

Original Paper

## Preoperative White Matter Lesions Are Independent Predictors of Long-Term Survival after Internal Carotid Endarterectomy

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### Key Words

Carotid artery stenosis · White matter lesions · Carotid endarterectomy

### Abstract

**Background:** Cerebral white matter lesions (WMLs) predict long-term survival of conservatively treated acute stroke patients with etiology other than carotid stenosis. In carotid endarterectomy patients, WMLs are associated with severe carotid stenosis and unstable plaques, with the risk of perioperative complications and with increased 30-day perioperative risk of death. However, no data exist on their effect on postoperative long-term survival, a factor important when considering the net benefit from carotid endarterectomy. Whether this effect is independent of classical risk factors and indications for surgery is not known either. We hypothesized that WMLs could be evaluated from preoperative routine computed tomography (CT) scans and are predictors of postoperative survival, independent of classical cardiovascular risk factors, indication category and degree of carotid stenosis. **Methods:** A total of 353 of 481 (73.4%) consecutive patients subjected to carotid endarterectomy due to different indications, i.e. asymptomatic stenosis (n = 28, 7.9%), amaurosis fugax (n = 52, 14.7%), transient

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ischemic attack (n = 135, 38.2%) or ischemic stroke (n = 138, 39.1%), from prospective vascular registries during the years 2001–2010 with digital preoperative CT scans, were included in the study. WMLs were rated by a radiologist (Wahlund criteria) in a blinded fashion. Internal carotid artery (ICA) stenoses were angiographically graded (<50, 50–69, 70–99 and 100%). Odds ratios (ORs) and hazard ratios (HRs) are reported (ORs and HRs  $\leq 1$  indicate a beneficial effect). The median follow-up time was 67 months (interquartile range 45.5, range 0–129 months). Spearman's rho was used to estimate intraobserver agreement. Binary logistic regression was performed to analyze the association of risk factors with WMLs. Cox regression proportional hazards analysis was used to study the effect of different factors on survival. **Results:** WML severity could be assessed with a substantial intraobserver agreement (Spearman's rho 0.843,  $p < 0.0001$ ). Only age (OR 1.10, 95% CI 1.06–1.15;  $p < 0.0001$  per year), degree of ipsilateral ICA stenosis (OR 2.22, 95% CI 1.08–4.55;  $p < 0.05$  per stenosis grade) and indication category (OR 1.63, 95% CI 1.19–2.24;  $p < 0.01$  per category) remained independently associated with WMLs. Age (HR 1.04, 95% CI 1.01–1.08;  $p < 0.05$  per year), diabetes (HR 1.59, 95% CI 1.01–2.49;  $p < 0.05$ ), peripheral arterial disease (HR 2.47, 95% CI 1.46–4.15;  $p < 0.01$ ), degree of ipsilateral ICA stenosis (HR 2.56, 95% CI 1.12–5.87;  $p < 0.05$  per stenosis grade) and WMLs (HR 3.83, 95% CI 1.17–12.5;  $p < 0.05$ ) remained independently associated with increased long-term mortality. **Conclusions:** WMLs in a preoperative CT scan provide a substantially reliable estimate of postoperative long-term survival of carotid endarterectomy patients independent of currently used criteria, i.e. cardiovascular risk factors, indication category and degree of ipsilateral ICA stenosis.

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## Introduction

White matter lesions (WMLs) are a more common finding in ischemic stroke patients than in other populations [1]. WMLs are closely associated with aging, are a surrogate of small-vessel disease and occur in patients with multiple risk factors for atherosclerosis [2].

In the general population, in subjects 65–84 years of age, mild or moderate WMLs are found in up to every third subject [3]. WMLs predict impairment of functional status and hospitalization [4], as well as mortality of elderly people without a history of stroke [5–8] and both mortality [9–11] and recurrent strokes [12, 13] in patients with acute stroke. The association of WMLs with poor long-term survival was independent of classical cardiovascular risk factors [9].

Previous data on the effect of WMLs in carotid surgery patients are limited. In ischemic stroke patients, stroke subtype is a strong determinant of new vascular events and survival [14]. Therefore, existing knowledge on stroke patients of other etiologies cannot be directly extrapolated to those with large artery atherosclerosis of the carotid region fulfilling indications for carotid surgery. Previously, WMLs were associated with severe carotid stenosis [15] and unstable plaques [16], with the risk of perioperative complications and increased blood-brain permeability [17], with the need for perioperative shunting [18] and with increased risk of periprocedural stroke in the International Carotid Stenting Study [19]. Therefore, it was concluded that the presence of WMLs should be considered when selecting patients for carotid revascularization [19]. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), severe WMLs were associated with increased 30-day perioperative risk of any stroke or death and increased risk of recurrent stroke within 3 years from operation [20]. In patients with asymptomatic or symptomatic carotid stenosis, those with multiple cardiovascular risk factors had impaired survival in a 5-year follow-up [21, 22].

At present, WMLs are not evaluated before carotid surgery and no data exist on their effect on postoperative long-term survival, a factor important when considering the net benefit from carotid endarterectomy. Whether this effect is independent of classical risk factors and indications for surgery is not known either. We hypothesized that WMLs could be evaluated from digital preoperative routine computed tomography (CT) scans and are predictors of postoperative survival, independent of classical cardiovascular risk factors, indication category and degree of carotid stenosis.

## Materials and Methods

Consecutive patients (n = 481) from the prospective vascular registries of Tampere University Hospital (TUH) (n = 313) and Kuopio University Hospital (KUH) (n = 168) subjected to carotid endarterectomy during the years 2001–2010 were selected for the study. During that period, our indications were based on published guidelines [23]. Of these 481 patients, those with a digital preoperative CT scan available (n = 353, 73.4%) comprised the final study population. Cardiovascular risk factors obtained from the vascular registries were defined based on previous diagnosis and current medication as follows: diabetes mellitus (DM; diagnosis/insulin or oral hypoglycemic medication), arterial hypertension (AHT; diagnosis/anti-hypertensive medication), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography, or congestive heart failure), pulmonary risk factor (diagnosis of chronic obstructive pulmonary disease), renal risk factor (diagnosis of renal insufficiency), peripheral arterial disease (PAD; diagnosis/peripheral vascular intervention or amputation) and dyslipidemia (diagnosis/antihyperlipidemic medication). Smoking was defined as smoking within the last 5 years or current smoking. The study was approved by the ethics committee of TUH and KUH.

### *Radiological Assessment*

All patients were routinely subjected to brain CT and CT angiography using 256 slices of 1 mm thickness. Internal carotid artery (ICA) stenoses were determined (NASCET criteria) and categorized (<50, 50–69, 70–99 and 100%) [24] by a neurointerventional radiologist (J.P.P.). The brain CTs were rated in a blinded fashion by an interventional radiologist (J.P.P.) according to the Wahlund criteria (no lesions, focal lesions, beginning confluence, and diffuse confluence) [25]. Seventy CT scans were first randomly selected and the analysis performed in a random and blinded fashion for a total of three times for each scan. A substantial intraobserver agreement was achieved for the Wahlund criteria (Spearman's rho 0.843,  $p < 0.0001$ ). After the intraobserver agreement analysis, the rater proceeded with the rest of the scans.

### *Survival and Causes of Death*

Comprehensive long-term survival data on the status of the patients (alive/dead) and date of death were obtained from the databases of the TUH and KUH on December 31, 2012. These databases provided full coverage of all the patients included in the study. The median follow-up time was 67 months (interquartile range 45.5, range 0–129 months). At the end of the follow-up, 89 patients were dead (25.2%). No patients were lost to follow-up. The outcome event was all-cause death. The causes of death based on the International Statistical Classification of Diseases and Related Health Problems (on ICD-9 and ICD-10) were obtained and divided further into cardiac (coronary artery disease, valvular heart disease, arrhythmia and congestive heart disease), cerebral (ischemic or hemorrhagic stroke, cerebral bleeding, vascular dementia), peripheral vascular (PAD, aneurysms), cancer, infection, trauma and other categories (Statistics Finland).

### Statistical Analysis

According to power analysis, 300 patients were needed to achieve a power of 0.9 to detect a significant difference in postoperative survival between different original Wahlund WML categories. Spearman's rho was used to estimate intraobserver agreement. The  $\chi^2$  test was performed to compare categorical variables. Continuous variables were analyzed with the Kruskal-Wallis test. Binary logistic regression was used to analyze the association of risk factors with WMLs and the Kaplan-Meier log rank survival analysis to estimate mean survival time. The Cox regression proportional hazards analysis was carried out to study the effect of different factors on survival. The factors were tested for the proportional hazards assumption and this was met for all the factors included in multivariate models. WML severity was further categorized as no lesions versus any lesion (focal lesions and beginning and diffuse confluence) since according to the Cox regression proportional hazards analysis, evidence of any WML was associated with impaired survival. Since data from two separate sites were used (TUH and KUH), all analyses were repeated adjusting for study site.

## Results

### Patient Characteristics

There were 56 (15.9%) patients without any WMLs. In univariate analyses, compared with those without lesions, patients with WMLs were older ( $p < 0.0001$ ), had more seldom dyslipidemia ( $p < 0.05$ ) and were more seldom smokers ( $p < 0.01$ ). Ischemic stroke and transient ischemic attack (TIA) were more frequent in patients with WMLs. Amaurosis fugax was less frequent in patients with WMLs ( $p < 0.01$ ) (table 1).

### Association of Patient Demographics, Risk Factors and Indication for Surgery with Focal WMLs

In univariate analyses, increasing age (OR 1.11; 95% CI 1.07–1.15,  $p < 0.0001$  per year), dyslipidemia (OR 0.50; 95% CI 0.26–0.94), smoking (OR 0.38; 95% CI 0.21–0.68,  $p < 0.01$ ), degree of ipsilateral ICA stenosis (OR 1.94; 95% CI 1.01–3.73,  $p < 0.05$ ) and indication category (OR 1.65; 95% CI 1.23–2.22,  $p < 0.01$  per category) were associated with WMLs (table 2). In multivariate analyses including significant factors from univariate analyses, only age (OR 1.10; 95% CI 1.06–1.15,  $p < 0.0001$ ), degree of ipsilateral ICA stenosis (OR 2.22; 95% CI 1.08–4.55,  $p < 0.05$ ) and indication category (OR 1.63; 95% CI 1.19–2.24,  $p < 0.05$  per category) remained independently associated with WMLs (table 2). Study site did not affect the results of the multivariate analyses.

### Association of Preoperative WMLs with Long-Term Mortality

According to the Kaplan-Meier log rank analysis, those with any WML had a mean survival of 98.4 months (95% CI 93.3–103.6) as opposed to 118.5 months (95% CI 112.4–124.5) in those without any lesions ( $p < 0.01$ ). In the Cox proportional hazards univariate analyses, age [hazard ratio (HR) 1.05; 95% CI 1.03–1.07,  $p < 0.0001$  per year], DM (HR 1.62; 95% CI 1.14–2.31,  $p < 0.01$ ), cardiac risk factor (HR 1.60; 95% CI 1.13–2.27), renal risk factor (HR 2.52; 95% CI 1.11–5.73,  $p < 0.05$ ), PAD (HR 1.95; 95% CI 1.29–2.94,  $p < 0.01$ ), degree of ipsilateral ICA stenosis (HR 2.64; 95% CI 1.18–5.91,  $p < 0.05$  per stenosis grade) and WMLs (HR 5.97; 95% CI 1.89–18.9,  $p < 0.01$ ) were associated with increased mortality (table 3). In contrast, dyslipidemia (HR 0.71; 95% CI 0.50–1.00,  $p < 0.05$ ) and smoking (HR 0.65; 95% CI 0.43–0.98,  $p < 0.05$ ) were associated with decreased mortality (table 3).

In multivariate analyses including significant factors from univariate analyses, age (HR 1.04; 95% CI 1.01–1.08,  $p < 0.05$  per year), DM (HR 1.59; 95% CI 1.01–2.49,  $p < 0.05$ ), PAD

**Table 1.** Characteristics of carotid endarterectomy patients

Risk factor	All (n = 353)	WML		p
		no (n = 56)	any (n = 297)	
Age				<0.0001
Median	71.0	63.5	73.0	
IQR	13	11	11	
Female, n	95 (26.9)	16 (28.6)	79 (26.6)	n.s.
DM, n	102 (28.9)	12 (21.4)	90 (30.3)	n.s.
AHT, n	265 (75.1)	45 (80.4)	220 (74.1)	n.s.
Cardiac, n	189 (53.5)	31 (55.4)	158 (53.2)	n.s.
Dyslipidemia, n	212 (60.1)	41 (73.2)	171 (57.6)	<0.05
Renal, n	9 (2.5)	2 (3.6)	7 (2.4)	n.s.
PAD, n	48 (13.6)	10 (17.9)	38 (12.8)	n.s.
Pulmonary, n	42 (11.9)	7 (12.5)	35 (11.8)	n.s.
Smoking, n	99 (28.0)	26 (46.4)	73 (24.6)	<0.01
IL stenosis				n.s.
<50%, n	3 (0.9)	1 (1.8)	2 (0.7)	
50–69%, n	44 (12.6)	11 (20.0)	33 (11.2)	
70–99%, n	303 (86.6)	43 (78.2)	260 (88.1)	
100%, n	0 (0)	0 (0)	0 (0)	
CL stenosis				n.s.
<50%, n	223 (63.4)	34 (60.7)	189 (63.9)	
50–69%, n	60 (17.0)	9 (16.1)	51 (17.2)	
70–99%, n	56 (15.9)	13 (23.2)	43 (14.5)	
100%, n	13 (3.7)	0 (0)	13 (4.4)	
Indication category				<0.01
Asymptomatic, n	28 (7.9)	7 (12.5)	21 (7.1)	
Amaurosis, n	52 (14.7)	16 (28.6)	36 (12.1)	
TIA, n	135 (38.2)	20 (35.7)	15 (38.7)	
Ischemic stroke, n	138 (39.1)	13 (23.2)	125 (42.1)	

Figures in parentheses are percentages. The category any WML includes focal lesions, and beginning and diffuse confluence according to the Wahlund criteria. Cardiac risk factor: diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography and congestive heart failure. IL = Ipsilateral; CL = contralateral.

(HR 2.47; 95% CI 1.46–4.15,  $p < 0.01$ ), degree of ipsilateral ICA stenosis (HR 2.56; 95% CI 1.12–5.87,  $p < 0.05$  per stenosis grade) and WMLs (HR 3.83; 95% CI 1.17–12.5,  $p < 0.05$ ) remained independently associated with increased mortality (table 3). Study site did not affect the results of the multivariate analyses.

#### *Causes of Death*

During the follow-up, 89 patients of the whole study population ( $n = 353$ ) died. The causes of death were cardiovascular (59.5%), i.e. cerebral (15.7%), cardiac (40.4%), peripheral vascular (3.4%), due to cancer (18.0%), infectious (1.1%), traumatic (1.1%) or classified as other causes of death (7.9%) (table 4).

**Table 2.** Association of risk factors with preoperative CT WMLs

Risk factor	Univariate	Multivariate
Age (per year)	1.11 (1.07–1.15)***	1.10 (1.06–1.15)***
Female gender	0.91 (0.48–1.71)	not included
DM	1.59 (0.80–3.16)	not included
AHT	0.70 (0.34–1.42)	not included
Cardiac	0.92 (0.52–1.63)	not included
Dyslipidemia	0.50 (0.26–0.94)*	0.54 (0.27–1.09)
Renal	0.65 (0.13–3.22)	not included
PAD	0.68 (0.31–1.45)	not included
Pulmonary	0.94 (0.39–2.23)	not included
Smoking	0.38 (0.21–0.68)**	0.91 (0.45–1.83)
IL stenosis	1.94 (1.01–3.73)*	2.22 (1.08–4.55)*
CL stenosis	0.96 (0.70–1.32)	not included
Indication category	1.65 (1.23–2.22)**	1.63 (1.19–2.24)**

Figures are ORs with 95% CIs in parentheses. Binary logistic regression analysis with a ‘no lesions’ category as a reference. WMLs include focal lesions, and beginning and diffuse confluence according to the Wahlund criteria. The multivariate model was adjusted to the significant factors from the univariate analysis. Cardiac risk factor: diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography and congestive heart failure. IL = Ipsilateral; CL = contralateral stenosis (<50%, 50–69%, 70–99%, 100%). Indication category: (1) asymptomatic, (2) amaurosis fugax, (3) TIA, (4) ischemic stroke. \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.0001.

**Table 3.** Effect of preoperative CT WMLs on long-term survival in carotid endarterectomy patients

Risk factor	Univariate	Multivariate
Age (per year)	1.05 (1.03–1.07)***	1.04 (1.01–1.08)*
Female gender	0.97 (0.65–1.43)	not included
DM	1.62 (1.14–2.31)**	1.59 (1.01–2.49)*
AHT	0.94 (0.65–1.37)	not included
Cardiac	1.60 (1.13–2.27)**	1.26 (0.80–1.99)
Dyslipidemia	0.71 (0.50–1.00)*	0.82 (0.53–1.27)
Neurological	0.93 (0.64–1.34)	not included
Pulmonary	1.22 (0.70–2.12)	not included
Renal	2.52 (1.11–5.73)*	2.16 (0.78–6.02)
PAD	1.95 (1.29–2.94)**	2.47 (1.46–4.15)**
Smoking	0.65 (0.43–0.98)*	0.94 (0.51–1.73)
IL stenosis	2.64 (1.18–5.91)*	2.56 (1.12–5.87)*
CL stenosis	1.15 (0.92–1.43)	not included
Indication category	1.06 (0.89–1.27)	not included
Any WML	5.97 (1.89–18.9)**	3.83 (1.17–12.5)*

Figures are HRs with 95% CIs in parentheses. Cox regression proportional hazards analysis. The multivariate model was adjusted to the significant factors from the univariate analysis. Cardiac risk factor: diagnosis of myocardial infarction, coronary intervention, angina pectoris or ischemia on electrocardiography and congestive heart failure. IL = Ipsilateral; CL = contralateral. Indication category: (1) asymptomatic, (2) amaurosis fugax, (3) TIA, (4) stroke. Any WML includes focal lesions, and beginning and diffuse confluence according to the Wahlund criteria. \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.0001.

**Table 4.** Causes of death in carotid endarterectomy patients

Cause of death	
Cardiovascular	53 (59.5)
Cerebral	14 (15.7)
Cardiac	36 (40.4)
Peripheral vascular	3 (3.4)
Cancer	16 (18.0)
Infection	1 (1.1)
Trauma	1 (1.1)
Other	7 (7.9)

Figures are numbers with percentages in parentheses.

## Discussion

WMLs, a surrogate of small-vessel disease, are a common finding in preoperative brain CT. They are associated with age, degree of ipsilateral carotid stenosis and indication category (asymptomatic, amaurosis fugax, TIA, and stroke) for the procedure. WMLs provide a substantially reliable estimate of postoperative long-term survival of carotid endarterectomy patients independent of classical cardiovascular risk factors, indication category and degree of ipsilateral carotid stenosis.

Owing to limited data, direct comparison of patient characteristics can only be made with the work of Streifler et al. [20]. Our cohort based on prospective vascular registry data was characterized by more frequent risk factors, especially dyslipidemia. These studies represent two different eras without uniform definitions and treatment guidelines of the risk factors. In Streifler's work, only one third and in our cohort almost 87% had a carotid stenosis of >70%. The changes in risk factor management over time have led to a situation, where carotid plaques become symptomatic only at a more severe stenosis grade. The same trend in the prevalence of comorbid conditions and in the degree of symptomatic carotid stenosis can be detected in more recent studies [26–28]. It is noteworthy, however, that some of these studies comprised mainly asymptomatic patients, which is in contrast to our material [28].

Our finding of an association of age with WML severity is in line with previous findings [20, 29]. In the present study, the previous association of AHT with WMLs [20, 29, 30] was not replicated, which may be due to heterogeneity of the definition of hypertension including those with diagnosed hypertension under control and those without response. Both the frequency of dyslipidemia and smoking decreased with increasing WML severity, in line with a previous study [20]. Previously, dyslipidemia showed a similar association with WMLs (OR 0.63) [30]. These findings in univariate analyses may be explained in two ways. Firstly, during the study period, almost all cerebrovascular patients with dyslipidemia were on statin therapy, which may confer protection against WMLs. Secondly, there is a possible harvesting bias as described in the NASCET study – elderly patients were more likely to be smokers and had dyslipidemia more frequently than younger patients [24]. Interestingly, WMLs are linked to increased risk of vascular deaths [31] and both smoking [32] and dyslipidemia [33] are associated with the occurrence of WMLs. Therefore, due to a possible synergistic effect of these risk factors, those with widespread WMLs and dyslipidemia or smoking may have already deceased due to other cardiovascular causes before the development of carotid disease. Actually, in the present study, the association of dyslipidemia and smoking disappeared in multivariate regression analyses after adjustment to age, ipsilateral stenosis and indication category. Our finding of increased WMLs in patients whose indication was previous stroke is in line with a previous study [34], which showed that the probability of stroke

increases with increasing WML severity. Our result of an association of ipsilateral ICA stenosis with WML severity is in line and supported by previous studies [15, 35] although contradicting evidence also exists from CT [30] and MRI studies [36]. While the pathophysiological mechanism behind this phenomenon is not clear, the degree of ICA stenosis may modulate the carotid plaque composition [37] although contradicting evidence also exists [38]. Furthermore, intraplaque hemorrhage [39], unstable plaques [16] and total plaque volume [40] are associated with WML severity.

Our present results in surgical patients are in line with previous findings that WMLs predict poststroke survival in acute stroke patients independent of classical cardiovascular risk factors and that cardiovascular deaths account for the majority of causes of deaths [9]. Our present results are novel since they not only extend the short-term results of the NASCET study analyzing the 30-day perioperative risk and risk of recurrent stroke within 3 years from operation but also provide data on long-term mortality [20]. Furthermore, the International Carotid Stenting Study analyzed the association of WMLs with periprocedural stroke but provided no data on long-term follow-up [19]. Long-term results are important since the limited net benefit from carotid procedures is dependent on the remaining life span of the patient. Furthermore, previous knowledge on the association of WMLs with survival was obtained on stroke patients of other ischemic subtypes (cardioembolism, small-vessel occlusion, stroke of undetermined etiology). Those findings cannot be directly extrapolated to those of patients with large artery atherosclerosis of the carotid region fulfilling indications for carotid surgery since future vascular events and survival vary significantly across different stroke subtypes [14]. We suppose that these data could be utilized in optimal patient selection for surgery especially in patients with asymptomatic stenosis and questionable net benefit from the procedure. Future studies powered to analyze this subgroup are warranted. The probable mechanism by which WMLs impact on mortality is explained by the concept of systemic small-vessel disease [10, 11]. This is highlighted by a close association of WMLs with impaired kidney function [11]. Our findings highlight the importance to develop strategies to slow down the advancement of WMLs [41], thus possibly resulting in improved survival. When considering the value of WMLs in patient risk stratification, it must also be considered that the procedure itself could induce regression of WMLs [42].

The main shortcoming of the study is the lack of data on incident cardiovascular events, which makes a direct comparison of our results difficult. Although we did not analyze the degree of gray matter lesions, according to our established and consistent indications, only patients with mild-to-moderate strokes were subjected to the procedure. In addition, postoperative CT was not performed routinely and therefore the effect of the operative procedure on WMLs could not be estimated. It must also be emphasized that MRI is the golden standard and more sensitive than CT in the detection of small WMLs while they have provided almost equal value in the detection of widespread WMLs [25]. However, the high availability and small costs of CT make it clinically applicable. All the study participants were of Caucasian origin and may not therefore be generalized to other populations. The strength of the study is comprehensive data with no missing data from two prospective vascular registries. Since the study population was collected from two separate study sites, all the analyses were repeated using a covariate adjusting for study site. Since this adjustment did not alter the results of the multivariate analyses, we consider that study site was not a significant source of bias.

In conclusion, the degree of WMLs, a surrogate of small-vessel disease, can be substantially reliably rated on preoperative routine CT and provides a long-term predictive value independent of classical cardiovascular risk factors, indication category (asymptomatic, amaurosis, TIA or stroke) and ipsilateral ICA stenosis. Therefore, in addition to a patient's symptoms and degree of carotid stenosis, after validation of the results in independent



cohorts and studies powered to stratify for different indication categories, we suggest that WMLs can also be an important factor to be utilized for the optimal selection of patients for carotid endarterectomy.

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### Disclosure Statement

The authors declare that there are no conflicts of interest.

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