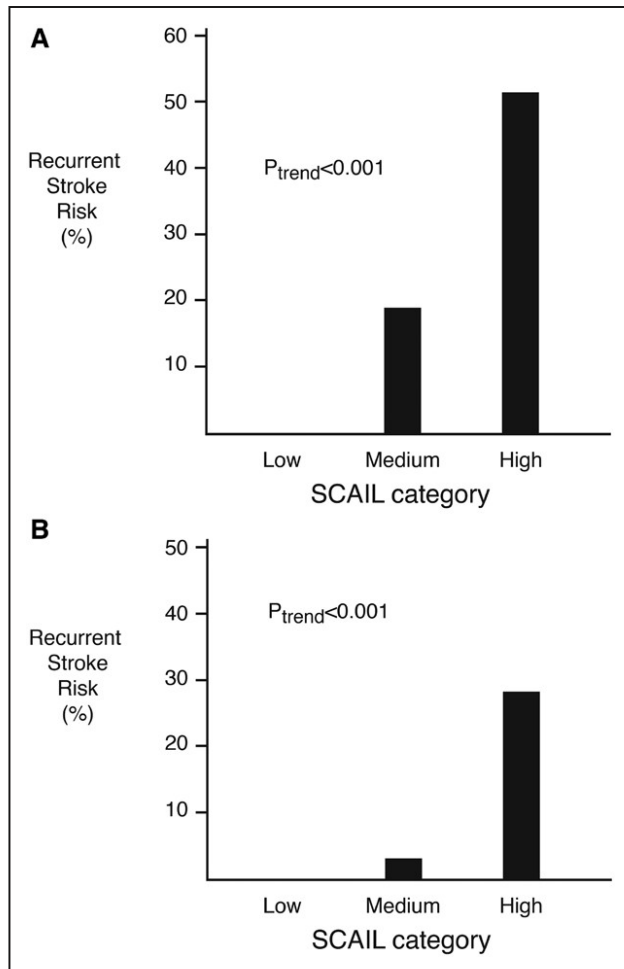


Figure 3. **A**, Risk of recurrent stroke in low, medium, and high symptomatic carotid atheroma inflammation lumen (SCAIL) categories (pooled cohorts, all recurrent stroke after index event; $P_{\text{trend}} < 0.001$). **B**, Risk of recurrent stroke in low, medium, and high SCAIL categories (pooled cohorts, post-positron emission tomography [PET] recurrent stroke only; $P_{\text{trend}} < 0.001$).

CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) randomized trial, specific anti-inflammatory therapy with an interleukin-1 β antagonist reduced vascular events in patients with stable coronary disease, without lowering low-density lipoprotein cholesterol.¹⁴ Injected radiolabeled ¹⁸F-FDG uptake imaged by PET is a marker of plaque inflammation and correlates with intraplaque macrophage density in animal models of atherosclerosis and excised human carotid plaque.^{8,9} Increased carotid ¹⁸F-FDG uptake is associated with markers of plaque inflammation and instability, such as circulating levels of inflammatory proteins, micro-embolic signals on transcranial Doppler ultrasound, unstable plaque morphology, and new clinical symptoms.^{15–18} In retrospective studies of patients imaged with whole-body PET for investigation of cancer, increased aortic ¹⁸F-FDG uptake was associated with late cardiovascular events, independently of established risk factors.^{19,20} However, few data exist on plaque ¹⁸F-FDG uptake and early recurrence in carotid stenosis, and no studies have investigated the prognostic utility of plaque inflammation combined with lumen stenosis to predict early recurrent stroke.

Strengths of our study include the prospective design, high rates of early treatment with antiplatelet agents and statins reflecting contemporary medical management, and validation of the SCAIL score in an independent cohort. However, we cannot exclude the possibility that some recurrent strokes may have occurred in the absence of a standard protocol requiring high-dose statins or dual antiplatelet agents for all patients. Our sample size was sufficient to allow analysis of the prognostic utility of the score for recurrent stroke after PET imaging. However, we also avoided misclassification bias by ascertaining recurrent stroke events which occurred before hospital presentation. We minimized the potential for recall bias by including patients only with definite focal neurological deficits, confirmed by a stroke physician, and independently adjudicated by a second study physician. Patients with prehospital TIA were included only if definite motor, speech, or monocular visual loss occurred.

We acknowledge some limitations. Statistical power was limited for some subgroup analyses, such as those in patients with mild or moderate stenosis. Consequently, the CI for some analyses is wide. Further studies of larger samples are needed to improve the precision of risk estimates of the score, as relatively few patients had scores of 4 or 5. We acknowledge the possibility that statin therapy may have attenuated plaque inflammation in some patients. However, our multivariable Cox regression models were adjusted for statin therapy, and the association between SCAIL score and recurrent stroke remained in adjusted analyses.

Unlike the Oxford risk score which calculates 5-year risk of stroke and death based on observed rates in medical arms of endarterectomy randomized trials,²¹ we derived and validated the SCAIL score to identify early stroke risk in patients before surgery and in those for whom surgery was not planned due to an unfavorable risk-benefit assessment. However, the risk of recurrent stroke is greatest within days of the initial event and prevention of early recurrence is an important goal of medical treatment and surgery. Further studies are needed to determine the utility of the SCAIL score to predict late recurrent stroke in medically treated patients.

Our study suggests that incorporating plaque inflammation-related metabolism imaged by PET with lumen-stenosis imaged on CTA in the SCAIL score might have clinical utility to identify patients most likely to benefit from early surgery after hospital presentation. A selection strategy which combines information about plaque inflammation and lumen narrowing might be most useful for patients who had least benefit from surgery in pivotal trials when categorized by lumen stenosis alone, such as women with moderate stenosis or those with delayed presentation after symptom onset. Before the score is used in clinical practice, we emphasize that further studies are needed to further validate and refine the precision of SCAIL risk estimates in patients treated with modern medical therapy and to further investigate its utility in patient subgroups. Randomized trials and cost-effectiveness studies are needed to test the hypothesis that the SCAIL score may have utility for patient selection for endarterectomy, in situations where the benefit of surgery is currently uncertain.

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