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## Carotid Plaque Echolucency Increases the Risk of Stroke in Carotid Stenting

### The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) Study

Giorgio M. Biasi, MD, FRCS; Alberto Froio, MD; Edward B. Diethrich, MD; Gaetano Deleo, MD; Stefania Galimberti, PhD; Paolo Mingazzini, MD; Andrew N. Nicolaides, MS, FRCS; Maura Griffin, MSc, PhD; Dieter Raitzel, MD; Donald B. Reid MD, FRCS; Maria Grazia Valsecchi PhD

**Background**—Carotid artery stenting (CAS) has recently emerged as a potential alternative to carotid endarterectomy. Cerebral embolization is the most devastating complication of CAS, and the echogenicity of carotid plaque has been indicated as one of the risk factors involved. This is the first study to analyze the role of a computer-assisted highly reproducible index of echogenicity, namely the gray-scale median (GSM), on the risk of stroke during CAS.

**Methods and Results**—The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) registry included 418 cases of CAS collected from 11 international centers. An echographic evaluation of carotid plaque with GSM measurement was made preprocedurally. The onset of neurological deficits during the procedure and the postprocedural period was recorded. The overall rate of neurological complications was 3.6%: minor strokes, 2.2%, and major stroke, 1.4%. There were 11 of 155 strokes (7.1%) in patients with  $\text{GSM} \leq 25$  and 4 of 263 (1.5%) in patients with  $\text{GSM} > 25$  ( $P=0.005$ ). Patients with severe stenosis ( $\geq 85\%$ ) had a higher rate of stroke ( $P=0.03$ ). The effectiveness of brain protection devices was confirmed in those with  $\text{GSM} > 25$  ( $P=0.01$ ) but not in those with  $\text{GSM} \leq 25$ . Multivariate analysis revealed that GSM (OR, 7.11;  $P=0.002$ ) and rate of stenosis (OR, 5.76;  $P=0.010$ ) are independent predictors of stroke.

**Conclusions**—Carotid plaque echolucency, as measured by  $\text{GSM} \leq 25$ , increases the risk of stroke in CAS. The inclusion of echolucency measured as GSM in the planning of any endovascular procedure of carotid lesions allows stratification of patients at different risks of complications in CAS. (*Circulation*. 2004;110:756-762.)

**Key Words:** carotid arteries ■ plaque ■ stents ■ stroke ■ ultrasonics

Stroke is a leading cause of death and disablement in Western countries. As demonstrated in multicenter randomized trials,<sup>1,2</sup> carotid endarterectomy (CEA) is the gold standard to reduce stroke in symptomatic and asymptomatic patients with significant carotid stenosis.

Carotid artery stenting (CAS) has recently emerged as a potential alternative to CEA<sup>3</sup> because of less invasiveness and a shorter hospitalization. The number of CAS procedures performed has steadily increased and currently makes up 9% of the total number of carotid procedures, with favorable results.<sup>4,5</sup> The use of balloon angioplasty and stenting in carotid arteries is still limited because of concern about the lack of long-term results and neurological complications during CAS. Cerebral embolization from carotid plaque is indeed the most severe complication of CAS.<sup>6</sup>

Several randomized trials are at present comparing CEA with CAS.<sup>7</sup> Inclusion and exclusion criteria for these trials usually consider the degree of carotid stenosis and the presence or absence of neurological symptoms, without paying any attention to the morphology of the carotid plaque.<sup>8</sup>

Early studies evaluated the relationship between the characteristics of the plaque and the presence or absence of neurological symptoms or cerebral CT lesions, with conflicting results. However, the advent of high-resolution B-mode scanners and the use of a quantitative computer-assisted index of echogenicity such as gray-scale median (GSM), introduced by our teams, have greatly improved the correlation between plaque characterization and clinical features.<sup>9,10</sup> Only after the introduction of the image normalization did GSM become a highly-reproducible index of the echolucency

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of carotid plaques with low interobserver and interscanner variability.<sup>11</sup>

Several studies indicated that echogenicity is related to the histological components of carotid plaques<sup>12,13</sup> and that carotid plaque echolucency (low echogenicity) is associated with the development of neurological events<sup>14–17</sup> and with an increased number of emboli after CEA and CAS.<sup>18–20</sup> On the basis of these assumptions, our groups suggested that plaque echogenicity measured by GSM can be a useful indicator of embolic potential in the carotid arteries.<sup>8,21</sup>

The aim of the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) registry<sup>22</sup> was to determine the preprocedural echographic criteria that may identify the carotid plaque related to a higher risk of stroke during CAS so that a better selection of candidates for CAS can be performed.

## Methods

### Study Design

ICAROS was an international multicenter registry that collected cases of carotid angioplasty and stenting procedures between July 2000 and December 2001 from 11 participating centers. The institutional review board approved the study. Patients included received full details about the procedure and the follow-up scheme and signed an informed consent. Information on devices (guidewires, catheters, balloons, stents, brain protection devices [BPDs]) and stenting procedures was collected, together with demographic and clinical characteristics, on a data form sent by mail to the coordinating center (Bassini Teaching Hospital). Patient investigation was made in detail as previously described.<sup>22</sup>

Inclusion criteria (defined before the study) were the following: hemodynamic ( $\geq 70\%$ ) carotid stenosis, neurologically symptomatic and asymptomatic, and both NASCET/ACAS eligible and ineligible. Exclusion criteria included the following: nonhemodynamic stenosis ( $< 70\%$ ); highly calcified, prolonged stenosis extensively involving the bifurcation beyond the internal carotid artery (ICA); an angulated ICA; intraluminal thrombus (discrete intraluminal filling defects with reduced contrast density, haziness, and irregular lesion contour); extensive aortic or brachiocephalic trunk plaque; neurologically unstable; and a life expectancy of  $< 5$  years.

A brain CT scan was considered positive for ischemic lesions if a discrete ( $> 1$  cm) subcortical or cortical infarction was present in the anterior and middle cerebral artery territories in the absence of cardioembolism (excluded on the basis of medical history and ECG).

To assess the role of GSM in different subsets, patients were subcategorized in eligible and ineligible according to NASCET and ACAS inclusion and exclusion criteria.<sup>1,2</sup>

### Carotid Plaque Imaging

Degree of stenosis was calculated as the ratio of the peak systolic velocity of the ICA to that of the common carotid artery.<sup>23</sup> This hemodynamic evaluation of carotid stenosis was based on velocity cutoff points related to angiographic evaluation of stenosis used in NASCET.<sup>1</sup> Angiographic evaluation was performed as previously described.<sup>22</sup>

Several training courses were organized worldwide for ultrasonographers from the participating centers on how to set up the duplex scanner to standardize the collection of images. B-mode scan settings were adjusted as previously described.<sup>11</sup>

A 15-second super-VHS video or magneto-optical disk recording was performed to show the vessel and plaque from a longitudinal view. Images were then sent to the coordinating center and transferred onto a personal computer. Image normalization and calculation of the GSM were performed by the same operator, who was blinded to clinical data and outcome and used Adobe Photoshop 5.0 software as previously described (Figure 1).<sup>11</sup>

### Follow-Up

The occurrence of any stroke and transient ischemic attack (TIA) during the procedure, at discharge, and after 30 days was carefully evaluated by means of CT or MR and by an independent neurologist who was blinded to clinical data, outcome, and GSM value. A TIA was defined as a focal neurological deficit lasting  $< 24$  hours. A stroke was considered disabling (major) if patients had a Rankin score of  $\geq 3$  at 90 days.

### Statistical Analysis

A Wilcoxon rank-sum test was used for nonparametric comparisons of the medians of GSM. Comparisons between event rates in different subgroups (univariate analysis) were performed by means of Fisher's exact test.

A logistic regression model was applied to investigate the impact of various factors on the odds of any stroke and death (primary end-point analysis) or of any stroke and death plus TIA (secondary end-point analysis) as occurred during the procedure or within 30 days. The regression factors considered were related to both relevant clinical aspects and the procedure, namely GSM, degree of stenosis, neurological symptoms, preprocedural brain CT, type of lesion, use of BPD, age, sex, and NASCET/ACAS eligibility.

A backward procedure was performed ( $\alpha=0.10$ ) to identify the final model, and ORs with 95% CIs were estimated. The presence of possible interactions was also considered when applicable. All tests were performed with a significance level of  $\alpha=0.05$  (2 sided).

A receiver-operating characteristic (ROC) curve was used to choose the GSM cutoff value with the best sensitivity and specificity. The logistic model was used to analyze the role of different GSM values on the basis of maximization of the likelihood of stroke and minimization of probability value.

## Results

ICAROS reported 496 cases of CAS worldwide, of which 78 (15.7%) were excluded because of low-quality images or incomplete information on data forms.

The risk factors and clinical features of the 418 patients analyzed are summarized in Table 1. In particular, the GSM distribution is shown in Figure 2. There was no correlation between GSM and degree of stenosis ( $r=0.09$ ).

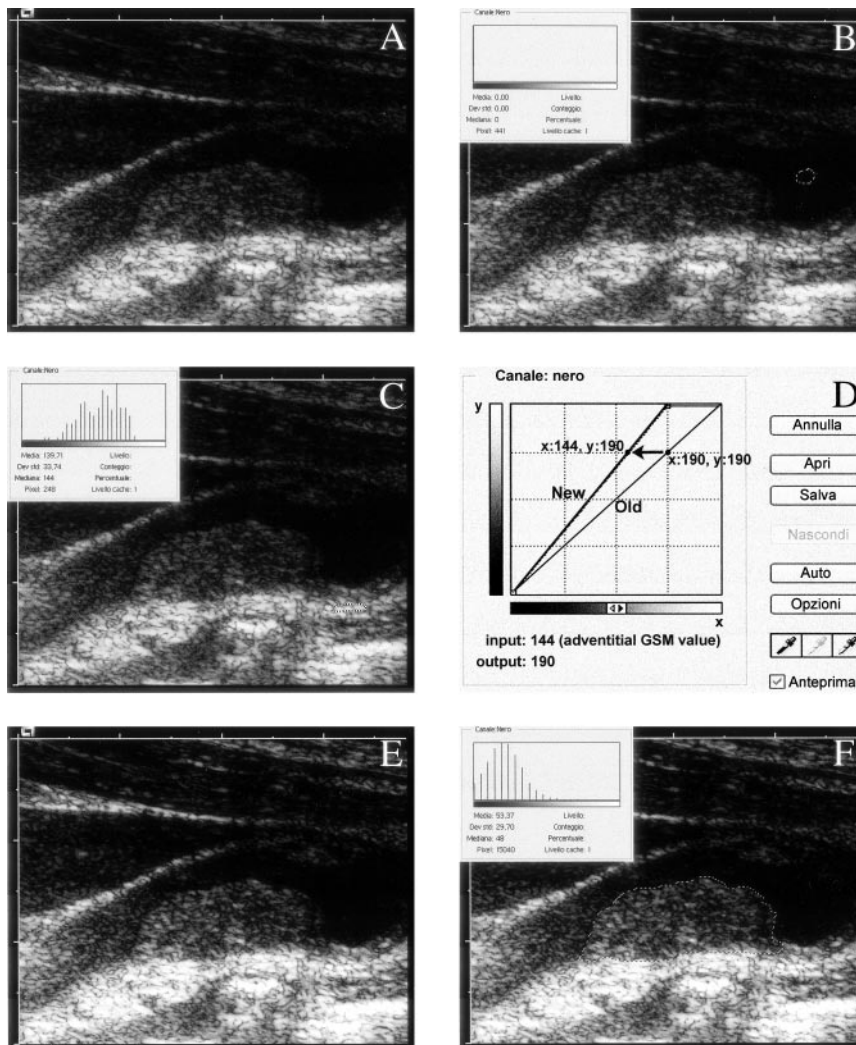
Stenting procedures were performed in 415 cases (99.3%). A BPD was applied in 219 patients (52.4%): 210 distal (95.9%) and 9 proximal BPDs (4.1%).

There were 13 TIAs (3.1%; 10 ipsilateral), 9 minor strokes (2.2%; 7 ipsilateral), and 6 major strokes (1.4%; 6 ipsilateral); no deaths were observed. The 30-day combined death and any stroke rate was 3.6%.

The GSM value in complicated patients was significantly lower than in uncomplicated patients in both the stroke ( $20.80 \pm 17.43$  versus  $35.07 \pm 19.60$ ;  $P=0.0036$ ; Figure 3A) and the stroke plus TIA ( $20.93 \pm 15.47$  versus  $35.53 \pm 19.61$ ;  $P=0.0001$ ) subsets (Figure 3B).

Figure 4A shows an ROC curve used to determine the cutoff value of GSM to identify patients at higher risk of complications during CAS; a GSM value of 25 was used as the threshold. A comparison of the significance and risk of complications at different GSM values using the logistic regression model was used to analyze the role of different GSM cutoff points (Figure 4B).

Eleven of 155 patients with a GSM  $\leq 25$  had complications compared with 4 of 263 patients with GSM  $> 25$  ( $7.1 \pm 2.1\%$  versus  $1.5 \pm 0.8\%$ ;  $P=0.005$ ; Figure 5A). The event rates increased to 12.9% and 3.0%, respectively, when both stroke



**Figure 1.** GSM calculation. A, B-mode image of plaque. B, Measurement of GSM in blood. C, Measurement of GSM in adventitia. D, Normalization (standardization) based on algebraic linear scaling of image using “curve” function of software. Gray-scale values of all pixels in image are adjusted according to input and output values of 2 reference points (blood: input value is measured GSM before linear scaling and output value is 0 to 5; adventitia: input value is measured GSM before linear scaling and output value is 185 to 195). In resultant image, GSM of blood equals 0 to 5, and that of the adventitia equals 185 to 195. E, Normalized image. F, Calculation of GSM in normalized plaque (GSM=48).

and TIA were counted ( $12.9 \pm 2.7\%$  versus  $3.0 \pm 1.1\%$ ;  $P=0.002$ ; Figure 5B).

Detailed descriptions of the outcome by subgroups defined according to each factor considered and GSM levels are reported in Table 2.

There were 5 of 219 complications (2.3%) in protected and 10 of 199 (5.0%) in unprotected procedures ( $P=0.188$ ). However, protection gave different results in the GSM subgroups. In patients with  $GSM \leq 25$ , the use of a BPD tended to increase the risk of complications ( $P=0.153$ ), whereas it had a protective value in the  $GSM > 25$  subgroup ( $P=0.010$ ).

The overall complication rate was higher in primitive lesions than in restenosis (5.2% versus 2.2%;  $P=0.117$ ). This difference was also observed in  $GSM > 25$  patients (4.0% versus 0%;  $P=0.020$ ) but not in  $GSM \leq 25$  patients (6.6% versus 7.8%;  $P=0.762$ ).

Multivariate regression analysis revealed that GSM (OR, 7.11;  $P=0.002$ ) and degree of stenosis (OR, 5.76;  $P=0.010$ ) are significant independent predictors of stroke alone, whereas preprocedural symptomatology and preprocedural brain CT are borderline significant (Table 3). Similar results were found in the analysis of stroke plus TIA as end points

(data not shown). The logistic regression model confirmed the role of GSM as a predictor of stroke in both NASCET/ACAS-eligible ( $P=0.024$ ) and -ineligible ( $P=0.031$ ) patients.

## Discussion

The ICAROS study was the first large study that was aimed at evaluating the relationship between the echolucency of carotid plaque, as measured by GSM, and the risk of stroke during CAS.

In the ICAROS study, the rate of stroke was higher in  $GSM \leq 25$  patients than in those with  $GSM > 25$ , which confirms that echolucent plaques have a significantly higher embolic potential when treated with angioplasty and stenting. This finding was also confirmed in a multivariate analysis in which degree of stenosis was the only other relevant independent predictor of stroke.

The role of GSM as predictor of stroke was confirmed in both NASCET/ACAS-eligible and -ineligible patients.

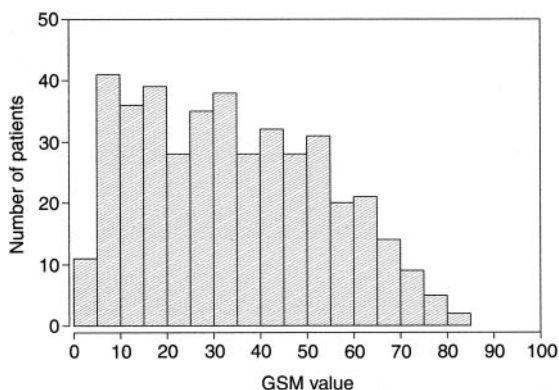
The higher neurological complication rate in patients with severe stenosis could be explained by a higher number of embolic particles released from the crossing of endovascular devices through a tighter lesion.<sup>18</sup>

**TABLE 1. Risk Factors and Clinical Features of the 418 Patients**

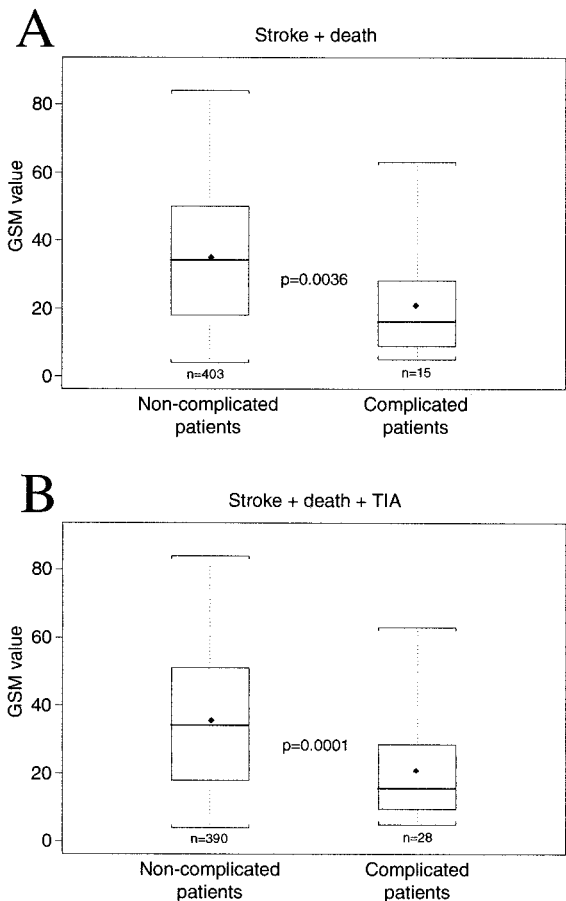
Risk Factors	
Male gender, n (%)	297 (71.1)
Restenosis, n (%)	227 (54.3)
GSM ≤25, n (%)	155 (37.1)
Preprocedural positive brain CT, n (%)	91 (21.8)
Preprocedural TIA, n (%)	95 (22.7)
Preprocedural stroke, n (%)	37 (8.9)
Age >80, n (%)	15 (3.6)
Age, mean±SD, y	68.2±8.1
Degree of stenosis, mean±SD, %	82.9±8.3
Hypertension, n (%)	286 (68.4)
Coronary artery disease, n (%)	186 (44.5)
Dyslipidemia, n (%)	131 (31.3)
Diabetes mellitus, n (%)	130 (31.1)
Smokers, n (%)	112 (26.8)
Peripheral artery disease, n (%)	101 (24.2)
Chronic obstructive pulmonary disease, n (%)	62 (14.8)
Chronic renal insufficiency, n (%)	21 (5.0)
NASCET ineligible (symptomatic), n (%)	100/132 (75.8)
ACAS ineligible (asymptomatic), n (%)	208/286 (72.7)

The complication rate was 5.3% for symptomatic and 2.8% for asymptomatic patients. These rates are within limits set by the American Heart Association (6% for symptomatic, 3% for asymptomatic patients) for CEA.<sup>24</sup> In the GSM >25 subset, results were far better, with a rate of 3.3% for symptomatic and 0.6% for asymptomatic patients. The selection of patients according to their risk factors (echoluency may be one of these, but many unknown factors remain) could be very important for improving the outcome of CAS.

The use of BPDs reduced neurological complications (although not significantly) in the overall population, as previously described.<sup>20,25</sup> Nevertheless, in the GSM ≤25 subset, BPDs did not seem to maintain their efficacy. It should be noted that the BPDs used in the different centers were almost exclusively distal BPDs (96% of the total), requiring the passage of the device across the lesion with the inherent risk of embolization. A proximal BPD based on



**Figure 2.** Distribution of GSM in 418 cases of CAS reported in this study.



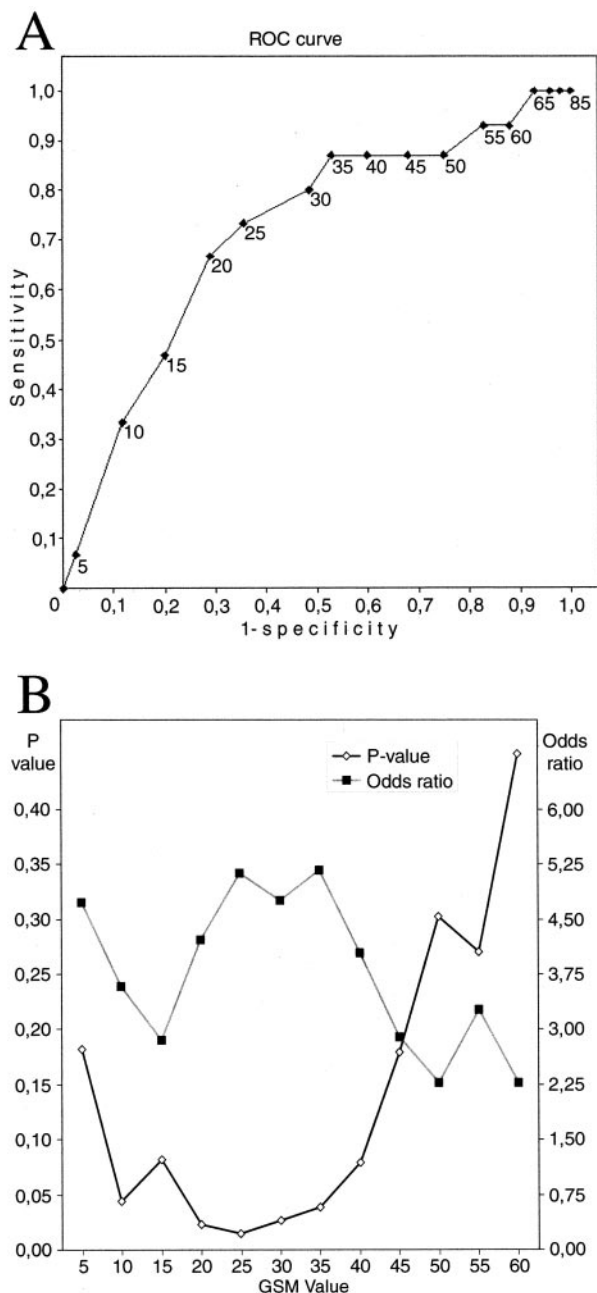
**Figure 3.** Box and whisker plots of GSM in subgroups of patients who did and did not experience complication (A, stroke; B, stroke plus TIA). Box includes all observations between first and third quartiles. Bold line represents median; diamond, mean. Whiskers extend from edges of box to extreme values.

reverse flow (with no crossing of the plaque) could eventually be a better option in this kind of plaque. On the other hand, the use of BPDs in GSM >25 plaques provided significant protection.

Restenosis, frequently with a homogenous fibrous content and a high GSM value, is associated with a low-embolic-risk endovascular procedure, as confirmed by our study. Nevertheless, the analysis of restenosis with a GSM value <25, although less frequent, showed for the first time a rate of stroke similar to that for primitive lesions.

Unlike a previous study, age was not a predictor of stroke in the present study, probably because of the smaller number of patients >80 years of age.<sup>5</sup>

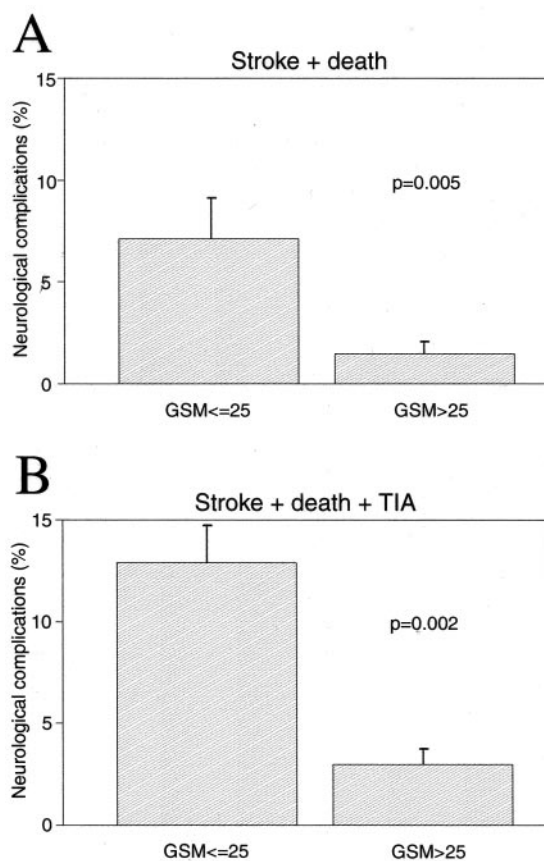
The first limitation of the present study is related to the observational and less rigorous design of a multicenter registry compared with a randomized trial in which the selection of patients is more accurate and the procedural protocol is more homogenous in all the centers, which is less likely to create bias. Second, in all the evaluations made, we discriminated between hypochoic and hyperechoic plaques using a cutoff value of 25. The clinical relevance of this cutoff should be validated in future studies. Third, we should



**Figure 4.** Analysis of different cutoff values of GSM for identification of patients at higher risk of stroke during CAS. A, ROC curve. B, Comparison of significance and risk of stroke at different cutoff values using logistic regression model.

remember that the reproducibility of the GSM after a training program is very high<sup>11</sup> but not absolute. Finally, a long-term analysis of the results of CAS should be performed that considers the change in the morphology of the carotid plaque over time.<sup>26</sup>

The high-resolution B-mode scanners provided a reliable analysis of echogenicity, allowing us to recognize the role of echolucency in predicting neurological events. Several studies analyzing >6000 patients showed that echolucent plaques have an increased risk of ischemic cerebrovascular events, with a relative risk of 1.9 to 4.6.<sup>14-17</sup>



**Figure 5.** Neurological complication rates in 2 subgroups identified by GSM levels (A, stroke; B, stroke plus TIA).

Our research teams separately evolved a similar computerized method for analyzing the echolucency of the carotid plaque. We demonstrated for the first time that patients with neurological symptoms and brain CT scans positive for stroke had an increased incidence of echolucent low-GSM-value plaques, which are correlated with high lipid and hemorrhagic content.<sup>9,10,12,21</sup> Only after the introduction of the image normalization did GSM become a highly reproducible index, allowing us to compare images from different scanners by different ultrasonographers and through different peripherals.<sup>11</sup>

To establish an indication to treat patients with an echolucent plaque, we should compare the long-term results of the CAS (as emerging from the follow-up of the ICAROS patients) with those of medical therapy and CEA. The ongoing Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study<sup>27</sup> is analyzing the rate of neurological events in patients with echolucent carotid plaques, as measured by GSM, treated with the best medical therapy alone. A study analyzing the relationship between GSM and the rate of complications in CEA is under consideration. Only by comparing these results will it be possible to choose the best treatment for patients with echolucent plaques stratified according to clinical characteristics (neurological symptomatology, degree of stenosis, etc). A GSM value <25 would not be a contraindication to endovascular treatment if the rate of complications after the best medical therapy or CEA was higher than CAS.

**TABLE 2. Univariate Analysis of Stroke in Overall Patients and GSM Subsets**

	Overall		GSM ≤25		GSM >25	
	N (%)	P	n (%)	P	n (%)	P
<b>GSM</b>						
≤25	11/155 (7.1)	0.005	—	—	—	—
>25	4/263 (1.5)		—		—	
<b>Stenosis, %</b>						
<85	3/202 (1.5)	0.033	3/92 (3.3)	0.051	0/110 (0.0)	0.142
≥85	12/216 (5.6)		8/63 (12.7)		4/153 (2.6)	
<b>Symptomatology</b>						
Asymptomatic	8/286 (2.8)	0.257	7/114 (6.1)	0.483	1/172 (0.6)	0.121
Symptomatic	7/132 (5.3)		4/41 (9.8)		3/91 (3.3)	
<b>Brain CT</b>						
Negative	8/327 (2.4)	0.026	6/111 (5.4)	0.295	2/216 (0.9)	0.148
Positive	7/91 (7.7)		5/44 (11.4)		2/47 (4.3)	
<b>Protection</b>						
Yes	5/219 (2.3)	0.188	5/40 (12.5)	0.153	0/179 (0.0)	0.010
No	10/199 (5.0)		6/115 (5.2)		4/84 (4.8)	
<b>Type of lesion</b>						
Primitive	10/191 (5.2)	0.117	6/91 (6.6)	0.762	4/100 (4.0)	0.020
Restenosis	5/227 (2.2)		5/64 (7.8)		0/163 (0.0)	
<b>Sex</b>						
Male	12/297 (4.0)	0.569	9/110 (8.2)	0.512	3/187 (1.6)	1.000
Female	3/121 (2.5)		2/45 (4.4)		1/76 (1.3)	
<b>NASCET/ACAS eligibility</b>						
Yes	5/120 (4.2)	0.772	4/34 (11.8)	0.259	1/86 (1.2)	1.000
No	10/298 (3.4)		7/121 (5.8)		3/177 (1.7)	
<b>Age</b>						
≤50th percentile (≤69 y)	7/208 (3.4)	1.000	5/79 (6.3)	0.762	2/129 (1.6)	1.000
>50th percentile (>70 y)	8/210 (3.8)		6/76 (7.9)		2/134 (1.5)	

It should be noted that CAS is to date an experimental procedure. For patients at high risk or unsuitable for surgery, CAS could be considered only if physicians with high-level skills and techniques are available and if at least equivalent (if not better) results for CAS than CEA can be shown. Low-risk patients should be treated with CAS only within a clinical trial.<sup>28</sup>

**TABLE 3. Results of the Final Logistic Multivariate Model on Stroke**

	OR	P	95% CI
<b>GSM</b>			
≤25 vs >25	7.11	0.002	2.06–24.57
<b>Stenosis, %</b>			
≥85 vs <85	5.76	0.010	1.51–21.91
<b>Symptomatology</b>			
Symptomatic vs asymptomatic	2.92	0.061	0.95–8.93
<b>Brain CT</b>			
Positive vs negative	2.54	0.099	0.84–7.47

Type of lesion, BPD, age, sex, NASCET/ACAS eligibility: P=NS.

Further studies are required to assess the difference between bare, drug-eluting, and coated stents for the reduction of embolization to the brain.

In our study, asymptomatic patients were included. Nevertheless, the indication for both surgical and endovascular treatment for these patients remains controversial.<sup>29</sup> Selecting asymptomatic patients according to their risk factors (such as echolucency in the ACSRS study)<sup>27</sup> may allow only subsets at higher risk to be treated, with maximum advantage for patients and a reduction in expense for the community through the avoidance of unnecessary procedures.

The clinical impact of GSM relies on the ability to identify a wide number of patients (155 of 418, 37%) at higher risk of stroke during CAS and to distinguish subsets of patients (with restenosis or with protected procedure) in whom the rate of complications is different from the overall population.

In conclusion, carotid plaque echolucency, as measured by GSM <25, increases the risk of stroke in CAS. Measuring echolucency is a simple method to identify preprocedurally carotid plaques at higher risk of stroke. Therefore, in addition to neurological symptomatology and degree of stenosis, GSM should always be considered in the planning of any endovascular treatment of carotid lesions.

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