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CLINICAL INVESTIGATIVE STUDY

Carotid plaque surface echogenicity predicts cerebrovascular events: An Echographic Multicentric Swiss Study

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Abstract

Background and Purpose: To determine the prognostic value for ischemic stroke or transitory ischemic attack (TIA) of plaque surface echogenicity alone or combined to degree of stenosis in a Swiss multicenter cohort

Methods: Patients with ≥60% asymptomatic or ≥50% symptomatic carotid stenosis were included. Grey-scale based colour mapping was obtained of the whole plaque and of its surface defined as the regions between the lumen and respectively 0-0.5, 0–1, 0–1.5, and 0–2 mm of the outer border of the plaque. Red, yellow and green colour represented low, intermediate or high echogenicity. Proportion of red color on surface (PRCS) reflecting low echogenictiy was considered alone or combined to degree of stenosis (Risk index, RI).

Results: We included 205 asymptomatic and 54 symptomatic patients. During follow-up (median/mean 24/27.7 months) 27 patients experienced stroke or TIA. In the asymptomatic group, RI ≥0.25 and PRCS ≥79% predicted stroke or TIA with a hazard ratio (HR) of respectively 8.7 $p = 0.0001$ and 10.2 $p < 0.0001$. In the symptomatic group RI ≥0.25 and PRCS ≥81% predicted stroke or TIA occurrence with a HR of respectively 6.1 $p = 0.006$ and 8.9 $p = 0.001$. The best surface parameter was located at 0-0.5mm. Among variables including age, sex, degree of stenosis, stenosis progression, RI, PRCS, grey median scale values and clinical baseline status, only PRCS independently prognosticated stroke ($p = 0.005$).

Conclusion: In this pilot study including patients with at least moderate degree of carotid stenosis, PRCS (0-0.5mm) alone or combined to degree of stenosis strongly predicted occurrence of subsequent cerebrovascular events.

KEYWORDS
carotid plaque echogenicity, carotid plaque surface, degree of stenosis, duplex ultrasound, stroke

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INTRODUCTION

Degree of atherosclerotic narrowing of the extracranial carotid artery is used to predict the risk of future ischemic strokes. This strategy has limitations as severe carotid atherosclerotic lesions may remain asymptomatic for years, while others, more moderate, may progress rapidly and lead to ischemic stroke.[1–2]

Carotid plaque morphology has been shown to be an independent predictor of ipsilateral stroke risk.[3–5] Noninvasive imaging techniques such as high-resolution ultrasound have emerged in recent years for the characterization of arterial wall pathology.[5–9] Most studies performed in this field are based on visual plaque analysis alone with a poor inter- and intraobserver agreement.[10] As a consequence more operator-independent approaches have been developed using a computer-assisted analysis of grey-scale values. The first and most widely used method is the grey-scale median (GSM) measurement.[11–18] In fact, various studies demonstrated that plaques with low GSM values were associated with an increased risk of subsequent stroke.

We reported an alternative method consisting of a more regional analysis of plaque components and in particular of plaque surface with the use of colour mapping.[19–21] In our previous study we could show that plaque surface echogenicity alone or combined to degree of stenosis (Risk index) allowed to distinguish between symptomatic and asymptomatic patients with diagnostic accuracy.[21] The aim of the present work was to determine prospectively the prognostic value for stroke or transitory ischemic attack (TIA) of plaque surface echogenicity alone or combined to degree of stenosis in a multicenter Swiss cohort of patients with ≥ 60% asymptomatic or ≥ 50% symptomatic carotid stenosis.

METHODS

There were 6 participating Swiss Stroke centers (Geneva, Basle, Berne, Lausanne, St. Gallen and Zurich) which included consecutive patients with≥ 60% asymptomatic or ≥ 50% symptomatic carotid artery stenosis.

Two groups were included: Patients with ischemic stroke occurring within the last 6 months and patients with asymptomatic carotid stenosis. These two groups defined the clinical baseline status. Clinical history, presence of vascular risk factors and usual treatment were assessed. The interventional management of carotid stenosis (surgery, stenting) was similar in all participating centers: an intervention was recommended in patients with symptomatic 50–99% stenosis, and in patients with asymptomatic ≥80% stenosis. Patients were asked to participate in the present study, when they either refused the aforementioned recommendations or were considered not to be candidates for a carotid intervention, e.g. because of reduced life expectancy. Patients with a potential cardio-embolic source of stroke and who were not under anticoagulants were excluded from the study.

All the participants gave informed consent before taking part.

Ultrasound criteria

All investigations were performed using ultrasound devices (Phillips iU22, Siemens

Antares, Toshiba and LOGIQ P6 GE) with 4–8MHz tranducers. The patients were examined in the supine position, with their head slightly rotated to the opposite side of the carotid artery being imaged. All plaques were examined on an axial and longitudinal plane. For analysis, however, only the longitudinal plane was considered. Probe placement and site of plaque delineation, e,g near or far wall, were left to the appreciation of the sonographer.

The flow velocity and stenosis rate were measured at the site of the common carotid artery, bulb, and proximal internal carotid artery (ICA). Peak systolic velocities (PSV) at the level of the stenosis and the ICA/ common carotid artery (CCA) ratio were used in order to distinguish the different groups of degree of stenosis: 50%—59% with PSV >120 cm/sec and ICA/CCA >1.5; 60%—69% with PSV >170 cm/sec and ICA/CCA>3.2 and 70%—99% with PSV >220cm/sec and ICA/CCA>3.7. Stenosis of >80% were considered whenever end-diastolic velocity was >130 cm/sec.[22–26] These velocity criteria similar to the North American Symptomatic Carotid Endarterectomy Trial grading were applied across all centers. The plaque with the highest degree of stenosis was considered whenever presence of asymptomatic bilateral or tandem stenoses.

Stenosis progression was defined as a change of degree of stenosis moving from moderate (50%—69%) to severe (70%—99%).[27]

Gray-scale based colour mapping

The spatial distribution of grey scale values of the pixels of the plaque was used as the measurement of echogenicity. Three colours were chosen for colour mapping according to the intensity of echogenicity: red for low, yellow for intermediate and green for high. Five different thersholds were considered: grey-scale values of <60,50,40,30 and 20 mapped in red, between 60 and 90, 50 and 80, 40 and 70, 30 and 60 and 20 and 50, mapped in yellow and >90, 80,70,60 and 50 mapped in green. The surface was further divided into four levels: level 1: between 0-0.5mm, level 2: between 0.5-1mm, level 3: between 1-1.5mm and level 4 between 1.5-2mm. For each plaque the proportion of each colour present on the surface, subdivided into four different levels, was assessed automatically (Figure 1).

The different steps are shown on Figure 2.

Patients presenting acoustic shadowing due to calcifications rendering plaque visualization not possible were not included in the study.

To facilitate assessment of degree of stenosis, we integrated to the colour mapping analysis a morphological measurement of diameter reduction according to the European Carotid Surgery Trial criteria for all patients.[28–30]

The Risk index was established on a combination of degree of stenosis as assessed by means of the morphological measurement and the

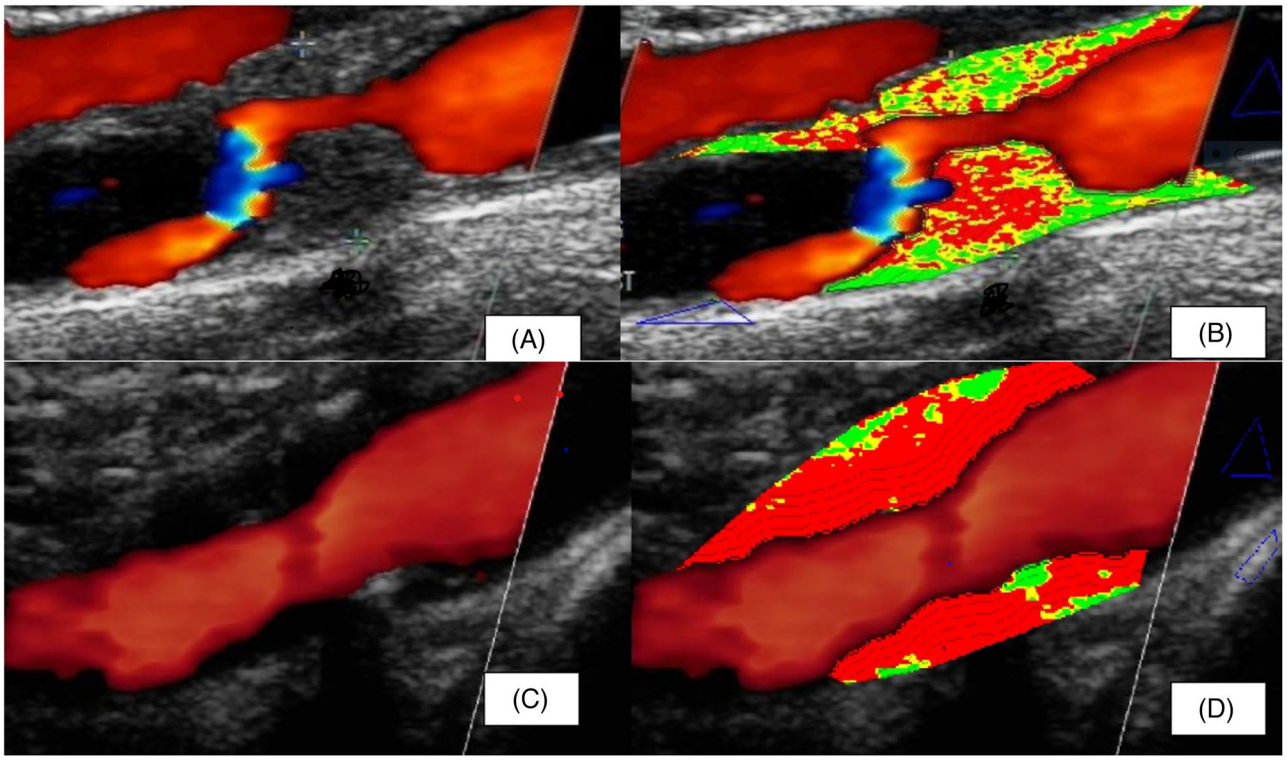

FIGURE 1 Examples of a heterogeneous (A-B) and a homogeneous plaque (C-D)

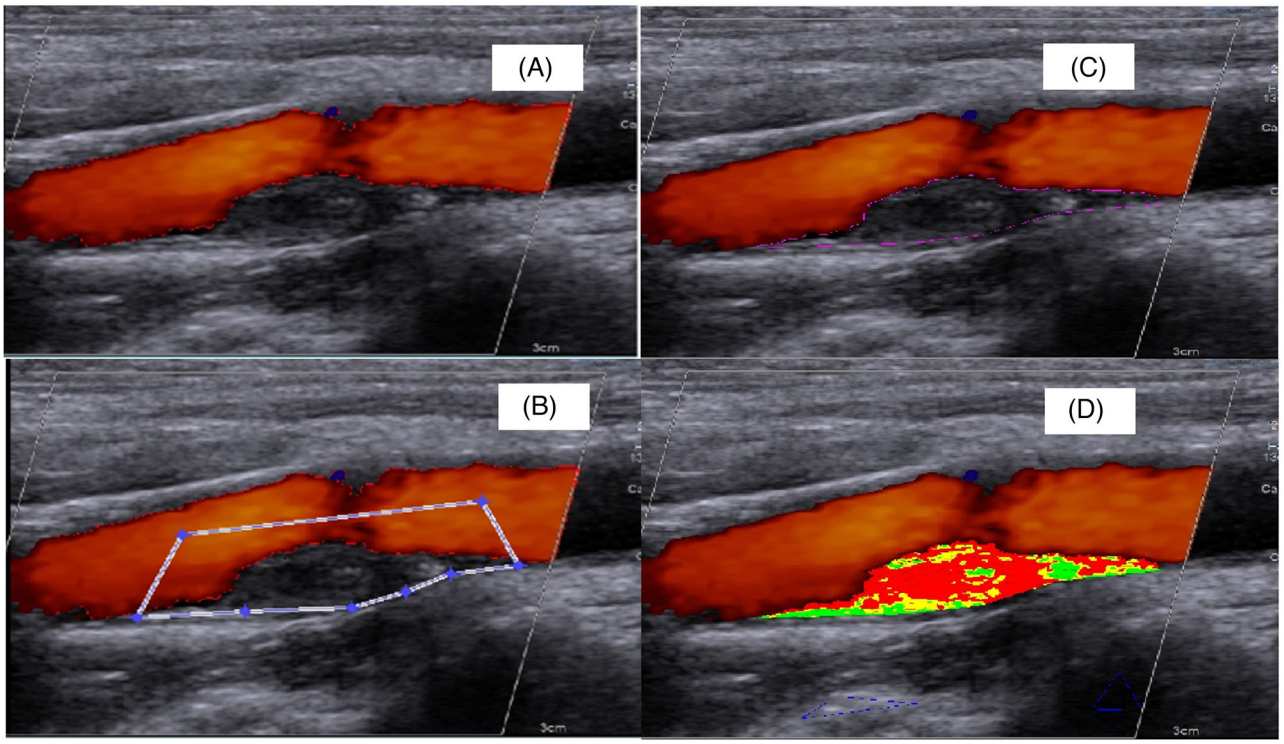

FIGURE 2 A. Echogenic characteristics of the plaque. B. The colour flow is automatically outlined (see red lines). C. Manual delineation of the adventitia. D. Plaque normalization is performed by selecting with blue triangles the darkest and the brightest regions according to the standard grey scale values of 0–190. Colour mapping of the plaque is then established

proportion of the red colour on the surface (PRCS). The measurements were used according to the following formula[21]:

$$RI = \frac{\exp(-8.98404 + 0.0458 \times \text{degree of stenosis} + 0.06018 \times \text{proportion of red on the surf})}{1 + \exp(-8.98404 + 0.0458 \times \text{degree of stenosis} + 0.06018 \times \text{proportion of red on the surf})}$$

We also investigated the correlation, between risk index and proportion of red colour on the surface in order to assess whether the systematic use of both parameters was necessary or whether the use of only one of may be sufficient.

Colour mapping was performed by all centers and were sent to Geneva center where all native datasets were centralized. All colour mapping images were then reanalysed by a trained nurse technician blinded to the clinical history of the patients (DW) and in case of discordance validated by an experienced medical doctor (RS). Values were considered discordant whenever there was a difference for RI of more than 20% and/or a difference for PCRS of more than 15%.

Gray scale median assessment of the whole plaque

Grey median scale values of the whole plaque were obtained according to the method described by El-Barghouty and colleagues.[12] The GSM computation was also implemented in our software.

MRI examination

In the symptomatic group, brain MRI was performed within a time span of 48–72 hours and in asymptomatic one, within a delay of 10 days after the detection of the carotid stenosis. When present on diffusion-weighted sequences, the lesion was considered as acute. MRI scans were also used to confirmed the clinical baseline status (asymptomatic versus symptomatic) and to distinguished in those patients who became symptomatic during the follow-up period whether they had a stroke or TIA.[31] An experienced neuroradiologist (K.L.) who was not aware of clinical history reviewed all images.

Statistics

Statistical analysis was performed with Medcalc (version 17.5). Categorical and continuous variables are shown respectively as numbers and percentages (%) or as mean values and standard deviation values. For the longitudinal studies we used the mean values of all ultrasound investigations performed for each patient. To define the best surface level and the best grey-scale threshold value we performed multiple receiver operating curves (ROC) comparisons. We used chi-square and Mann-Whitney tests for comparisons. For assessment of threshold values of Kaplan-Meier curves, we performed ROC to determine the highest sensibility and specificity. Cox proportional hazards regression was used to define the best outcome predictor among different echographic and clinical parameters of stroke or TIA in asymptomatic and symptomatic patients. To establish the correlation between Risk index and PRCS, we used the Rank correlation with Spearman's rho correlation coefficient. The rate of agreement was measured according to kappa values. A probability value of less than 0.05 was chosen as level of significance. For Tables 1 and 2 due to multiple testing, we used the level of significance of less than 0.0017 according to Bonferroni's method.

RESULTS

From 2008 to 2016, we included 282 patients. All patients were monitored every 6 months by ultrasound investigation during the follow-up. Their baseline characteristics are given on Table 3.

Overall 1086 ultrasound investigations were performed by all centers and reanalyzed by a trained nurse technician. All discordant results were reviewed and validated by an experienced medical ultrasonologist (RS). The most frequent cause of incorrect application of the software leading to discordant results consisted in a wrong plaque delineation which included partly the lumen. This occurred in 12% (n = 130) of all the ultrasound investigations. Kappa values were further of 0.79 [95% Confidence Interval (CI) 0.73 to 0.86] for RI and 0.76 (95%CI 0.70 to 0.83) for the PRCS. Accordingly we could use for our study the results of all centers (n = 956), except for those where a wrong plaque delineation was observed (n = 130). In these cases we used the results after reanalysis by the trained nurse technician and an experienced medical ultrasonologist.

Of the 282 patients initially included, 23 were lost for follow-up (Figure 3). All patients were treated during the follow-up period with antiplatelet and lipid lowering therapy. The number of strokes or TIAs occurring in the asymptomatic group was of 11(5.4%) and of 8 (16%) in the symptomatic one ($p < 0.01$). Stenosis progression was observed among 14 of 234 (6%) subjects free of events and among 14 of 27 (15%, $p < 0.1$) who experienced stroke or TIA during their follow-up. The mean delay between the first US investigation and occurrence of stroke was of 31 months (12-62) in the asymptomatic group and of 27.2 months (11-35) in the symptomatic group. Revascularisation was usually performed within the first 2 weeks after the event.

The best surface parameter was located at 0-0.5mm and the best grey scale interval between <60 and <90 (Tables 1 and 2). Accordingly RI and PRCS refered to these two values.

TABLE 1 Risk index: Comparisons of receiver operating curves for the prediction of stroke or transitory ischemic attack according to 4surface levels and 5 grey-scale thresholds

Grey-scale theresholds	RI Level 1 0-0.5mm	RI Level 2 0.5-1mm	RI Level 3 1-1.5mm	RI Level 4 1.5-2mm
<60 and <90				
AUC	0.797	0.735	0.734	0.762
95%CI	0.743 to 0.845	0.677 to 0.788	0.675 to 0.787	0.705 to 0.813
*P values		0.0060 (L1vsL2)	0.0131 (L1vsL3) 0.9234 (L2vsL3)	0.2175(L1vsL4) 0.1885 (L2vsL4) 0.1161 (L3vsL4)
<50 and <80				
AUC	0.734	0.695	0.697	0.722
95%CI	0.676 to 0.787	0.635 to 0.750	0.637 to 0.752	0.663 to 0.775
P values		0.2317(L1vsL2)	0.3273(L1vsL3) 0.8595 (L2vsL3)	0.7835 (L1vsL4) 0.2741 (L2vsL4) 0.1990 (L3vsL4)
<40 and <70				
AUC	0,683	0.672	0.692	0.708
95%CI	0.623 to 0.740	0.611 to 0.729	0.632 to 0,748	0.649 to 0.763
P values		0.8286 (L1vsL2)	0.8681 (L1vsL3) 0.0443 (L2 vsL3)	0.6827(L1vsL4) 0.1641 (L2vsL4) 0.3988 (L3vsL4)
<30 and <60				
AUC	0.626	0.652	0.674	0.707
95%CI	0.564 to 0.686	0.590 to 0.710	0.613 to 0.731	0.648 to 0.762
P values		0.2992 (L1vsL2)	0.1348 (L1vsL3) 0.0749 (L2vsL3)	0.0436 (L1vsL4) 0.0424 (L2vsL4) 0.0914 (L3vsL4)
<20 and <50				
AUC	0.648	0.631	0.0490	0.686
95%CI	0,587 to 0.707	0.569 to 0.690	0.614 to 0.731	0.626 to 0.742
P values		0.5669 (L1vsL2)	0.3665 (L1vsL3) 0.0244 (L2vsL3)	0.3544 (L1vsL4) 0.0317 (L2vsL4) 0.5537 (L3vsL4)

RI = Risk index L1, L2, L3, L4 = Level 1, Level 2, Level 3, Level 4 vs = versus *P value cutoff <0.0017 (Bonferroni correction) AUC = area under the curve 95%CI: 95% Confidence Interval.

Our results show that PCRS alone or combined to degree of stenosis (RI) predicted stroke or TIA in a cohort of asymptomatic and symptomatic patients followed during a median period of 2 years (Figures 4 and Table 4). Furthermore among different variables including age, sex, degree of stenosis, stenosis progression, RI, PRCS, grey median scale values and clinical baseline status, only PRCS independently prognosticated stroke (p = 0.005) (Table 5).

DISCUSSION

In the present study we could show that PCRS alone or combined to degree of stenosis expressed as the Risk index were strong predictors of stroke or TIA in patients with asymptomatic or symptomatic carotid stenosis (Figure 4, Table 4). Threshold values which may used for asymptomatic and symptomatic patients were similar regarding RI, but slightly different regarding PRCS (respectively 79% versus 81%) (Table 4 and Figures 4 and 5). Furthermore although the majority of patients who experienced stroke or TIA during the follow-up period had both parameters located above the threshold values, the systematic use of both for plaque analysis is nevertheless necessary as in some cases one value may be still located outside of its respective limit (Figure 5).

In the Cox regression model, neither RI, nor degree of stenosis, nor stenosis progression resulted to be significant when compared to PRCS. These findings suggest regarding prognosis a possible

TABLE 2 Proportion of red colour on surface: Comparisons of receiver operating curves for the prediction of stroke or transitory ischemic attack according to 4 surface levels and 5 grey-scale thresholds

Grey-scale theresholds	PCRS Level 1 0-0.5mm	PCRS Level 2 0.5-1mm	PCRS Level 3 1-1.5mm	PCRS Level 4 1.5-2mm
<60 and <90				
AUC	0.850	0.766	0.755	0.782
95%CI	0.800 to 0.892	0.709 to 0.817	0.697 to 0.806	0.727 to 0.831
*P values		0.0013 (L1vsL2)	0.0012 (L1vs L3) 0.5(L2 vs L3)	0.035 (L1vs L 4) 0.01 (L2 vs L4) 0.13 (L3vs L4)
<50 and <80				
AUC	0.781	0.736	0.755	0.776
95%CI	0.725 to 0.830	0.678 to 0.788	0.698 to 0.806	0.721 to 0.826
P values		0.11 (L1vsL2)	0.42 (L1vsL3) 0.09 (L2vsL3)	0.03 (L1vsL4) 0.12 (L2vsL4) 0.24 (L3vsL4)
<40 and <70				
AUC	0.632	0.726	0.744	0.764
95%CI	0.570 to 0.691	0.668 to 0.780	0.686 to 0.796	0.708 to 0.815
P values		0.01(L1vs L2)	0.01(L1vsL3) 0.14 (L2vsL3)	0.009 (L1vsL4) 0.12 (L2vsL4) 0.32(L3vsL4)
<30 and <60				
AUC	0.719	0.713	0.731	0.747
95%CI	0.659 to 0.773	0.654 to 0.768	0.672 to 0.784	0.690 to 0.799
P values		0.8 (L1vs L2)	0.6 (L1vsL3) 0.08 (L2vsL3)	0.4 (L1vsL4) 0.22(L2vsL4) 0.4 (L3vs L4)
<20 and <50				
AUC	0.712	0.699	0.712	0.727
95%CI	0.653 to 0.767	0.639 to 0.754	0.652 to 0.766	0.669 to 0.781
P values		0.5 (1vs L2)	0.9 (L1vsL3) 0.2 (L2vsL3)	0.7 (L1vsL4) 0.3 (L2vsL4) 0.5 (L3vsL4)

PCRS = proportion of red colour on the surface L1, L2, L3, L4 = Level 1, Level 2, Level 3, Level 4 vs = versus *P value cutoff <0.0017 (Bonferroni correction) AUC = area under the curve 95%CI: 95% Confidence Interval.

superiority of the morphological component PRCS over degree of stenosis (Table 5). Characteristic features commonly thought to be associated with an increased cerebrovascular risk include plaques with low echogenicity also called echolucent and opposed to echogenic or non-echolucent ones.[32–36] Histologically echolucent plaques indicate the presence of a large necrotic core, whereas non echolucent plaques reflect a predominantly fibrotic component.[5–9] Studies comparing carotid plaques removed from symptomatic and asymptomatic patients have revealed that the main features of unstable plaques include surface ulceration, thining and/or rupture of the fibrous cap.[37] The size of the necrotic has not been shown to be significantly different between these two groups.[37] Accordingly an echolucent plaque even though reflecting the presence of an important necrotic core is not necessarily unstable. On the other hand, the proximity between the necrotic core and the lumen may exert a critical role with respect to plaque instability.[5,37–38] The distance between the necrotic core and the lumen is determined by the thickness of the fibrous cap. On ultrasound, plaque surface appears echogenic when the fibrous cap is thick whereas it becomes more hypo- or anechogenic when the cap is thin or ruptured.

In a systematic review, Brinjikji and colleagues demonstrated that plaques with complex features, particularly those with echolucency, neovascularization, ulceration and intraplaque motion were associated with ischemic symptoms.[39] In this meta-analysis whole plaque and surface parameters presented similar predictive values. A recent study analysed multiparametric indices including a vulnerability index,

TABLE 3 Baseline characteristics of the cohort of 259 patients with follow-up

Number of patients n = 259	Asymptomatic n = 205	Symptomatic n = 54	P values
Age (mean)	80	79.7	0.32
Male Sex	140 (68%)	33 (61%)	0.5
High blood pressure	173(84%)	43(80%)	0.5
Dyslipidemia	160 (78%)	42 (77%)	0.9
Diabetes	48 (23%)	10 (19%)	0.3
Tobacco	88(43%)	9 (17%)	<0.001*
Coronary heart disease	60 (29%)	13 (24%)	0.5
Any prior stroke	68 (33%)	10 (19%)	0.05
Atrial fibrillation	22 (11%)	2 (4%)	<0.05*
Antiplatelet treatment (at admission)	185** (90%)	45** (83%)	0.1
Oral Anticoagulants	36*** (18%)	3 (5.5%)	<0.05*
Lipid lowering treatment (at admission)	188 (92%)	42 (77%	0.9
Antihypertensive treatment	162 (79%)	40 (74%)	0.5
Degree of stenosis	64.3%	61.4%	0.1
50-69%	123 (59%)	40 (74%)	
70–99%	82 (41%)	14 (26%)	0.1
Mean GSM values	56.3	55.2	0.4
Bilateral stenosis	10 (4.8%)	2 (3.7%)	0.9

Abbreviations: GSM = grey median scale; n = number of patients; *P value cutoff <0.05 **25 asymptomatic and 12 symptomatic patients with dual antiplatelet therapy *** all patients under oral anticuogulants also received antiplatelet therapy.

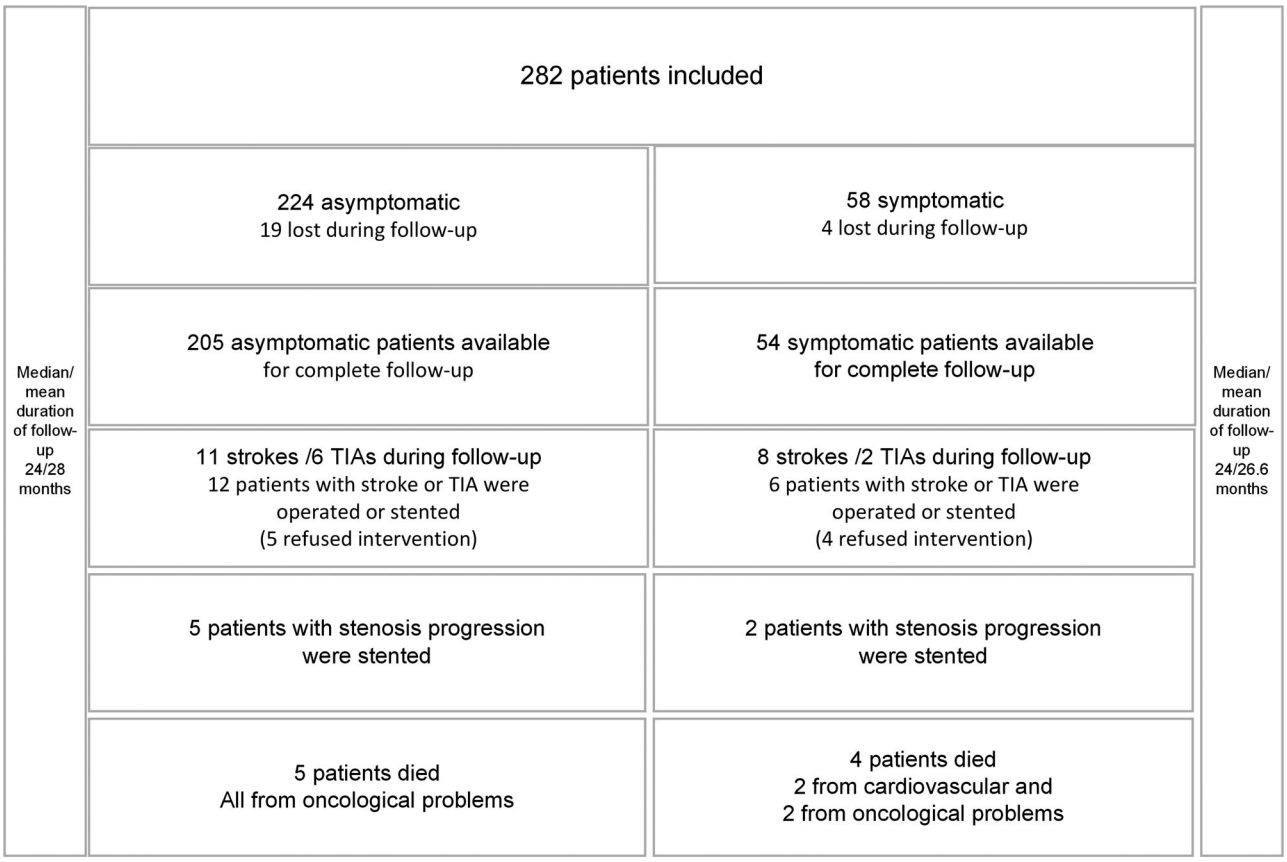

FIGURE 3 Flowchart of the follow-up of all patients included in the study. Abbreviation: TIA = transitory ischemic attack

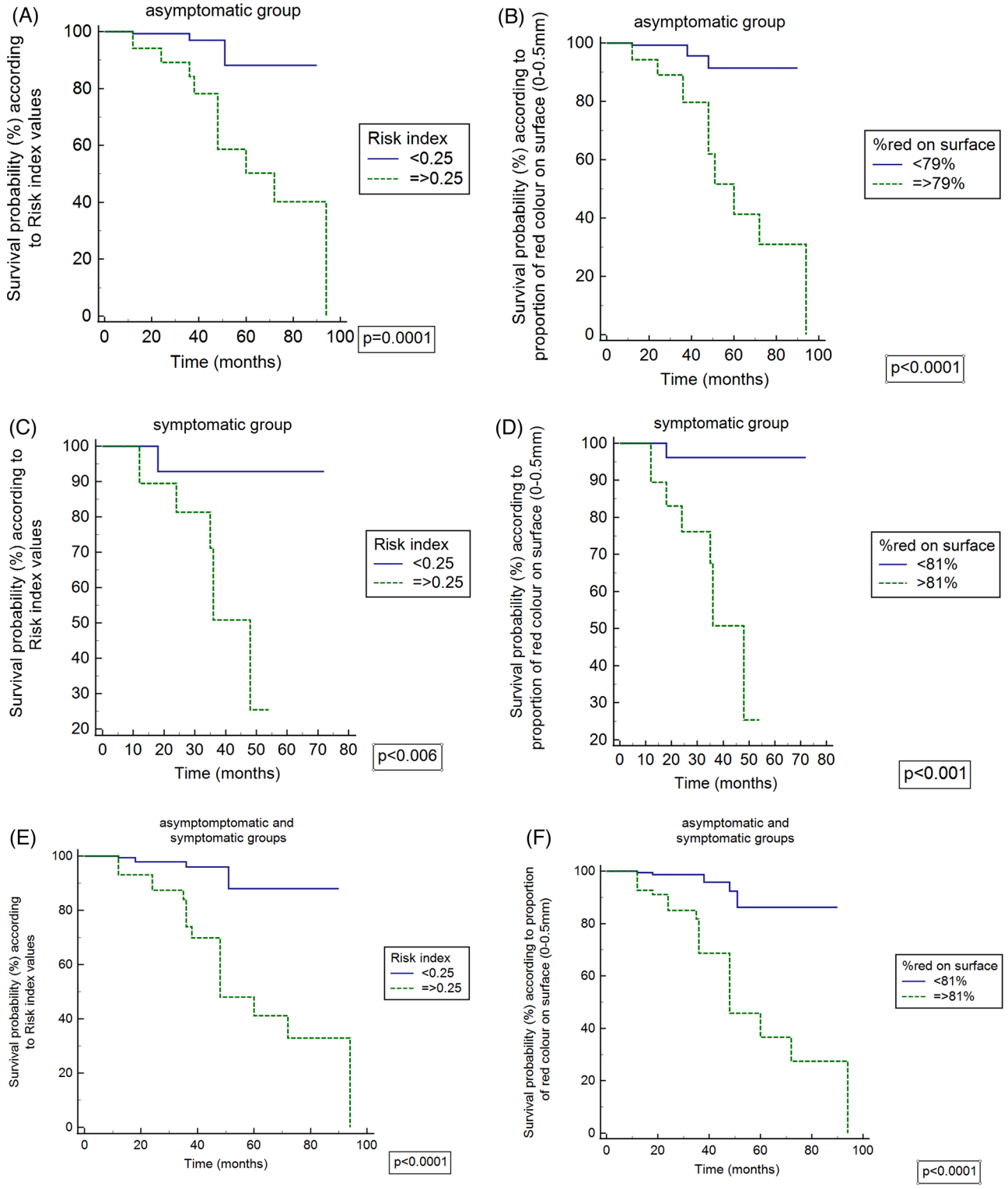

FIGURE 4 A,B,C,D,E,F: stroke or TIA-free survival in the asymptomatic (A and B, n = 205), in the symptomatic group (C and D, n = 54) and in both groups (E and F, n = 259). Abbreviations: n = number of patients; TIA = transitory ischemic attack

combining the degree of stenosis, grey-scale median, and a quantitative measure of surface irregularity (surface irregularity index) derived from color Doppler imaging and contrast-enhanced ultrasonography. The authors showed in a cross-sectional cohort of 54 patients higher values of vulnerability index among symptomatic as compared to asymptomatic plaques.[40–41] In another study using a multimodal ultrasound model including plaque surface morphology, intraplaque neovascularization and degree of stenosis, it could be shown during a follow-up of one year that these parameters predicted independently the occurrence of ischemic vascular events.[42]

TABLE 4 Predictive values of risk index and proportion of red colour on the surface

Asymptomatic n = 205	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	Hazard ratio (95%CI)
Risk index Criterion ≥0.25	82% (56%–96%)	71% (64%–77%)	0.80 (0.735 to 0.85) p < 0.001*	8.7 (3.05 to 24) p = 0.0001*
Proportion of red colour on the surface (0-0.5mm) Criterion ≥79%	82% (56%–96%)	70% (63%–76%)	0.81 (0.75 to 0.86) p < 0.001*	10.2 (3.5 to 29) p < 0.0001*
Symptomatic n = 54	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**AUC (95%CI)**	**Hazard ratio (95%CI)**
Risk index Criterion ≥0.25	80% (44%–97%)	72% (57%–85%)	0.80 (0.67 to 0.89) p < 0.001*	6.1 (1.8 to 35) p = 0.006*
Proportion of red colour on the surface (0-0.5mm) Criterion ≥81%	90% (55%–99%)	75% (59%–86%)	0.86 (0.74 to 0.94) p < 0.001*	8.9 (2.4 to 32) p = 0.001*
Symptomatic and asymptomatic n = 259	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**AUC (95%CI)**	**Hazard ratio (95%CI)**
Risk index Criterion ≥0.25	81% (61%–93%)	71% (65%–77%	0.79 (0.73 to 0.84)	7.5 (3.3 to 17) P < 0.0001
Proportion of red colour on the surface (0-0.5mm) Criterion ≥81%	81% (61%–93%)	73% (67%–79%)	0.82 (0.77 to 0.87)	10.6 (4.6 to 24) P < 0.0001

Abbreviations: AUC = area under the curve; CI = confidence interval *P value cutoff <0.05; n = number of patients.

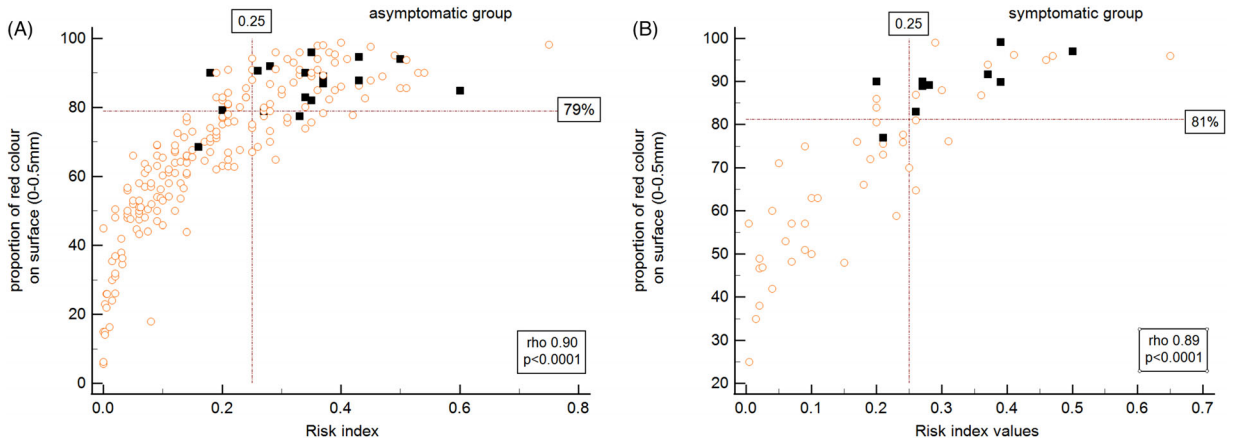

FIGURE 5 A,B: correlation between Risk index and proportion of red colour on the surface (0-0.5mm). Threshold values are given by means of horizontal (Proportion of Red Colour on Surface) and vertical bars (Risk Index). Patients who experienced stroke or TIA during the follow-up are represented with black boxes. In the asymptomatic (A), 76% (n = 13/17) and in the symptomatic group (B), 80% (n = 8/10) had both parameters located above the threshold values. Abbreviations: n = number of patients; TIA = transitory ischemic attack

Pedro and colleagues examined plaque surface echogenicity in 74 patients and showed by visual analysis that in homogenous plaques an echogenic cap was found in 8.3% of symptomatic and in 33.9% of asymptomatic patients (p < 0. 05).[18] Other more recent studies sought to determine in ultrasonic images of internal carotid artery plaques, the diagnostic value of the juxtaluminal anechogenic area without a visible echogenic cap. The authors found in a multiple logistic regression model an association between hemispheric symptoms, increasing stenosis (mild, moderate, severe), low GSM values (<15) and a juxtaluminal black (hypoechoic) area equal or greater than 8 mm^2.[18,33,43]

Our study was exploratory as the thresholds for RI and PRCS were not predefined, but established on ground of the present findings (Table 4). Our study was further limited by the small number of patients,

TABLE 5 Prediction of stroke or transitory ischemic attack for asymptomatic and symptomatic patients (n = 259) according to age, sex, risk index, proportion of red colour on the surface, degree of stenosis, stenosis progression, grey median scale and clinical baseline status

Variable	Hazard Ratio	95% CI	P values*
Age (years)	1.01	0.97 to 1.05	0.5
Sex	1.1	0.39 to 3.12	0.8
risk index	0.1	0.0001 to 175	0.5
proportion red colour surface	1.09	1.03 to 1.15	0.005*
degree of stenosis	1.0	0.96 to 1.06	0.4
stenosis progression	1.00	0.92 to 1.09	0.9
grey median scale values	0.99	0.97 to 1.01	0.8
clinical status at baseline**	1.6	0.70 to 3.1	0.5

Abbreviations: n = number of patients CI = confidence interval *P value cutoff <0.05 **symptomatic or asymptomatic at baseline.

however the duration of the follow-up period was relatively long and also the number of events resulted to be sufficient in order to obtain significant findings. We further found 12% of discordant findings of colour mapping performed by the various centers. Although the rate of agreement was acceptable, these results suggest nevertheless that the method needs careful monitoring and cannot be used without a previous training.

To conclude, we found in our cohort of patients that PRCS alone or combined to degree of stenosis expressed as the Risk index were strong predictors of ischemic stroke or TIA in patients with asymptomatic or symptomatic carotid stenosis. These findings suggest the importance of plaque surface echogenicity as a potential criterion for assessment of the embolic risk in asymptomatic or symptomatic carotid disease. Furthermore as surface echogenicity may be difficult to assess visually in clinical practice, echographic computerized approaches should be preferred.

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REFERENCES

1. Naylor AR, Rothwell PM, Bell PR. Overview of the principal results and secondary analyses from the European and North American randomised trials of endarterectomy for symptomatic carotid stenosis. Eur J Vasc Endovasc Surg 2003;26:115–29.
2. Barnett HJ, Meldrum HE, Eliasziw M. The dilemma of surgical treatment for patients with asymptomatic carotid disease. Ann Intern Med 1995;123:723–5.
3. Hatsukami TS, Ferguson MS, Beach KW, Gordon D, Detmer P, Burns D, et al. Carotid plaque morphology and clinical events. Stroke 1997;28:95–100.
4. Liapis CD, Kakisis JD, Kostakis AG. Carotid stenosis: factors affecting symptomatology. Stroke 2001;32:2782–6.
5. Sztajzel R. Ultrasonographic assessment of the morphological characteristics of the carotid plaque. Swiss Med Wkly 2005;135:635–43.
6. AbuRahma AF, Wulu JT Jr, Crotty B. Carotid plaque ultrasonic heterogeneity and severity of stenosis. Stroke 2002;33:1772–5.
7. Aburahma AF, Thiele SP, Wulu JT. Prospective study of the natural history of asymptomatic 60% to 69% carotid stenosis according to ultrasonic plaque morphology. J Vasc Surg 2002;36:437–42.
8. Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromso study. Circulation 2001;103:2171–5.
9. Steinke W, Hennerici M, Rautenberg W, Mohr JP. Symptomatic and asymptomatic high-grade carotid stenoses in Doppler color-flow imaging. Neurology 1992;42:131–8
10. Mayor I, Momjian S, Lalive P, Sztajzel R. Carotid plaque: comparison between visual and grey-scale median analysis. Ultrasound Med Biol 2003;29:961–6.
11. Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001;104:68–73.
12. El-Barghouty N, Geroulakos G, Nicolaides A, Androulakis A, Bahal V. Computer-assisted carotid plaque characterisation. Surg Eur J Vasc Endovasc 1995;9:389–93.
13. Tegos TJ, Sabetai MM, Nicolaides AN, Pare G, Elatrozy TS, Dhanjil S, et al. Comparability of the ultrasonic tissue characteristics of carotid plaques. J Ultrasound Med 2000;19:399–407.
14. Russell DA, Wijeyaratne SM, Gough MJ. Relationship of carotid plaque echomorphology to presenting symptom. Eur J Vasc Endovasc Surg 2010;39:134–8.
15. Biasi GM, Sampaolo A, Mingazzini P, De Amicis P, El-Barghouty N, Nicolaides AN. Computer analysis of ultrasonic plaque echolucency in identifying high risk carotid bifurcation lesions. Eur J Vasc Endovasc Surg 1999;17:476–9.
16. Hashimoto H, Tagaya M, Niki H, Etani H. Computer-assisted analysis of heterogeneity on B-mode imaging predicts instability of asymptomatic carotid plaque. Cerebrovasc Dis 2009;28:357–64
17. Matsagas MI, Vasdekis SN, Gugulakis AG, Lazaris A, Foteinou M, Sechas MN. Computer-assisted ultrasonographic analysis of carotid plaques in relation to cerebrovascular symptoms, cerebral infarction, and histology. Ann Vasc Surg 2000;14:130–7.
18. Pedro LM, Pedro MM, Goncalves I, Carneiro TF, Balsinha C, Fernandes e Fernandes R, et al. Computer-assisted carotid plaque analysis: characteristics of plaques associated with cerebrovascular symptoms and cerebral infarction. Eur J Vasc Endovasc Surg 2000;19:118–23.
19. Sztajzel R, Pizzolatto GP. Stratified gray-scale median analysis and color mapping of the carotid plaque: correlation with endarterectomy specimen histology of 28 patients. Stroke 2005;36:741–45
20. Momjian I, Momjian S, Albanese S, Comelli M, Lovblad K, Sztajzel R. Visual analysis or semi-automated gray-scale-based color mapping of the carotid plaque: which method correlates the best with the presence of cerebrovascular symptoms and/or lesions on MRI? J Neuroimaging 2009;19:119–26.
21. Momjian-Mayor I, Kuzmanovic I, Momjian S, Bonvin C, Albanese S, Bichsel D, et al. Accuracy of a novel risk index combining degree of stenosis of the carotid artery and plaque surface echogenicity. Stroke 2012;43:1260–5.
22. De Bray JM, Glatt B. Quantification of atheromatous stenosis in the extracranial carotid artery. Cerebrovasc Dis 1995;5:414–26.
23. Wardlaw JM, Lewis S. Carotid stenosis measurement on colour Doppler ultrasound: agreement of ECST, NASCET and CCA methods

applied to ultrasound with intra-arterial angiographic stenosis measurement. Eur J Radiol 2005;56:205–11.
24. Eliasziw M1, Rankin RN, Fox AJ, Haynes RB, Barnett HJ. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Stroke 1995;26:1747–52.
25. Von Reutern GM, Goertler MW, Bornstein NM, Del Sette M, Evans DH, Hetzel A, et al. Grading carotid stenosis using ultrasonic methods. Stroke 2012;43:916–21.
26. AbuRahma AF, Robinson PA, Strickler DL, Alberts S, Young L. Proposed new duplex classification for threshold stenoses used in various symptomatic and asymptomatic carotid endarterectomy trials Ann Vasc Surg 1998;12:349–58.
27. Winter WK, Zorach BB, Arpin PA, Nelson J, Mackey WC. Progression of moderate-to-severe carotid disease J Vasc Surg 2016;63:1505–10.
28. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379–87.
29. Oates CP, Naylor AR, Hartshorne T, Charles SM, Fail T, Humphries K, et al. Joint Recommandations for reporting carotid ultrasound investigations in the United Kingdom. Eur J Vasc Endovasc Surg 2009;37:251–61.
30. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, et al. Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischemic event: results from the ACSRS study. Eur J Vasc Endovasc Surg 2005;30:275–84.
31. Mohamed Al-Khaled MD. Magnetic resonance imaging in patients with transient ischemic attack. Neural Regen Res 2014;9:234–5.
32. Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambrone AE, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke. 2015;46:91–7.
33. Jashari F, Ibrahimi P, Bajraktari G, Grönlund C, Wester P, Henein MY. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. Eur J Neuro 2016;23:1241–7.
34. Rothwell PM. Carotid artery disease and the risk of ischemic stroke and coronary vascular events. Cerebrovasc Dis 2000;10:21–33
35. Griffin MB, Kyriacou E, Pattichis C, Bond D, Kakkos SK, Sabetai M, et al. Juxtaluminal hypoechoic area in ultrasonic images of carotid plaques and hemispheric symptoms. J Vasc Surg 2010;52:69–76
36. Prati P, Tosetto A, Casaroli M, Bignamini A, Canciani L, Bornstein N, et al. Carotid plaque morphology improves stroke risk prediction: usefulness of a new ultrasonographic score. Cerebrovasc Dis 2011;31:300–4.
37. Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. Stroke 2000;31:774–81.
38. Bassiouny HS, Sakaguchi Y, Mikucki SA, McKinsey JF, Piano G, Gewertz BL, et al. Juxtalumenal location of plaque necrosis and neoformation in symptomatic carotid stenosis. J Vasc Surg 1997;26:585–94.
39. Brinjikji W1, Rabinstein A, Lanzino G, Murad MH, Williamson EE, DeMarco JK, et al. Ultrasound characteristics of symptomatic carotid plaques: a systematic review and meta-analysis. Cerebrovasc Dis 2015;40:165–74.
40. Rafailidis V, Chryssogonidis I, Xerras C, Grisan E, Cheimariotis GA, Tegos T, et al. An Ultrasonographic multiparametric carotid plaque risk index associated with cerebrovascular symptomatology: a study comparing color doppler imaging and contrast-enhanced ultrasonography. Am J Neuroradiol 2019;40:1022–8.
41. Kanber B, Hartshome TC, Horsfield MA, Naylor RA, Robinson TG, Ramnarine KV. Quantitative assessment of carotid plaque surface irregularities and correlation to cerebrovascular symptoms, Cardiovascular Ultrasound 2013;38:1–8.
42. Li Y, Zheng S, Wang F, He W. Multimodal ultrasound parameters aided carotid plaque risk stratification in patients with asymptomatic carotid stenosis Acta Radiol 2022;63:278–86.
43. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T, et al. Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic plaques predicts the occurrence of stroke. J Vasc Surg 2013;57:609–61.

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