Ultrasonic Characterization of Carotid Plaques and Its Clinical Implications

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Andrew Nicolaides, Stavros Kakkos, Maura B. Griffin, and Efthyvoulos Kyriacou

Abstract

In recent years, it has become apparent that the severity of an asymptomatic carotid stenosis is not sufficient to assess the risk of stroke. Although the risk of stroke increases with increasing grades of stenosis, and as a result a stenosis of ≥80% is used by many surgeons as an indication for surgery, this subgroup does not contain the majority of strokes that will subsequently occur. In addition, because the severity of stenosis cannot identify subgroups with stroke risk higher than 2.5%, a very large number of operations (approximately 90) with an asymptomatic stenosis of ≥80% would need to undergo carotid endarterectomy to prevent one stroke for one year of follow-up.

The aim of this chapter is to present the rationale and practical development of image analysis of ultrasonic plaque images for the identification of texture features that can be used to stratify patients according to stroke risk.

Two important advances contributed to the success of this approach. First, image analysis has enabled us to obtain reproducible measurements of gray scale from the same plaques irrespective of equipment and gain used. Second was the realization that, similar to plaque histology, not a single feature on imaging could by itself detect all the structural abnormality characteristic of potentially unstable and high-risk plaques.

The ability of a combination of texture features to identify unstable plaques and stratify patients according to stroke risk was tested in both cross-sectional studies and validated in a large prospective cohort (ACSRS study).

Keywords

Ultrasound imaging • Asymptomatic carotid stenosis • Plaque characterization • Image analysis • Plaque texture features • Stroke risk stratification

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Introduction

In recent years, it has become apparent that the severity of an asymptomatic carotid stenosis is not sufficient to assess the risk of stroke. Although the risk of stroke increases with increasing grades of stenosis, and as a result a stenosis of ≥80% is used by many surgeons as an indication for surgery and identification of a high-risk subgroup, this subgroup does not contain the majority of strokes that will subsequently occur. For example, in the ACSRS (Asymptomatic Carotid Stenosis and Risk of Stroke) study, the annual stroke

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rate was 2.4% in the 80–99% stenosis group (325 patients), 1.6% in the 60–80% stenosis group (311 patients), and 1% in the <60% stenosis group (485 patients). However, during the subsequent follow-up period (mean 4 years), there were 25, 13, and 21 strokes, respectively, in these subgroups. Therefore of the 59 strokes that occurred overall during the follow-up period, only 25 (42%) were in 80–99% stenosis group [1]. In addition, because the severity of stenosis cannot identify subgroups with stroke risk higher than 2.5%, a very large number of operations (approximately 90) with an asymptomatic stenosis of ≥80% would need to undergo carotid endarterectomy to prevent one stroke for one year of follow-up.

In order to provide better stratification of the risk of stroke in patients with asymptomatic stenosis, efforts have been made to identify potential features of vulnerable or unstable plaques. Most ischemic strokes are the result of embolic plaque debris or fragments of thrombi that form on the luminal surface of plaques. Some plaques are prone to rupture because they are unstable, consisting of a large lipid core and a thin fibrous cap that is often eroded by macrophages. Other plaques are more stable and consist of fibrous tissue with a thick fibrous cap and a small lipid core, but—although these plaques rarely rupture—they may develop a thrombus on their surface that may subsequently embolize. Plaques may also rupture because of mechanical forces such as a high pulse pressure.

A key message that has emerged in recent years is that there is not a single feature on imaging that by itself could detect all the structural abnormalities listed above and thus identify the potentially unstable and high-risk plaques. Therefore, it has been argued that a combination of plaque features would perform better at predicting the risk of stroke than a single feature alone. Indeed this hypothesis was tested and validated in the ACSRS cohort.

The aim of this chapter is to present the rationale and practical development of image analysis of ultrasonic plaque images for the identification of texture features that can be used to stratify patients according to stroke risk.

The Need for Image Normalization

In the 1980s and early 1990s, ultrasonic plaque characterization was highly subjective. When the examination was performed in a dimly lit room, the gain was usually reduced by the operator; when it was performed in a brightly lit room, the gain was increased. Although the human eye could adjust to the image brightness to a certain extent, reproducible measurements of echodensity when the same patient was scanned in another room and on different equipment were not possible. Ultrasonic image normalization, which has been introduced in the late 1990s, has enabled us to overcome this problem.

Computer-assisted plaque measurements of echodensity were initially made from digitized B-mode images of plaques taken from a duplex scanner with fixed instrument settings including gain and time control [1]. Because the frequency distribution of gray values of the pixels within the plaque was skewed, it was suggested that the gray-scale median (GSM) value rather than the mean should be used as the measurement of echodensity (gray scale on a computer is usually in the range of 0–255; 0 = absolute black, 255 = absolute white, as a result of 8-bit pixel coding). Early work had demonstrated that plaques with a GSM of less than 32, i.e., echolucent plaques, had a fivefold increase in the prevalence of silent brain infarcts on CT brain scans [2]. Other teams found similar results, but the cutoff point was higher than 32 because they used a higher gain setting [3]. Soon it became apparent that ultrasonic image normalization was necessary, so that images captured under different instrument settings, from different scanners, by different operators, and through different peripherals (storage devices) such as video or magneto-optical disk could be comparable. As a result a method was developed to normalize images by means of digital image processing using blood and adventitia as two reference points [4].

Development of Image Normalization

With the use of commercially available software in the 1990s (Adobe Photoshop™ version 3.0 or later, Adobe Systems Inc.) and the "histogram" facility, the gray-scale medians (GSM) of the two reference points (blood and adventitia) in the original B-mode image were determined. Algebraic (linear) scaling of the image was performed with the "curves" option of the software so that in the resultant image the GSM of blood was equal to 0 and that of the adventitia to 190. Thus, the gray-scale value (brightness) of all pixels in the image including those of the plaque became adjusted on a linear scale defined by these two reference points [4].

Selection of the two reference points was based on the argument that a black area representing blood and a relatively bright band representing adventitia should always be present in a B-mode image of a vessel. Determination of the optimum gray values of the two reference points was made by first selecting a number of images that in the eyes of two experienced ultrasonographers appeared to be of high qual-

ity and subsequently measuring the gray-scale value of blood and adventitia. The gray value of blood was found to be in the range of 0–5 and that of adventitia 180–190. The choice of gray value of adventitia as 190 meant that calcification would be represented with higher values often closer to and including 255 [4].

Two major reproducibility studies have been performed by our team in order to establish the validity of the method of image normalization and the value of GSM measurements [5, 6]. These studies have demonstrated that GSM after image normalization is a highly reproducible measurement that could be used in natural history studies of asymptomatic carotid atherosclerotic disease, aiming to identify patients at higher risk of stroke. For the first time, it became possible to obtain the same GSM value for a plaque even when a patient was scanned by different ultrasonographers on different equipment on different days. A subsequent third reproducibility study by Seo and his team [7] in 30 patients scanned on two different equipment has confirmed our findings. The correlation of the GSM of the plaques between the systems was high ($Y = 1.01X - 0.47$, $R^2 = 0.938$); in addition, the intra- and interobserver variability in 100 plaques were 5.1 ± 2.3% and 6.2 ± 2.5%, respectively. As a result of these studies, guidelines for equipment settings and image normalization technique were produced (see below). Key issues for the successful reproducibility of normalized images were (a) imaging the vessel with the ultrasound beam at right angles to the vessel wall, (b) minimizing but not abolishing "noise" in the vessel lumen, and (c) that only the innermost (central) two fourths of the brightest section of adventitia should be sampled for normalization. This meant that training of both the ultrasonographer and the operator performing image normalization were essential.

Current Guidelines for Maximization of Reproducibility of GSM

Image Acquisition

As mentioned above a number of prerequisites for image acquisition and normalization are essential for achieving a high reproducibility of GSM (and other texture features) [8]. These are listed below.

1. Maximum dynamic range was used which ensured the greatest possible display of gray-scale values and hence texture detail.
2. Persistence was set on low and frame rate on high, ensuring good temporal resolution.
3. The time gain compensation curve (TGC) was sloping through the tissues but was positioned vertically through the lumen of the vessel because the ultrasound beam is not attenuated as it passes through blood. This ensured that the adventitia of the anterior and posterior walls had similar brightness.
4. The overall gain was adjusted to give optimum image quality. This was achieved by adjustment of the gain control to minimize but not abolish noise. In practice, the gain was turned down so that noise was abolished and then it was gradually turned up until some noise appeared in the lumen. This ensured that the gain was not reduced too much to lose low-intensity features in the plaque and that there was a black area without noise in the lumen to be used for normalization.
5. A linear post-processing curve was used. In the absence of a linear curve, the one closest to linear was used.
6. The ultrasound beam was at 90° to the arterial wall.
7. The minimum depth was used so that the plaque occupied a large part of the image.
8. The position of the probe was adjusted so that adventitia adjacent to the plaque was clearly visible as a hyperechoic band that could be used for normalization.

In images that contained hypoechoic plaques or plaques whose edge was not clearly visible, a second image was saved using the color or power Doppler facility to indicate the outline of the plaque taking care to avoid color overspill (Fig. 8.1a, b). If the outline of the plaque could not be clearly defined with color, a third black and white image was saved with the plaque outlined using the on-screen calipers of the ultrasonic equipment (Fig. 8.1c).

Technique of Image Normalization and Measurement of GSM Using Adobe Photoshop

The details and reproducibility of this method have been described in several publications [4–6]. Briefly, the GSM of blood (B) and adventitia (A) were obtained using the "histogram" facility of the program. This was achieved by selecting an area of noiseless blood from the vessel lumen and the inner two fourths of the brightest area of adventitia adjacent to the plaque (Fig. 8.2). Zooming so that the area of adventitia was enlarged made this procedure easier to perform. Also, selecting the inner two fourths of the brightest area of adventitia was essential for ensuring high reproducibility. Normalization was subsequently performed using the "curves" facility and adjusting the straight line of the "curves" diagram so that the value of B would become zero

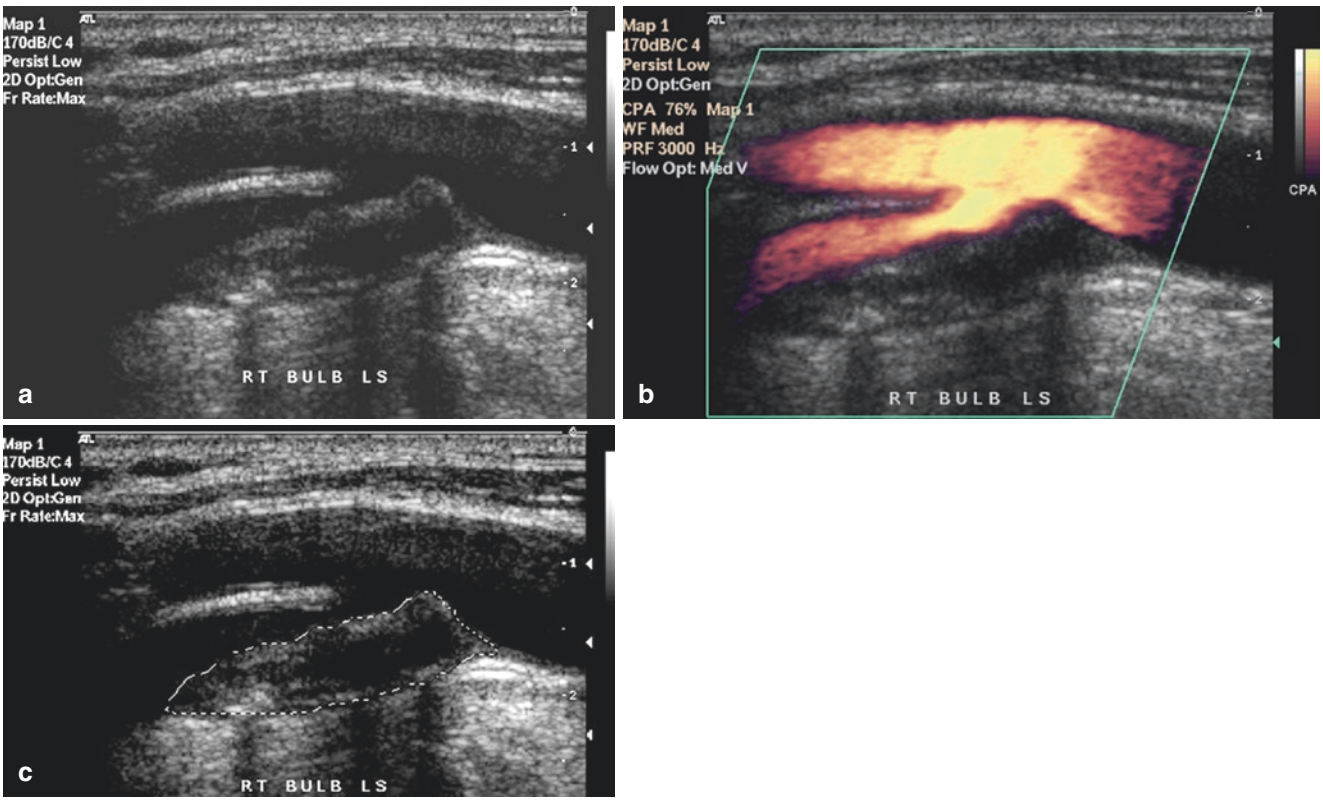

Fig. 8.1 Atherosclerotic plaque at the origin of right internal carotid artery producing a severe stenosis. (**a**) Gray-scale image. Rectangular box in vessel lumen shows an area of blood free from noise used for image normalization. (**b**) Power Doppler highlighting the outline of plaque. (**c**) Plaque outlined by ultrasonographer at the time of image capture using the on-screen calipers of the ultrasound equipment. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

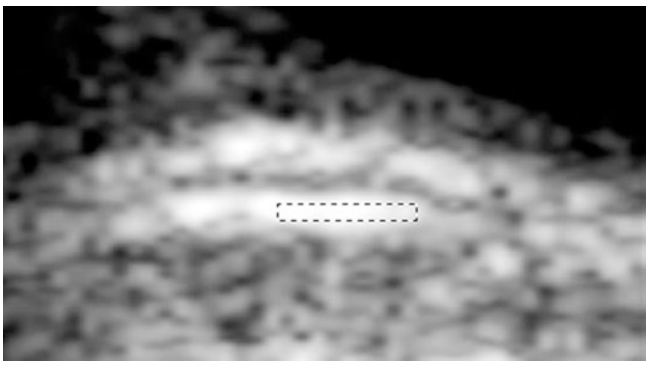

Fig. 8.2 Magnified area of arterial wall from Fig. 8.1a showing the most echogenic segment of arterial wall adjacent to the plaque. The rectangle demonstrates the correct sampling of adventitia (central 2/4ths of the adventitia). From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

and the value A would become 190 in the final image. Thus, all the pixels in the image would adjust automatically according to the new linear scale defined by these two reference points. Subsequently, the plaque in the final image was outlined with the mouse and the GSM was obtained from the "histogram" facility.

The use of Adobe Photoshop™ was adequate for image normalization and measurements of GSM as a measure of plaque overall density although time-consuming. However, this software could not provide any measurements of texture, i.e., the spatial distribution of pixel gray scale in the plaque area. This has now been overcome by dedicated software [8].

Dedicated Software

The Plaque Texture Analysis software LifeQ Medical (info@lifeqmedical.com) which is a dedicated research software package for image normalization and extraction of plaque texture features including GSM became available in 2004. This software has five modules [8]:

1. Image histogram normalization: it provides a user-friendly way to normalize images with blood and adventitia as reference points (Fig. 8.3).

2. Measurements: it provides a means of distance calibration, providing measurements of distance or area in mm and

mm², respectively (distances such as IMT, plaque thickness, and areas).

3. Pixel density standardization: it provides a method of normalizing images to a standard pixel density (20 pixels per mm). This is because a number of texture features are pixel density dependent [8]. Pixel density of images from different duplex scanning equipment has been found to vary from 10 to 30 pixels per mm. Also, various degrees of image magnification applied by the operator do alter the pixel density. Thus, the value of 20 pixels per mm has been suggested for a standard image.

4. Image crop: This module has two windows, one for the normalized black and white image and the other for the color-flow image or image with the plaque outlined by the ultrasonographer (Fig. 8.4). The plaque in the normalized image is outlined with the mouse and saved as a new file with the same name and extension ".plq." Both components of a plaque (anterior and posterior wall) can be selected (Fig. 8.5). By pressing the "Features Extraction" button in this window or using the "Feature Extraction" module, a variety of texture features are automatically calculated (Fig. 8.6) including GSM and can be saved in a database that can be opened by "Windows Excel." Data can then be transferred to SPSS or any other statistical package.

5. Texture feature extraction: it extracts a number of plaque texture features including GSM (Fig. 8.6) and saves them on a file for subsequent statistical analysis (see section under "texture features" below). It classifies plaques according to the Geroulakos classification [9]. In addition, images of plaques are color contoured: pixels with a gray-scale value in the range of 0–25 are colored black. Pixels with values 26–50, 51–75, 76–100, 101–125, and values greater than 125 are colored blue, green, yellow, orange, and red, respectively. In addition, this module allows printing of the plaque images and selected features in the form of a report or saving the latter in a folder (Fig. 8.7).

For the purpose of automatic classification by computer, the Geroulakos classification has been redefined in terms of pixels and gray levels. Examples of plaque types 1–4/5 are shown in Fig. 8.8. For plaque type 5, only the calcified or

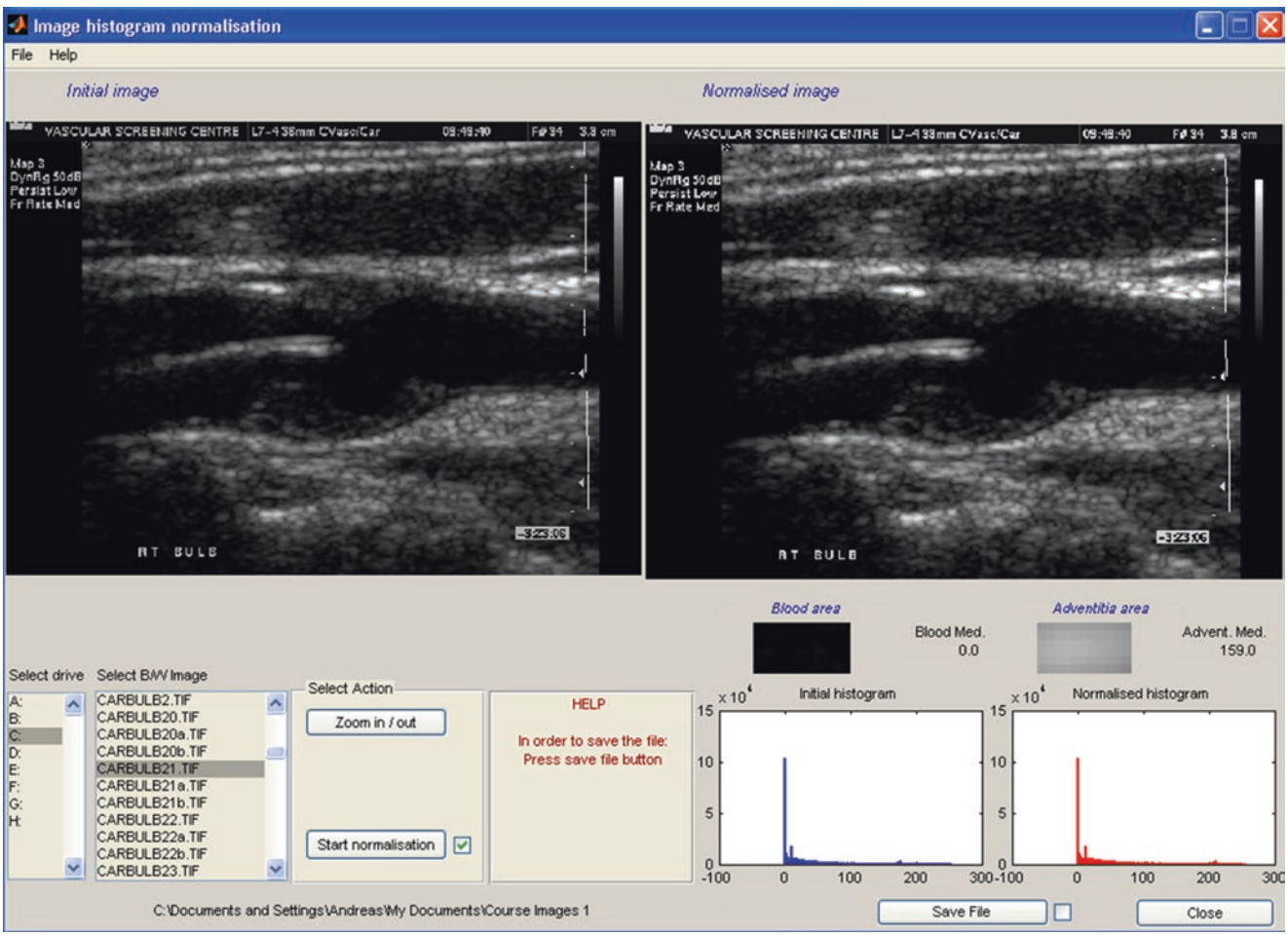

Fig. 8.3 Image normalization module. Image before normalization is on the left and normalized image on the right. In the original image, the gray value of blood was 0 and of adventitia 159. The normalized image can be saved using the "Save File" button at the bottom of the screen. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

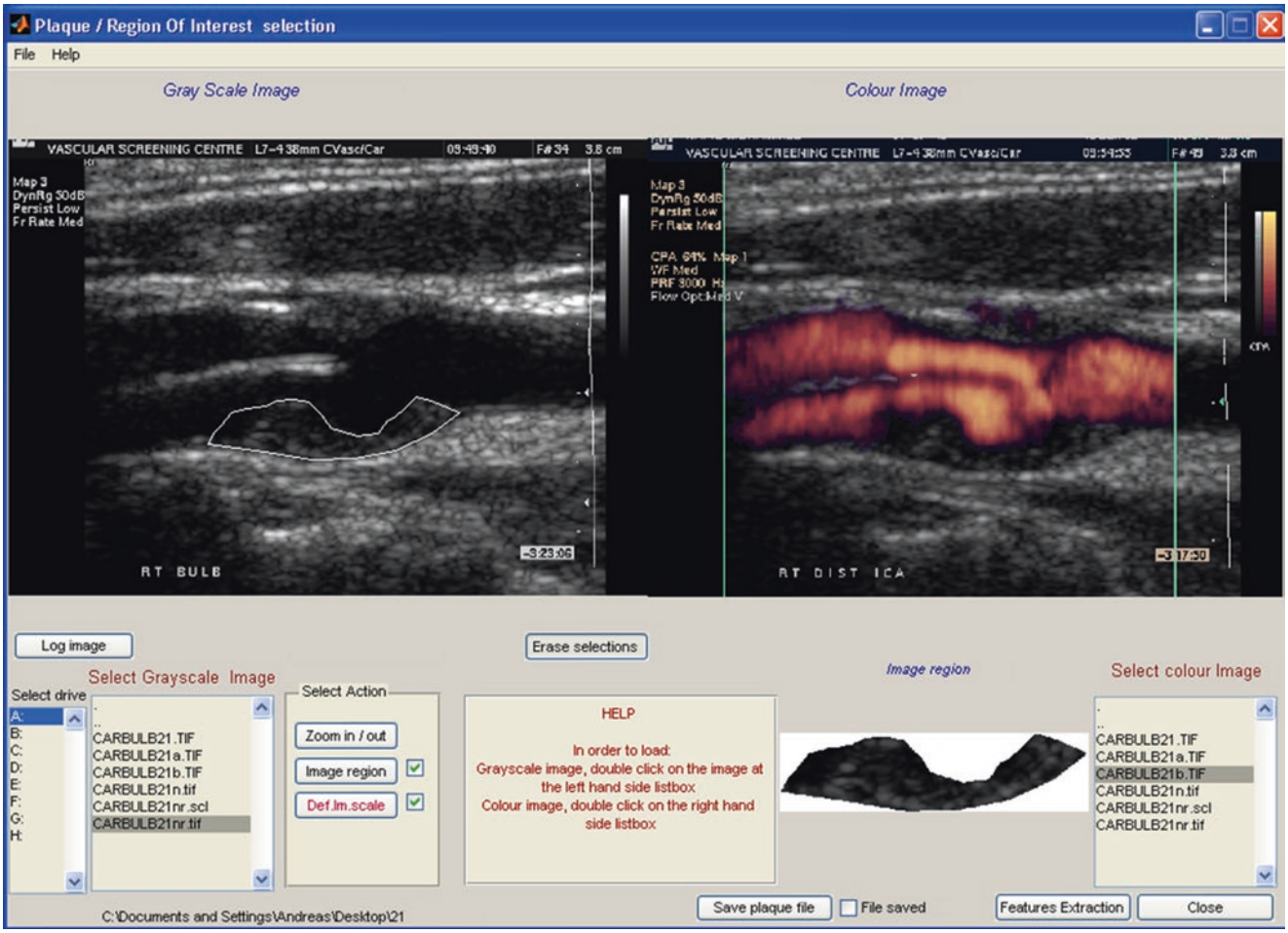

Fig. 8.4 Image crop module. The black and white normalized and standardized image is on the left, while the image with color flow, in this case power Doppler, is on the right. The outlined plaque is automatically extracted as a separate image that can be saved as a new file. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

visible bright areas of the plaque are selected ignoring the areas of acoustic shadows where information on plaque texture is lacking (Fig. 8.9).

Type 1 Uniformly echolucent (black): (Less than 15% of the plaque area is occupied by colored areas, i.e., with pixels having a gray-scale value greater than 25.) If the fibrous cap is not visible, the plaque can be detected as a black filling defect only by using color-flow or power Doppler.

Type 2 Mainly echolucent: (Colored areas occupy 15–50% of the plaque area.)

Type 3 Mainly echogenic: (Colored areas occupy 50–85% of the plaque area.)

Types 4 and 5 Uniformly echogenic: (Colored areas occupy more than 85% of the plaque area.)

Comparison of GSM Obtained Using Adobe Photoshop™ with GSM Obtained Using the Plaque Texture Analysis Software

In a comparison and reproducibility study, two operators normalized and measured the GSM of the 33 plaques using both methods [8]. Each image and plaque was initially processed using Adobe Photoshop™ and subsequently using the "Plaque Texture Analysis" software before proceeding to the next image. This ensured that the same area of adventitia and plaque was outlined when using each type of software. The two observers did not know the results of each other. For

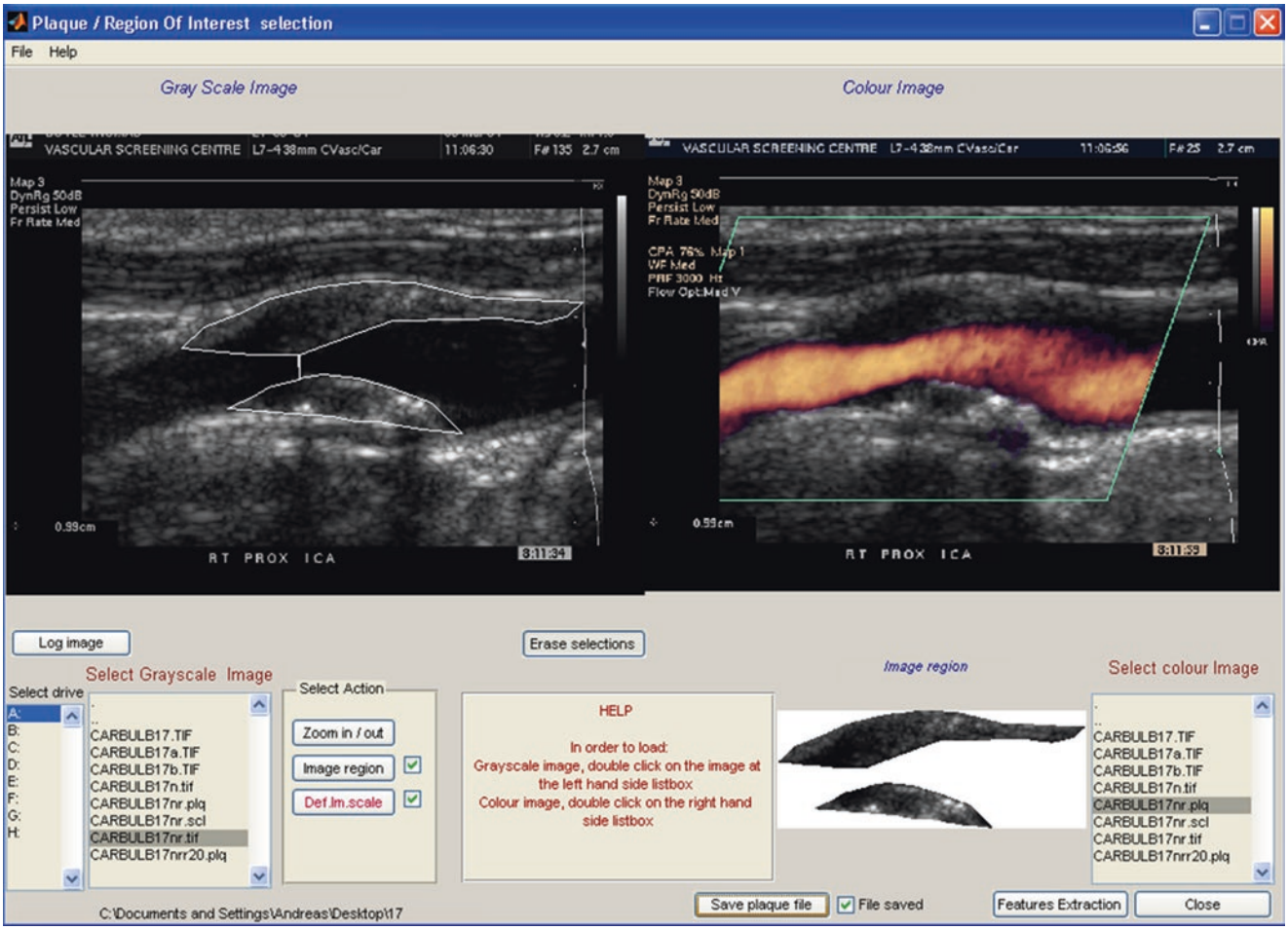

Fig. 8.5 Selection of both components (anterior and posterior) of a plaque. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

each observer the GSM values obtained with each software package were compared. The GSM values obtained by each operator using the "Plaque Texture Analysis" software were also compared.

There was a linear relationship between the GSM obtained using the Adobe Photoshop™ program and the Plaque Texture Analysis program with a correlation coefficient (r) of 0.990 (95% CI 0.984–0.996) for the first observer and 0.987 (95% CI 0.973–0.994) for the second observer. The interobserver GSM reproducibility using the Plaque Texture analysis by the two operators had a correlation coefficient (r) of 0.933 (95% CI 0.864–0.967) ($p < 0.0001$).

The results indicated a high intraobserver reproducibility of GSM when the same plaque images were analyzed using both Adobe Photoshop™ and the dedicated software. In addition, there was a high interobserver reproducibility when the dedicated software was used by each observer.

Effect of Image Normalization on Plaque Classification

The effect of image normalization on plaque classification and risk of ipsilateral ischemic neurological events in patients with asymptomatic carotid stenosis was tested in the first 1115 patients recruited to the ACSRS study with a follow-up of 6–84 months (mean 42) [9]. Duplex scanning was used for grading the degree of internal carotid stenosis and for plaque characterization visually (types 1–5) that was performed before and after image normalization and by the "Plaque Texture Analysis" software.

Images that were recorded on video tapes (S-VHS) were digitized off-line on a PC using a video grabber card (Videologic, TV Snap version 1.0.3 c 1990–1994) at a resolution of 640 × 480 pixels at the coordinating center by two

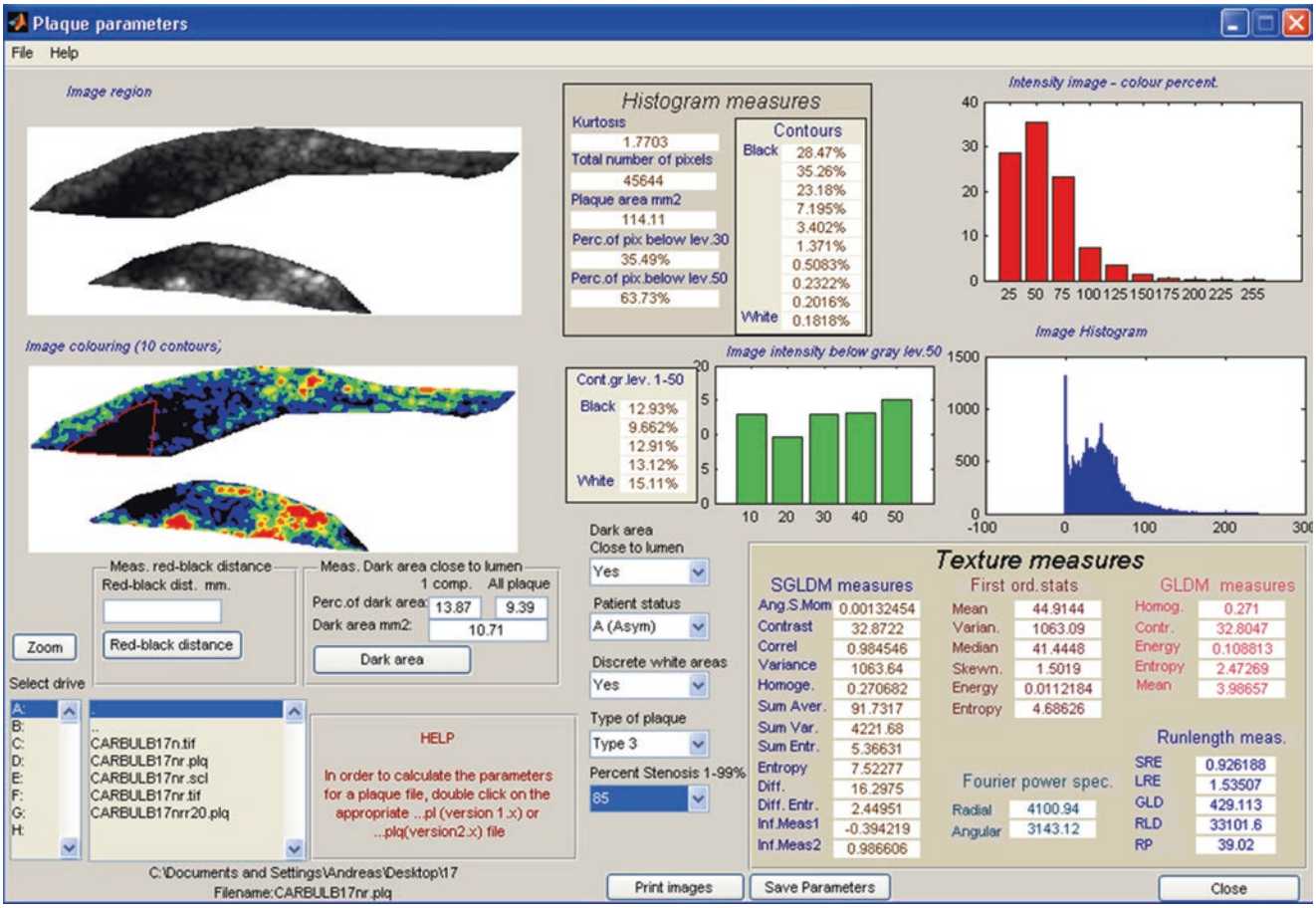

Fig. 8.6 Texture feature extraction module. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

members of the team who were experienced in carotid scanning. These two members performed plaque classification. Image normalization was performed by the same members of the team several months later using linear scaling with blood (gray-scale value assigned, 0) and adventitia (gray-scale value assigned, 190) as reference points using Adobe Photoshop™, and the plaques were reclassified without access to the results of the initial classification. As indicated above, before image normalization, plaques with a calcified cap that had more than 15% of the plaque obscured by an acoustic shadow were classified as type 5. After image normalization, both the calcified area and the area of the plaque adjacent to the calcification that was outside the acoustic shadow were considered.

The relationship between plaque classification before image normalization and after image normalization is shown in Table 8.1. Before image normalization 131 plaques were classified as type 1, 288 as type 2, 319 as type 3, 166 as type 4, and 188 as type 5. It can be seen that after image normalization, 66% of type 1, 49% of type 2, 46% of type 3, 66% of type 4, and 82% of type 5 were reclassified as a different plaque type (kappa statistic 0.22) [9].

The ipsilateral neurologic events (AF, TIAs, and stroke) that occurred during follow-up in patients with different types of plaque before and after image normalization are shown in Tables 8.2 and 8.3, respectively. It can be seen that after image normalization the incidence of events in relation to different plaque types has changed. After image normalization there was a decreased incidence in patients with plaques type 4 and 5 with the vast majority of events occurring in plaque types 1, 2, and 3. Before image normalization only 82 (71%) of the 116 neurologic events occurred in plaque types 1–3, but after image normalization, the number increased to 109 (94%).

When plaque types 1–3 were compared with plaque types 4 and 5 before image normalization, the relative risk of having an event was 1.12 (95% CI 0.76–1.66) (Chi Sq. $p = 0.45$). Also, 37 (73%) of the 51 ischemic strokes occurred in patients

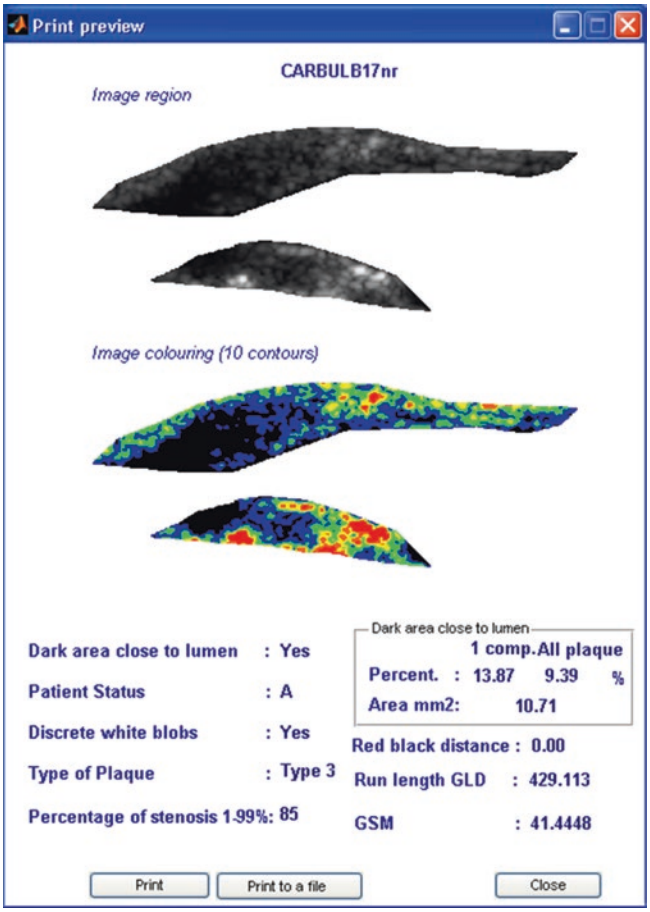

Fig. 8.7 Print preview of report which includes a number of selected key texture features. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

with plaque types 1–3 (Table 8.2). When plaque types 1–3 were compared with plaque types 4 and 5 after image normalization, the relative risk of having an event was 4.8 (95% CI 2.27–10.28) (Chi Sq. p = 0.0001). Also, 49 (96%) of the 51 ischemic strokes occurred in patients with plaque types 1–3 (Table 8.3).

When hypoechoic plaques (type 1 and 2) were compared with hyperechoic ones (type 3 and 4), the incidence of ipsilateral stroke was 45 out of 426 (annual stroke rate 3.0%) in the former and 14 out of 635 (annual stroke rate 0.6%) in the latter group (Table 8.4) (Chi Sq. p = 0.003).

When heterogeneous plaques (type 2 and 3) were compared with homogeneous plaques (type 1 and 4), the incidence of ipsilateral stroke was 49 out of 850 (annual stroke rate 1.6) in the former and 10 out of 271(annual stroke rate 1.2%) in the latter group (Table 8.4) (Chi Sq. p = 0.0001).

In summary, image normalization resulted in 60% of plaques being reclassified. Before image normalization a high event rate was associated with all types of plaque. After image normalization 58 (98%) of the strokes occurred in patients with plaques type 1–3. Thus, asymptomatic patients with plaque types 4 and 5 classified as such after image normalization are at low risk irrespective of the degree of stenosis.

Pixel Distribution Analysis (PDA)

This is a refinement of the GSM analysis of carotid plaque proposed by Lal and his colleagues [10, 11]. Plaques scanned with ultrasound were subjected to histological examination after carotid endarterectomy. After image normalization pixel distribution within the images was analyzed. The gray-scale ranges of known tissues obtained from control subjects was used to define the amount of intraplaque hemorrhage, lipid, fibromuscular tissue, and calcium within the plaque images. This analysis was correlated with tissue composition on the corresponding histologic sections. It was found that in control subjects, the median gray-scale value (and range) was 2 (0–4) for blood, 12 (8–26) for lipid, 53 (41–76) for muscle, 172 (112–196) for fibrous tissue, and 221 (211–255) for calcium. PDA-derived predictions for blood, lipid, fibromuscular tissue, and calcium within the plaques correlated with the histologic estimates of each tissue. A higher amount of blood and lipid was seen within symptomatic plaques compared with asymptomatic plaques, and a larger amount of calcification was noted within asymptomatic plaques. In addition, lipid cores were larger and their distance from the lumen was lower in symptomatic plaques.

A similar approach was used by Madycki and his team in a study of 76 patients scheduled for carotid endarterectomy [12]. The investigators chose five partitions of gray-scale values corresponding to the echogenicity of blood (0 to 9), lipid (10 to 31), muscle (32 to 74), fibrous tissue (75 to 111), and calcified tissues (112 to 255). These reference points were normalized for every tissue in every subject: blood-lumen of the artery, lipid-subcutaneous tissue, muscle-sternomastoid muscle, fibrous-anterior rectus abdominis sheath and calcium-the transverse process of a cervical vertebra. These gray-scale partitions were coded into five different colors depending on the gray-scale range. MRI-brain scans were performed routinely two days prior to and two days after the operation. TCD was used perioperatively to monitor microembolic (ME) signals in the middle cerebral artery. Excised carotid plaques were classified into three types according to histological criteria: (1) combined plaque (presence of thrombus, ulceration, disintegration, or intraplaque hemorrhage), (2) fibrous plaque, and (3) solid plaque according to previously published criteria [13]. In this series 17 (22%) of the 76 patients had new ischemic lesions on the

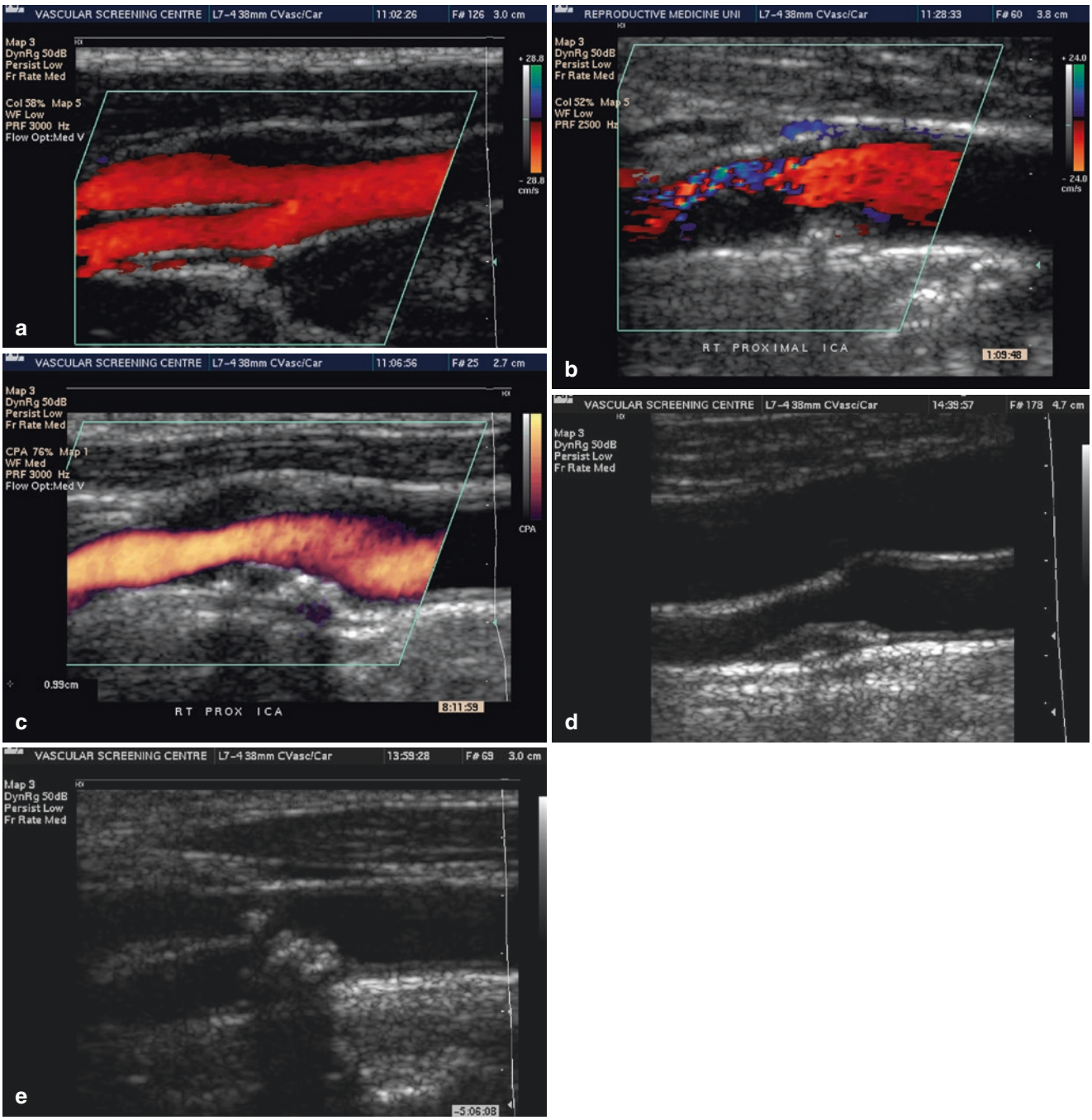

Fig. 8.8 (**a**) Type 1, (**b**) type 2, (**c**) type 3, (**d**) type 4, and (**e**) type 5 plaques. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

postoperative MRI. ME signals were a potent predictor of new lesions. Median GSM was 16 (0–29) and 38 (12–49) for the groups with new perioperative brain infarcts and without new perioperative brain infarcts, respectively. Patients with a percentile content of partitions 1, 2, and 3 (hypoechoic) exceeding 72% of the plaque area were associated with a higher rate of perioperative complications including brain infarcts and a higher rate of ME signals.

A slightly different approach was used by Sztajzel and his colleagues in 28 patients (31 plaques) scheduled for carotid endarterectomy [14]. Thirteen patients were symptomatic and 15 asymptomatic. After image normalization a profile of the regional GSM as a function of distance from the plaque surface was generated, realizing a stratified determination of the GSM. Plaque pixels were further mapped into three different colors depending on their GSM value (<50 red, 50–80

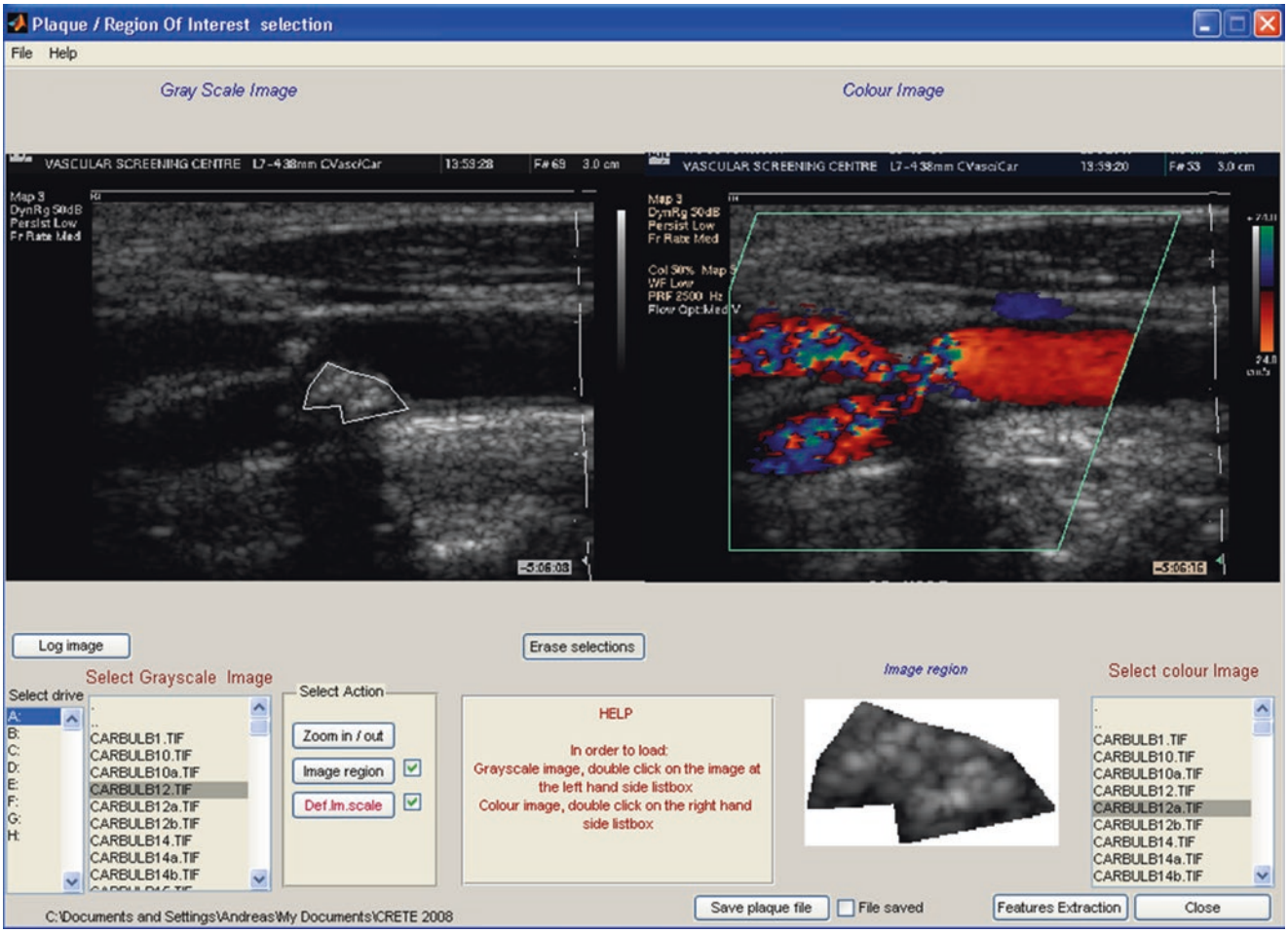

Fig. 8.9 Selection of the calcified or visible bright areas of the plaque is selected ignoring the area of acoustic shadow where information on plaque texture is lacking. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

Table 8.1 Lack of agreement between plaque classification before and after image normalization ($\kappa = 0.22$)

	Plaque type after image normalization (%)					
Plaque type before image normalization	1	2	3	4	5	Total
1	44 (34)	54 (41)	22 (17)	11 (7)0	0	131 (100)
2	23 (8)	148 (51)	97 (34)	16 (6)	4 (1.4)	288 (100)
3	10 (3)	68 (21)	173 (54)	54 (17)	14 (4)	319 (100)
4	0	35 (21)	62 (37)	57 (34)	12 (7)	166 (100)
5	0	27 (19)	96 (51)	47 (25)	18 (10)	188 (100)
Total	77 (7)	332 (31)	450 (41)	185 (17)	48 (6)	1092 (100)

Table 8.2 The ipsilateral AF, TIAs, and strokes that occurred during follow-up in patients with different types of plaque before image normalization

Plaque type	Events absent (%)	AF (%)	TIAs (%)	Stroke (%)	All events (%)	Total (%)
1	125 (95.4)	1 (0.8)	4 (3.1)	1 (0.8)	6 (4.6)	131 (100)
2	243 (84.4)	3 (1.0)	19 (6.6)	23 (8.0)	45 (15.6)	288 (100)
3	288 (90.3)	5 (1.6)	13 (4.0)	13 (4.0)	31 (9.7)	319 (100)
4	146 (88.0)	6 (3.6)	4 (2.4)	10 (6.0)	20 (12.0)	166 (100)
5	174 (92.5)	4 (2.1)	6 (3.2)	4 (2.6)	14 (7.5)	188 (100)
Total	976 (89.4)	19 (1.7)	46 (4.2)	51 (4.7)	116 (10.6)	1092 (100)

Table 8.3 The ipsilateral AF, TIAs, and strokes that occurred during follow-up in patients with different types of plaque after image normalization

Plaque type	Events absent (%)	AF (%)	TIAs (%)	Stroke (%)	All events (%)	Total (%)
1	70 (91.0)	2 (2.6)	1 (1.3)	4 (5.2)	7 (9.1)	77 (100)
2	278 (84.1)	7 (2.1)	23 (6.7)	24 (7.1)	54 (15.9)	332 (100)
3	419 (93.1)	10 (2.2)	17 (3.8)	21 (4.7)	48 (10.7)	450 (100)
4	180 (97.3)	0	3 (1.6)	2 (1.1)	5 (2.7)	185 (100)
5	46 (95.8)	0	2 (4.2)	0	2 (4.2)	48 (100)
Total	976 (89.4)	19 (1.7)	46 (4.2)	51 (4.7)	116 (10.6)	1092 (100)

Table 8.4 The average annual stroke rate in individual plaque types (1–4) and when reclassified as homogeneous, heterogeneous, hypoechoic, or hyperechoic

	Homogeneous	Heterogeneous	Total
Hypoechoic	Type 1 (n = 85)	Type 2 (n = 341)	Type 1 and 2 (n = 426)
	Prevalence 7.6%	Prevalence 30.4%	Prevalence 38.0%
	Strokes 9	Strokes 36	Strokes 45
	Annual stroke rate 2.8%	Annual stroke rate 3.0%	Annual stroke rate 3.0%
Hyperechoic	Type 4 (n = 186)	Type 3 (n = 509)	Type 4 and 3 (n = 695)
	Prevalence 16.6%	Prevalence 45.4%	Prevalence 62%
	Strokes 1	Strokes 13	Strokes 14
	Annual stroke rate 0.4%	Annual stroke rate 0.8%	Annual stroke rate 0.6%
Total	Type 1 and 4 (n = 271)	Type 2 and 3 (n = 850)	
	Prevalence 24.1%	Prevalence 75.8%	
	Strokes 10	Strokes 49	
	Annual stroke rate 1.2%	Annual stroke rate 1.6%	

yellow, and >80 green). Histological examination of the excised plaques was performed. It was found that predominance of the red color on the plaque surface was associated with symptomatic patients and a necrotic core located near the surface or a thin fibrous cap.

In a subsequent study, the author's team investigated the diagnostic value of a juxtaluminal black (hypoechoic) area without a visible echogenic cap (JBA) in ultrasonic images of internal carotid artery plaques [15]. Ultrasonic images of plaques from 324 patients with asymptomatic (n = 139) and symptomatic (n = 185) internal carotid 50–99% stenosis in relation to the bulb referred for duplex scanning were studied. The JBA in mm^2 as outlined with color or power Doppler and the GSM were obtained after image normalization of the gray-scale image. Cutoff points for GSM and JBA (combined highest sensitivity with highest specificity) were determined from ROC curves. It was found that the presence of a JBA equal or greater than 8 mm^2 was associated with a high prevalence of symptomatic plaques in all grades of stenosis. In a multivariable logistic regression model, increasing stenosis (mild, moderate, severe), GSM $\leq$ 15, and JBA $\geq$ 8 mm^2 were associated with hemispheric symptoms. This model could identify a high-risk group of 188 plaques which contained 142 (77%) of the 185 symptomatic plaques (OR 6.7; 95% CI 4.08–10.91) ($P < 0.001$) (sensitivity 77%; specificity 66%; positive predictive value 75%; negative predictive value 68%).

The results in this study indicated the potential diagnostic value of the presence of a JBA, and for the first time suggested a cutoff point of 8 mm^2 for JBA. This cutoff point has been subsequently tested in the ACSRS prospective cohort (see below).

It can be argued that a juxtaluminal black area without a visible fibrous cap may represent a necrotic lipid core or a hemorrhage in the presence of a fibrous cap which may be too thin to be visualized by ultrasound and, also, an intraluminal thrombus on the plaque surface. Whatever the case, the risk of emboli and development of carotid territory symptoms would be high.

A prospective study investigated whether the distribution of pixel intensities could predict the instability of asymptomatic plaque [16]. GSM values were assigned for blood, lipid, muscle/fibrous tissue, and calcification by comparison to

endarterectomy specimens. The percent area of each tissue component was subsequently estimated for 297 asymptomatic plaques causing 40–99% stenosis in 250 patients. Eight infarcts occurred during a follow-up period of 22 ± 15 months. Plaques in the top tertile for the percent area of lipid-like echogenicity showed an association with future infarction according to Kaplan–Meier analysis. This remained significant after adjustment for the severity of carotid stenosis (hazard ratio 4.4) according to Cox proportional hazards analysis.

A similar approach to carotid plaque image analysis has been used with intravascular ultrasound (IVUS) and has been called "virtual histology" [17]. An advantage of IVUS is that the transducer is inside the vessel lumen and thus very close to the plaque. As a consequence higher frequencies producing higher resolution than that from external probes can be used. The reflected signals from the artery wall provide a color-coded map of the atherosclerotic plaque. Different constituents of the plaque produce different reflected signals, and these are assigned different colors: dark green for fibrous, yellow/green for fibrofatty, white for calcified, and red for necrotic lipid core. This color-coded map assists the interventionalist in understanding how the lesion will behave at the moment of treatment, whether it will resist stent deployment or be liable to produce emboli [18, 19]. A high correlation was found with true histology when performed in 15 patients having to carotid endarterectomy [20]. It has been suggested that IVUS virtual histology has the potential to improve the results of carotid artery stenting by optimizing the criteria of patient and lesion selection [21].

Prospective Studies

Several prospective studies have demonstrated that low GSM, found in hypoechoic plaques, could be used to predict the long-term risk of stroke, and a meta-analysis, involving 2095 patients, showed that low GSM even without image normalization was associated with a relative risk of stroke of 2.61 (95% CI 1.47–4.63) [22]. This is because lipids or hemorrhage appear as hypoechoic (black) areas, providing a low gray-scale median of a carotid plaque image. The meta-analysis also found that the high risk of stroke associated with low gray-scale median was irrespective of grade of stenosis (low, moderate, or high).

In the ACSRS study, a gray-scale median of <30 was found in 22% of plaques. While the annual stroke rate was 3% in the subgroup of patients that had plaques with gray-scale median of <30 [23], this subgroup contained only 54% of the strokes that occurred in the overall trial population during the extended follow-up period. By contrast, 71% of strokes that occurred during the extended follow-up period were in patients with a juxtaluminal black area of ≥8 mm^2 (the annual stroke rate was 4.1% in these patients) [24].

It should be emphasized that plaque area of ≥8 mm^2 and discrete white areas in hypoechoic plaques may also be used to predict stroke (independent of the degree of stenosis) [23]. However, reproducibility of these features has only become possible because of the development in the late 1990s of a method to provide image capture and image normalization and, more recently, the introduction of dedicated software (LifeQ Medical; info@lifeqmedical) to analyze carotid plaque [8].

Application of these plaque characteristics in ACSRS study and their full potential in identifying patients at increased risk and providing risk stratification are presented in the subsequent section.

The ACSRS Study

The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study was a multicenter natural history study. Its primary aim was to identify clinical, biochemical, and plaque features that when used in combination would allow risk stratification for ipsilateral carotid territory hemispheric ischemic events, especially stroke. It was planned in 1996, soon after the publication of the ACAS study [25], and recruitment started in 1998. The ACSRS is the largest natural history study of patients with asymptomatic carotid stenosis performed to date with 1121 patients followed for 6–96 months (mean 48 months). Results of different aspects such as quality control, stenosis and risk, factors associated with cardiovascular mortality, effect of image normalization on carotid plaque classification, silent ipsilateral cerebral embolic infarcts on CT brain scans and stroke risk, and stroke risk stratification using baseline plaque texture features have already been published [23, 24]. The aim of this section is to present the main messages that have come out of this study in relation to ultrasonic plaque characterization and highlight potential clinical applications.

The Value of Plaque Features after Image Normalization

In the initial analysis of the ACSRS study, five features emerged as independent predictors of stroke: severity of stenosis, history of contralateral transient ischemic attack or stroke, gray-scale median, plaque area, and presence of discrete white areas after image normalization [23]. In a second analysis when JBA was used, stenosis, history of contralateral transient ischemic attack or stroke, and presence of discrete white areas after image normalization were the only independent predictors.

Definitions and Reproducibility of Texture Features in the ACSRS

Gray-Scale Median (GSM)

This was the median of the gray values of all the pixels in the plaque image. In a reproducibility study of 35 plaques measured by two observers, the interobserver mean difference of GSM was 3.6, the within-subject standard deviation was 13.6, and the intra-class correlation coefficient was 0.93 [15].

Plaque Type

Plaques were classified automatically by the software into the following types according to a modified Geroulakos classification [26] as indicated earlier in this chapter.

Plaque Area

This was calculated by the software using the distance scale on the side of the image frame for calibration and the plaque area outlined by the operator. It was expressed in mm^2 [15, 27]. In a reproducibility study involving 50 plaques, the interobserver intra-class correlation coefficient was 0.73..

Discrete White Areas (DWA)

The presence of DWA defined as areas with pixels having gray-scale values >124 (colored red by the software for easy visual identification) not producing acoustic shadowing in plaque types 1–3 was noted. A reproducibility study involving 80 plaques classified visually after image normalization by two observers for the presence or absence of DWA had a kappa statistic of 0.83 ($P < 0.01$) [23].

Juxtaluminal Black Area Without a Visible Echogenic Cap (JBA)

This was measured as described earlier in this chapter. When the JBA (range 0–110 mm^2) of 324 plaques was measured by two observers using the "Plaque Texture Analysis" software, the interobserver mean difference between repeat measurements was 2.5 mm^2, the within-subject standard deviation was 6.9 mm^2, and the intra-class correlation coefficient was 0.94.

Ability of Individual Features to Identify High-Risk Groups

Stenosis

The stroke-free survival in relation to different grades of stenosis is shown in Fig. 8.10.

It can be seen that although some stroke risk stratification is possible, a large number of strokes occur in the low stenotic groups. The results indicate that severity of stenosis is a relatively poor indicator of stroke risk with a receiver operator characteristic (ROC) area under the curve (AUC) of 0.603 (95% CI 0.525–0.682). It has already been demonstrated that ECST percentage of stenosis has a linear relationship to risk, while NASCET percentage of stenosis does not [1]. The reason for this is probably the fact that ECST percentage of stenosis is related to plaque volume in the bulb, while NASCET percentage of stenosis is related to lumen diameter reduction in relation to the lumen diameter of the normal distal internal carotid artery.

Gray-Scale Median

The ACSRS study confirms the findings of other prospective studies [16, 28] that a low GSM is a strong predictor of future ipsilateral CORI events including stroke. GSM was high, >30 in 609 patients, 15–30 in 269 patients, and low <15 in 243 patients. These three ranges of GSM were associated with low, moderate, and high risk of stroke. The cumulative 5-year stroke rate for these three groups was 2%, 4%, and 15% (log rank test $P < 0.001$) giving an average annual stroke rate of 0.6%, 1.6%, and 3.6%, respectively (Fig. 8.11). During the entire period of follow-up, 11 strokes occurred in the high, 17 in the intermediate, and 31 in the low GSM group. Most important is that a GSM < 15 could identify a high-risk group consisting of 22% of patients (243 out of 1121 patients studied) that contained 52% of the strokes (31 out of 59) that occurred during follow-up.

Severe and fatal ipsilateral strokes ($n = 14$) (modified Rankin score 5 and 6) occurred exclusively in plaques with GSM < 30 (4 in plaques with GSM 15–30 and 10 in plaques with GSM < 15).

Plaque Type and Risk

As pointed out above, most natural history studies performed in the past have used different methods of plaque classification without prior image normalization. As indicated earlier in this chapter, image normalization results in a marked change in the appearance of plaques with reclassification of a large number. The automated classification of plaques (Geroulakos classification) using the "Plaque Texture Analysis" software has made this task easier and avoids subjective bias.

During the follow-up period, one stroke occurred in the 186 patients with plaque types 4 and 5 (classified as type 4 by the software), 13 strokes in 509 patients with plaque type 3, and 45 strokes in the 426 patients with plaque types 1 and 2. The cumulative 5-year stroke rate for these three groups was 2%, 4%, and 15% (log rank test $P < 0.001$) giving an average annual stroke rate of 0.4%, 0.8%, and 3.0%, respectively (Fig. 8.12).

Of the 186 patients with type 4 and 5 plaques, 51 had mild, 99 moderate, and 36 severe stenosis. Most important is that 76% of the strokes (45 out of 59) occurred in the 38% of patients (426 out of 1121 patients studied) with type 1 and 2

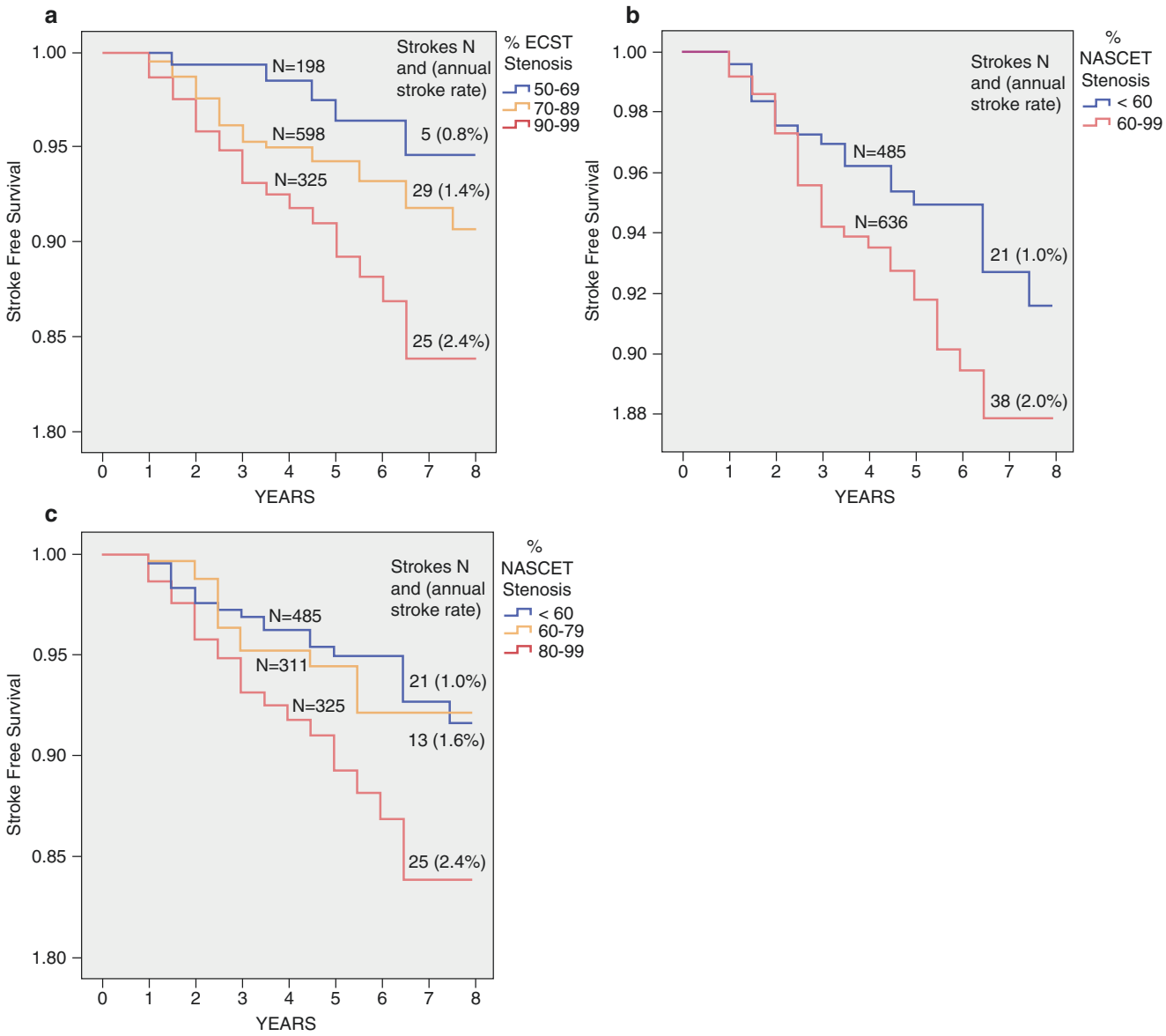

Fig. 8.10 Kaplan–Meier plots showing (**a**) ipsilateral cerebral ischemic stroke-free survival stratified by European Carotid Surgery Trial (ECST) stenosis: log rank *P* for trend = 0.002. Kaplan–Meier plots showing ipsilateral cerebral ischemic stroke-free survival stratified by North American Symptomatic Carotid Endarterectomy Trial (NASCET) stenosis (**b**) of <60% or >60% as used in the ACAS trial: log rank *P* for trend = 0.126 and (**c**) of <60%, 60–79%, and 80–99% stenosis, *P* for trend = 0.042. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

plaques at baseline. Severe and fatal ipsilateral strokes (n = 14) (modified Rankin score 5 and 6) occurred exclusively in plaque types 1 and 2 (10 in type 2 and 4 in type 1).

Several research teams have indicated that the risk for stroke is higher with echolucent plaques (type 1 and 2) when compared with echogenic plaques (type 3 and 4). Others have claimed that heterogeneous plaques are associated with a higher risk for stroke than homogeneous plaques. As pointed out earlier the results of the ACSRS study are compatible with both findings. This is because type 2 plaques that are associated with the highest stroke risk (Table 8.4) are included by most authors in both the echolucent (hypoechoic) and heterogeneous groups.

Plaque Area

Carotid plaque area has already been reported to be a strong predictor of myocardial infarction and stroke [27, 28] in patients with mild degrees of stenosis. The results from the ACSRS study show that plaque area can be used to stratify cerebrovascular risk in patients with plaques producing greater

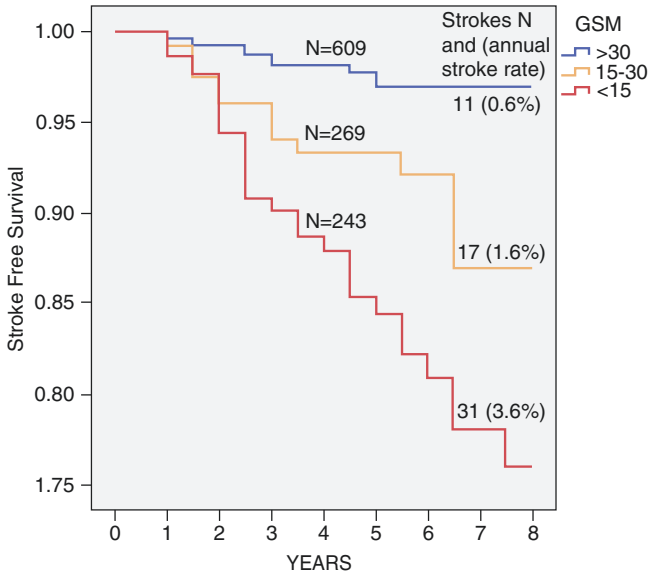

Fig. 8.11 Kaplan–Meier plots showing ipsilateral cerebral ischemic stroke-free survival stratified by gray-scale median (GSM) after image normalization: log rank *P* for trend <0.001. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

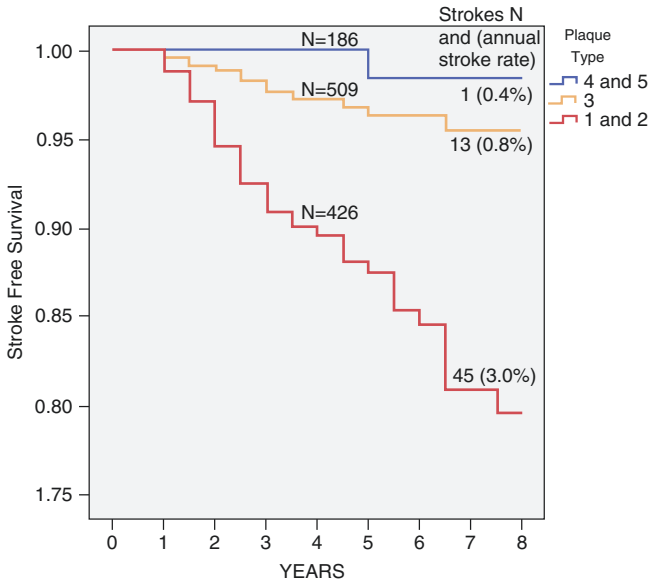

Fig. 8.12 Kaplan–Meier plot showing ipsilateral cerebral ischemic stroke-free survival stratified by plaque type after image normalization: log rank *P* for trend <0.001. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

than 50% stenosis (Fig. 8.13). Plaque area was small <40 mm^2 in 518 patients, intermediate 40–80 mm^2 in 489 patients, and large >80 mm^2 in 114 patients. These three ranges of plaque area were associated with low, moderate, and high risk of stroke, respectively. The cumulative 5-year stroke rate for these three groups was 5%, 7%, and 23%, respectively (log rank test $P < 0.001$) corresponding to an average annual stroke rate of 1.0%, 1.4%, and 4.6%, respectively (Fig. 8.13). During the entire period of follow-up, 15 strokes occurred in the small, 28 in the intermediate, and 16 in the large plaque area group (Fig. 8.13). Although plaque area greater than 80 mm^2 could identify a high-risk group consisting of 10.2% of patients (114 out of 1121 patients studied), it contained only 27% of the strokes (16 out of 59) that occurred during follow-up.

Discrete White Areas

Plaque heterogeneity has already been shown to be associated with symptomatic plaques [29]. With the exception of calcified plaques, it is the result of the presence of discrete white areas (DWA) without acoustic shadow in hypoechoic areas. These DWA are often hyperperfused as shown by ultrasonic contrast perfusion agents and correspond to areas of neovascularization and increased numbers of macrophages on histology [30]. Whether these areas are responsible for the development of intraplaque hemorrhage, nonuniform plaque stresses promoting plaque rupture or erosion of the fibrous cap by the macrophages merit further investigation.

The presence of DWAs (more than one) was associated with increased ipsilateral stroke events ($P < 0.001$) (Fig. 8.14). It is interesting to recognize that the increased stroke rate occurred after the first three years (Fig. 8.14).

Juxtaluminal Black Area Without a Visible Echogenic Cup

The JBA measurement has been applied to the plaque images of the ACSRS study. JBA was classified into four groups: <4,

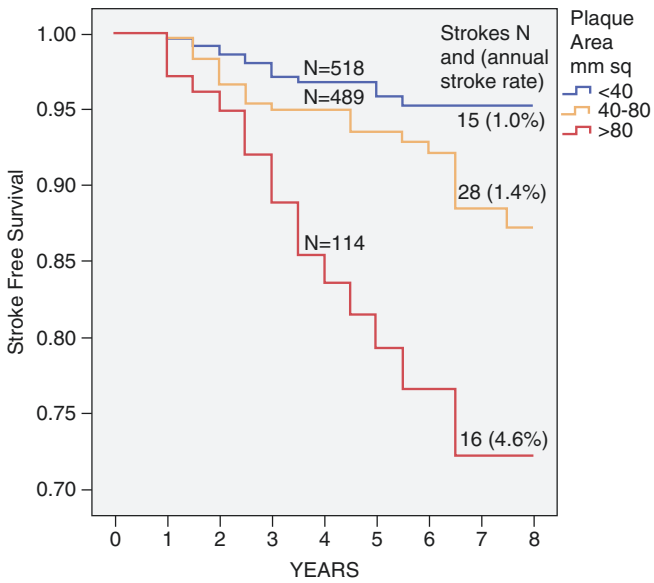

Fig. 8.13 Kaplan–Meier plots showing ipsilateral cerebral ischemic stroke-free survival stratified by plaque area: log rank *P* for trend <0.001. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

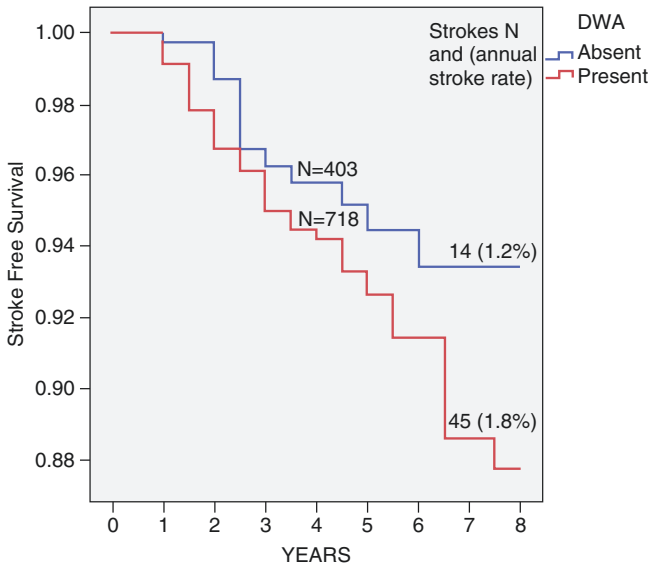

Fig. 8.14 Kaplan–Meier plots showing ipsilateral cerebral ischemic stroke-free survival stratified by the presence or absence of discrete white areas (DWA): log rank $P < 0.01$. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

4–8, 8–10, and >10 mm^2. JBA was <4 mm^2 in 704 patients, 4–8 mm^2 in 171 patients, 8–10 mm^2 in 46 patients, and >10 mm^2 in 198 patients. The cumulative 5-year stroke rate for these four groups was 2%, 7%, 16%, and 23% (log rank test $P < 0.001$) giving an average annual stroke rate of 0.4%, 1.4%, 3.2%, and 5.0%, respectively (Fig. 8.15a). During the entire period of follow-up, 8 strokes occurred in the <4 mm^2 group, 9 in the 4–8 mm^2 group, 6 in the 8–10 mm^2 group, and 36 in the 8–10 mm^2 group. The results indicate that a high-risk group can be identified, which contains the majority of the strokes and confirms the previous finding that 8 mm^2 is a critical cutoff point.

The stroke-free survival time of the two groups of patients based on the 8 mm^2 cutoff point is shown in Fig. 8.15b. The resulting two groups of 875 patients with JBA <8 mm^2 and 244 patients with JBA >8 mm^2 were associated with low and high risk of stroke. The cumulative 5-year stroke rate for the group with JBA <8 mm^2 was 3% and for the group with JBA >8 mm^2 was 23% (log rank test $P < 0.001$) corresponding to an average annual stroke rate of 0.6% and 4.6%, respectively (Fig. 8.15b). During the entire period of follow-up, 17 strokes occurred in the low risk and 42 in the high-risk group.

The design of the ACSRS did not foresee such a measurement, and the ultrasonographers were not trained to provide images of confirmed presence of JBA using multiple color-flow images in addition to the gray-scale image; however, a representative color-coded image and a loop on videotape were provided, minimizing errors. It may well be that some of the JBAs were an artifact by poor color filling of the lumen as often seen just distal to severely stenotic plaques, although even better predictive results would have been obtained in a perfect situation without artifacts. Thus, the results should be interpreted with caution and need to be validated in another prospective study. Ideally 3D imaging should be used for such a validation. If this finding can be validated, then the presence of a JBA could prove a powerful diagnostic tool. The presence of such an area would indicate a thin fibrous cap not detected by ultrasound overlying a large lipid core or an intraplaque hemorrhage close to the lumen; an alternative would be a fresh thrombus on the plaque surface.

Schulte-Altedorneburg reported that thrombosis at the plaque surface was often seen in "completely echolucent" plaques ($p < 0.001$) [31]. It is likely that the echolucent plaque component represents the thrombus or its combination with the lipid core. A recent study has demonstrated a strong association between symptomatic plaques and intraluminal thrombus attached to the plaque [32]. It may well be that the presence of a black area adjacent to the lumen identifies plaques many of which are associated with thrombus formation. This needs to be tested in future studies.

The Value of Clinical Features

Of the many clinical features assessed (such as age, hyperlipidemia, hypertension, diabetes, smoking, and elevated creatinine) in the ACSRS study for being risk factors for future stroke in patients with asymptomatic stenosis, only prior contralateral transient ischemic attack or stroke were independent predictors of future stroke [23] (Fig. 8.16). However, such a history was present only in 15% of patients with an asymptomatic stenosis. The poor ability of clinical risk factors to predict stroke has been attributed to the fact that the risk factors for atherosclerosis are present in nearly all patients with asymptomatic carotid stenosis.

Combination of Features and Calculation of Stroke Risk in Individual Patients

Stenosis, history of contralateral TIAs or stroke, GSM, plaque area, and presence of DWA proved to be not only associated with the development of future strokes in a univariate but also in a multivariate analysis [23]. In a Cox proportional hazard model, they were shown to be independent predictors of future events. On the basis of this model, the risk of any patient could be calculated (see "On Line Data Supplement" of reference [23]). Alternatively it can be obtained from risk tables (Fig. 8.17) derived from this model.

In the second analysis of the ACSRS, the JBA was included [24], and a new model was developed consisting of

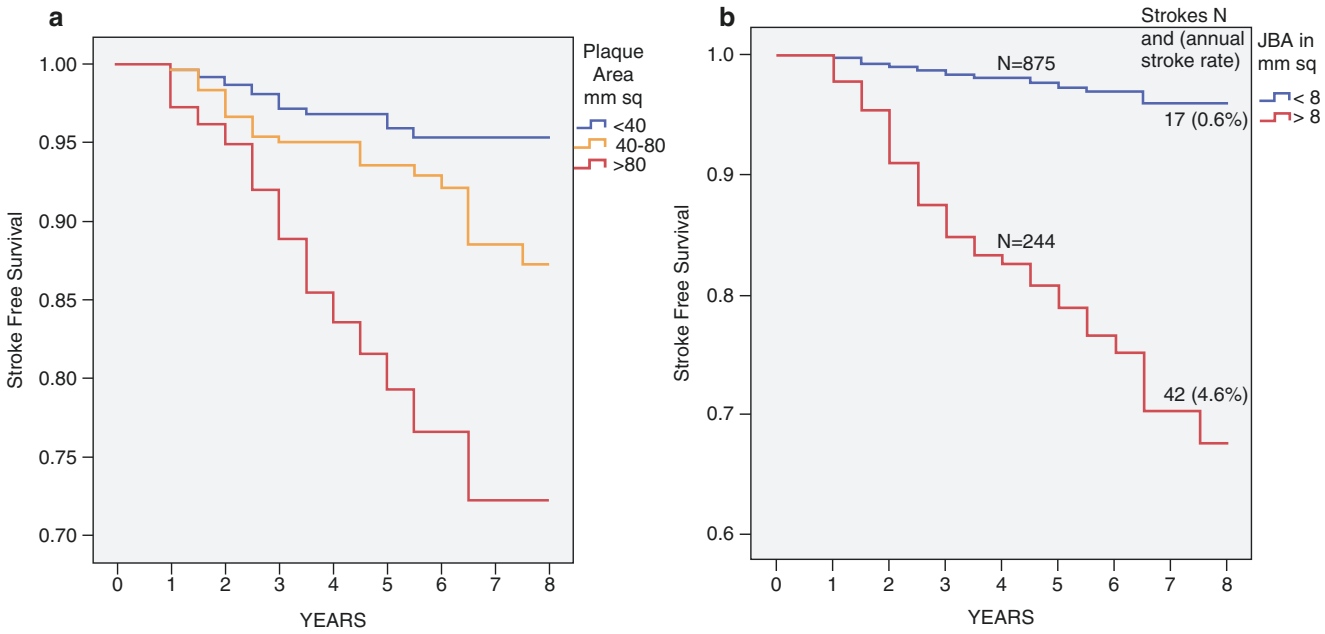

Fig. 8.15 Kaplan–Meier plots showing ipsilateral cerebral ischemic stroke-free survival stratified by (**a**) size of juxtaluminal plaque area: log rank *P* for trend <0.001and (**b**) by juxtaluminal plaque area less than 8 mm^2 or more than 8 mm^2, log rank *P* for trend <0.001. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

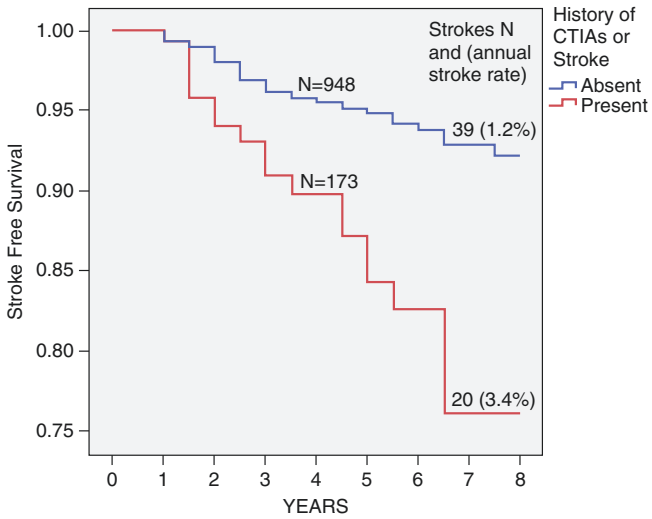

Fig. 8.16 Kaplan–Meier plot showing ipsilateral cerebral ischemic stroke-free survival stratified by the presence or absence of history of contralateral TIA (CTIA) or stroke: log rank *P* for trend <0.001. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

only four independent predictors: stenosis, JBA, history of contralateral TIAs or stroke, and presence of DWA [24].

The predicted 5-year percentage stroke rate (observed; 95% CI) was <5% (very low risk) in 654 (1%; 0.2–2), 5–9.9% (low risk) in 225 (8%; 5–13), 10–19.9% (moderate risk) in 156 (12%; 7–18), and ≥20% (high risk) in 86 patients (29%; 14–33). Of the 923 patients with ≥70% stenosis, 495 were included in the very low, 202 in the low, 142 in the moderate, and 84 in the high-risk group.

Semiautomated Method of Image Analysis and Stroke Risk Prediction

The "Plaque Texture Analysis Software" version 4.2 (LifeQ Medical; info@lifeqmedical.com) has now incorporated the calculation of risk for an individual patient based on the Cox model in the ACSRS study [23]. It provides a report of the measurement of key texture features including the predicted annual stroke risk (Fig. 8.17). The software is powerful yet user-friendly so that it can be used in all vascular laboratories or vascular departments. It has overcome the difficulties of image analysis and associated time-consuming procedures. The difficulty has now shifted to image capture and the essential training of ultrasonographers (see below).

STENOSIS 50-79% NASCET (n=598)
6 months to 8 year follow-up

Plaque Area (mm^2)	No history of Contralateral TIAs or Stroke			History of Contralateral TIAs or Stroke		
>80	1.0%	2.2%	4.4%	2.2%	5.2%	8.7%
40-80	0.5%	1.0%	2.1%	1.0%	2.5%	5.0%
<40	0.2%	0.7%	1.5%	0.9%	1.7%	3.5%
	≥30	15-29	<15	≥30	15-29	<15
		GSM			GSM	

Annual Stroke Rate %: ≥4 | 3.0-3.9 | 2.0-2.9 | 1.0-1.9 | < 1.0

STENOSIS 80-99% NASCET (n=325)
6 months to 8 year follow-up

Plaque Area (mm^2)	No history of Contralateral TIAs or Stroke			History of Contralateral TIAs or Stroke		
>80	1.2%	3.4%	5.9%	2.7%	4.0%	10.0%
40-80	0.6%	1.5%	3.0%	1.5%	3.5%	6.5%
<40	0.5%	1.0%	2.1%	1.0%	2.5%	4.7%
	≥30	15-29	<15	≥30	15-29	<15
		GSM			GSM	

Annual Stroke Rate %: ≥4 | 3.0-3.9 | 2.0-2.9 | 1.0-1.9 | < 1.0

Fig. 8.17 Estimated percent risk of annual ipsilateral ischemic cerebral stroke for patients with 50–79% (*upper table*) and 80–99% (*lower table*) ECST stenosis. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

General Remarks and Conclusions

The ACSRS is the largest prospective study of patients with asymptomatic carotid artery stenosis undergoing medical intervention alone. The results demonstrate that a number of baseline clinical characteristic and ultrasonic plaque features are independent predictors of subsequent ipsilateral stroke.

This study is unique not only because of the relatively large number of patients studied but also because, in contrast to previous studies that had concentrated on one feature only, it shows how plaque characteristics can add significantly to the improvement of risk stratification. It also provides a method that allows risk estimation for any patient.

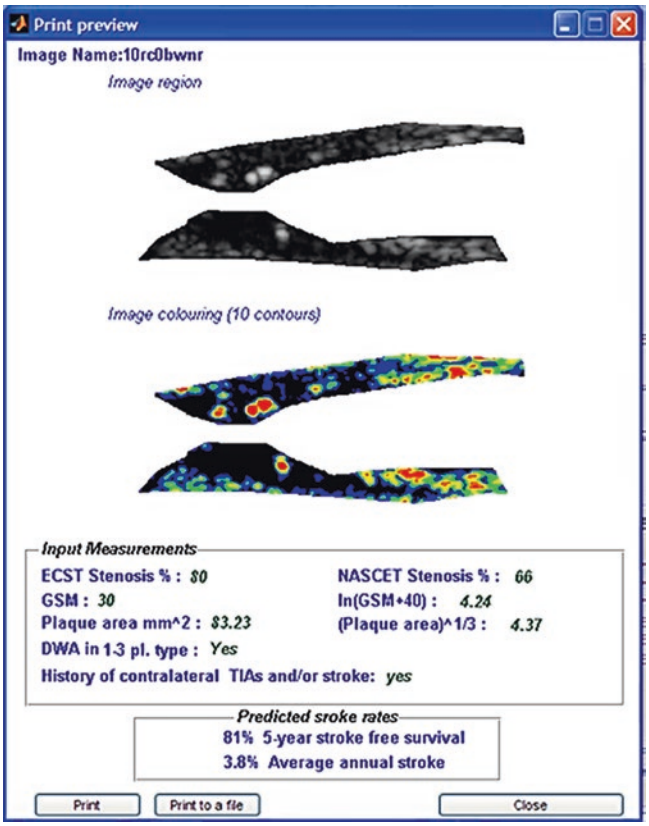

Fig. 8.18 Report produced by the "Plaque Texture Analysis Software" version 4.2. It includes the normalized plaque image, the color-contoured plaque image, the texture features, and their transformations as used in the Cox model and the predicted annual stroke rate [23]. From Nicolaides A, et al. Ultrasound and Carotid Bifurcation Atherosclerosis. Springer 2012. Reprinted with permission

Ultrasonic imaging is to a certain extent operator dependent. This can be overcome by training ultrasonographers in equipment presets and image capture, also by performing image normalization with computerized analysis. The importance of training vascular ultrasonographers in equipment settings and plaque imaging for optimal results cannot be overemphasized.

A limitation of the ACSRS study was that the medical management of patients was according to what was considered best medical therapy at each center at that time. At each center the clinician in charge was free to change therapy according to evolving indications. At the beginning of the study, only 84% of patients were on antiplatelet therapy and only 25% on lipid-lowering therapy. In addition, the intensity of the treatment varied and unlike current guidelines very few patients were treated to target cholesterol level. In addition, this "freedom" in management resulted in 129 (11.5%) patients having a carotid endarterectomy in the absence of symptoms soon after the results of the ACST were published. Despite this, follow-up to an event, to death, or to the end of the study was achieved in 87% of patients.

The clinical implication of the ACSRS study is that clinical and ultrasonic plaque features can be used to stratify risk and may lead to refinement of the indications for carotid endarterectomy. The availability of user-friendly software for image analysis and automatic calculation of risk can make the method part of routine practice in the vascular laboratory.

Validation of predicted risk in this study was limited since this was done internally, that is, for the same group of patients on whom the score was developed. The findings need to be validated in additional prospective observational studies using current medical intervention or in the medical arm of randomized controlled trials comparing carotid endarterectomy plus medical intervention to medical intervention alone.

The databases of plaque images from both the cross-sectional study and the ACSRS are a valuable source for exploring and testing new methods of image analysis and new algorithms for calculation of risk. The experience of the authors is available to all who wish to embark on future studies. Training courses for image capture and analysis are now established.

Review Questions

1. In a cohort of patients with > 50% asymptomatic carotid stenosis, operation (CEA) in those with ≥80% stenosis will prevent only ___ of strokes that will occur in the subsequent 5 years.
   a. 20%
   b. 30%
   c. 40%
   d. 50%
   e. 60%

2. Reproducible measurements of gray scale in ultrasound images of plaque became possible because of:
   a. Higher resolution of modern equipment
   b. High dynamic range
   c. Image normalization
   d. High pixel density
3. In patients with asymptomatic carotid stenosis, stroke is extremely unlikely to occur in the presence of:
   a. 50–70% stenosis
   b. Type 4 plaque
   c. Uniformly echolucent (homogenous) plaque
   d. Heterogenous plaque

4. Following image normalization and risk stratification using a combination of plaque texture features in a cohort with > 70% stenosis (NASCET), stroke risk was greater than 2% per year in:
   a. 10% of patients
   b. 25% of patients
   c. 35% of patients
   d. 45% of patients

Answer Key

1. c
2. c
3. b
4. b

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