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3D Ultrasound Measurement of Change in Carotid Plaque Volume

A Tool for Rapid Evaluation of New Therapies

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Background and Purpose—New therapies are being developed that are antiatherosclerotic but that lack intermediate end points, such as changes in plasma lipids, which can be measured to test efficacy. To study such treatments, it will be necessary to directly measure changes in atherosclerosis. The study was designed to determine sample sizes needed to detect effects of treatment using 3D ultrasound (US) measurement of carotid plaque.

Methods—In 38 patients with carotid stenosis >60%, age±SD 69.42±7.87 years, 15 female, randomly assigned in a double-blind fashion to 80 mg atorvastatin daily (n=17) versus placebo (n=21), we measured 3D plaque volume at baseline and after 3 months by disc segmentation of voxels representing carotid artery plaque, after 3D reconstruction of parallel transverse duplex US scans into volumetric 3D data sets.

Results—There were no significant differences in baseline risk factors. The rate of progression was 16.81±74.10 mm^3 in patients taking placebo versus regression of −90.25±85.12 mm^3 in patients taking atorvastatin ($P<0.0001$)

Conclusions—3D plaque volume measurement can show large effects of therapy on atherosclerosis in 3 months in sample sizes of ≈20 patients per group. Sample sizes of 22 per group would be sufficient to show an effect size of 25% that of atorvastatin in 6 months. This technology promises to be very useful in evaluation of new therapies. **(*Stroke*. 2005; 35:1904-1909.)**

Key Words: atherosclerosis ■ carotid artery plaque ■ ultrasonography

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With the completion of the human genome project, it is anticipated that many new therapeutic targets will be identified, and new therapies will be developed. One example is apolipoprotein A1 (ApoA1) Milano,[1–3] which was found to be protective against vascular events in carriers of this trait, and which led to a therapy that regressed coronary atherosclerosis in a matter of weeks.[4] Another potential example of such novel therapy is the inhibitors of acyl-coenzyme A:cholesterol acyltransferase, which are powerfully antiatherosclerotic in animal models but have little effect on plasma lipids in human subjects.[5–9]

Without a way of measuring efficacy, it would not be possible to develop such drugs because the duration and cost of studies based on vascular end points such as myocardial infarction or stroke would be excessive. Therefore, it will be necessary to use intermediate end points based on progression of atherosclerosis for dose-finding studies and for early proof of principle studies to demonstrate efficacy and thereby make it feasible to go on to larger studies based on end points.

Intravascular ultrasound (US) measurement of coronary plaque volume has been used to show efficacy of antiatherosclerotic therapies,[4,10] but this approach is invasive, potentially risky, and very expensive. Noninvasive approaches including measurement of carotid intima-media thickness (IMT) and coronary calcification have been used, but these approaches have relatively high cost because of large sample sizes and long durations of therapy, as well as other drawbacks relating to their biology.[11]

We have shown that carotid plaque area measured by US is a strong predictor of cardiovascular outcomes.[12] Here we report the results of the first study using this methodology for measuring effects of treatment. The purpose was to determine what sample size would be required to show effects of therapy on progression of carotid plaque volume. We studied 80 mg atorvastatin daily versus placebo for 3 months; this high dose of atorvastatin was used to maximize the likelihood of a measurable effect.

Methods

Study Population

We enrolled 53 patients with asymptomatic carotid stenosis >60% as defined by carotid Doppler flow velocities (validated against 200

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angiograms in which stenosis was measured in the North American Symptomatic Carotid Endarterectomy Trial), who were participating in a long-term follow-up study to investigate imaging methods that may identify high risk for cardiovascular events. According to Canadian consensus guidelines, endarterectomy is not routinely offered to patients with asymptomatic stenosis because in actual practice, the risk of endarterectomy is higher than the 3% risk in the clinical trials on which benefit is predicated.[13] This was discussed with the patients, and all who agreed to this approach and volunteered for the study were randomized. Patients who were taking lipid-lowering medication underwent a 6-week washout before randomization. Patients with a previous history of angina or myocardial infarction were excluded for safety reasons, but because carotid stenosis is associated with a high risk of cardiac events,[14] we did not wish to expose patients to a long duration of placebo therapy. All subjects gave consent to a protocol approved by the University of Western Ontario standing board of human research ethics and were randomized to placebo versus 80 mg atorvastatin daily for a duration of treatment of 3 months. Subjects were allocated in a double-blind fashion to identical placebo or 80-mg atorvastatin tablets (Lipitor) provided in a randomized sequence by Pfizer Canada Inc.

Imaging

Carotid US scans were performed at the Imaging Research Laboratories, Robarts Research Institute, using a Philips/ATL HDI 5000 US machine (Philips/ATL). An L12–5 probe with a central frequency of 8.5 MHz was used in the composite imaging (SonoCT) mode. The probe was attached to a motorized linear mover driven by a Life Imaging Systems L3Di 3D US acquisition system (Life Imaging Systems).[15–17] The acquisition system consisted of a Pentium III computer with a frame grabber digitizing 2D frames at 30 Hz from the US machine as the probe was moved along the neck at a uniform speed of 3 mm/s without cardiac triggering.[18] 3D volumes were constructed using the acquired frames and displayed using multiplanar reformatting.[14]

Imaging was conducted at baseline and 3 months later. Subjects were imaged while recumbent on a gurney with their upper torso inclined ≈15°. Both carotids were scanned multiple times (usually 4 to 5) over a scan distance of ≈4 cm along the carotid arteries, with the bifurcation located as closely as possible to the center of the volume. We reported previously[18] that using phantoms with known plaque volume ranging from 68.2 to 285.5 mm^3, we obtained a mean accuracy in plaque volume measurement of 3.1±0.9%; the SD in plaque volume measurement depended on the volume of the plaque, and was 4.0±1.0% and 5.1±1.4% for intraobserver and interobserver measurements, respectively.[18] In addition to studies with test phantoms, we investigated the observer variability in the measurement of plaque volume with 3D US images of 40 individuals with carotid plaques ranging from 37.4 to 604.1 mm^3. Our results demonstrated that the intraobserver and interobserver measurement reliability were 94% and 93.2%, respectively. The coefficient of variation (SD divided by the mean) of plaque volume measurement decreased with plaque volume from 27.1% to 2.2% over the range of plaque volumes measured. The variability of measurements from repeat 3D US scans was not different from that of measurements from single scans ($P=0.867$).[19]

Measurements

From the set of images obtained for each patient, the best image was selected on the basis of the position of the bifurcation in the volume and image qualities such as shadowing, cardiac motion, etc. The selection produced 1 volume for the left and right carotid arteries at baseline and follow-up for each subject. Some subjects were excluded from the measurements because of poor image quality or excessive carotid artery pulsatility.

Plaque volume measurements were performed with 3D Quantify software program (developed in our laboratory) using the disc segmentation method,[17,18] which involved outlining the plaque in sequential transverse slices, summing the calculated areas in each slice, and multiplying by the interslice distance. An operator (C.C.B.) who was experienced in looking at 3D US images was selected to make the measurements. The operator was blinded to whether the subject was receiving active or placebo therapy and was blinded to the sequence of the scans. All measurements were made from the bifurcation proximally along the common and distally along the external and internal carotids. This method was chosen because we have previously shown that variability in measurement resulted from scanning that began at the ends of plaques.[19] The entire vessel was outlined manually using an interslice distance of 1 mm, an interval which has been shown to optimize accuracy and reliability.[19] These contours were used to create a surface plot of each vessel and plaques and allowed for easy determination of the bifurcation.

During each imaging session, it was not possible to position the bifurcation in the midpoint of the scan with great accuracy. To reduce variability attributable to shifting of the position of the bifurcation in the images, each image was carefully examined to determine what would be the best possible distance over which to measure the plaque volumes. The distance used had to be usable superior and inferior to the bifurcation, at each time point. Total distances measured ranged from 1.8 to 3.6 cm (mean 2.8 cm).

Once the distance to be measured for each patient was determined, 3D Quantify allowed the user to set an axis through the volume along which the measurement steps would progress. The program automatically calculated the step size such that the first and last slice on the parallel axis were excluded from the measurement. All step sizes were ≈1 mm.

Before the manual planimetry was performed, the window and level were set so that the images presented a high contrast. At each step, points were laid down by clicking a cursor at regular intervals around the plaque. Each plaque was followed throughout the measurement distance or to its conclusion if that occurred within the measurement distance. If there were multiple plaques perceived within a slice, then that slice was returned to the volume and the process repeated for the next plaque. The sum of all plaque volumes within the measured segment was recorded for each patient at baseline and 3 months. Figure 1 shows the procedure for measurement of plaque volume. Differences were determined by subtracting the 3-month total volume from the baseline total volume in cubed millimeters.

To test operator variability, 30 3D images were randomized and blinded to the operator, and each image was measured 5 times to determine a mean volume and SD.

Plaque characteristics were classified according to the following American Heart Association classifications: I-II near normal, with some thickening; III diffuse intimal thickening, no calcification; IV-V lipid/necrotic core, fibrous tissue with possible calcification; VI complex plaque with surface defect, hemorrhage or thrombosis; VII primarily calcified plaque; and VIII fibrosis with calcification.[20]

Statistical Methods

Data were entered and analyzed in SPSS 11.0. ANOVA was used to test for significant differences between treatment groups with respect to parametric variables; nonparametric variables were compared using χ^2 analysis. The Kolmogorov–Smirnov test was used to assess whether the measured plaque volumes had a normal distribution. Sample size estimates were computed using the calculator provided by the University of California at Los Angeles Web site. Analysis of covariance, with treatment assignment as a fixed factor and baseline plaque volume as a covariate, was also performed in the general linear model.

Results

From an initial cohort of 53 patients, baseline and 3-month plaque volume measurements were obtained in 38 cases; these measurements form the basis of this report. Reasons for exclusion were that 13 did not have a second US measurement (1 died before the second US, 2 underwent carotid endarterectomy, 3 had a transient ischemic attack or stroke, and 7 did not return for the second measurement). In addition,

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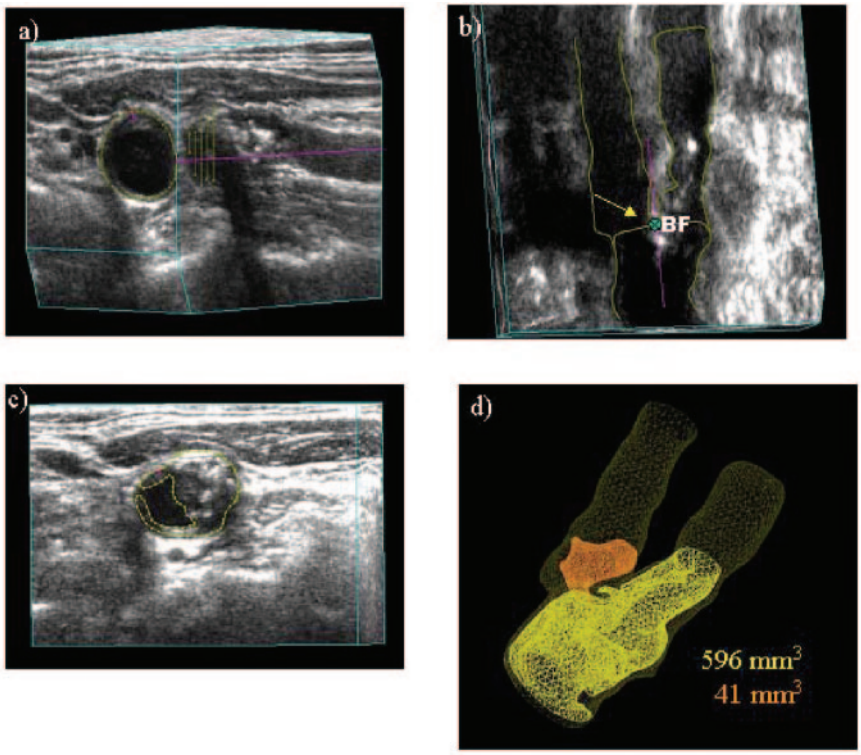

Figure 1. Procedure for determining plaque volumes from 3D US images. a, An approximate axis of the vessel is selected in a longitudinal view (colored line) and the internal elastic lamina and lumen boundary are outlined (yellow). b, Using the surfaces generated by the vessel contours and the 3D US image, the position of the bifurcation (BF; yellow arrow) is determined and marked. The axis of the vessel is selected based on the bifurcation point, and marked along the branch as far as the plaque can be measured (colored line). This axis will be used as a reference for distance measurements. c, All plaques within the measurable distance are outlined, different colors being used for each separate plaque to aid in identification. d, Volumes are calculated for each plaque, and surfaces of the vessel wall and plaques are generated to better visualize the plaques in relation to the carotid arteries.

images from 2 patients were not used because of poor image quality prohibiting the plaque measurements.

As shown by the baseline characteristics in Table 1, subjects were middle-aged or elderly vascular patients with the expected risk factors on treatment. There were no significant differences in risk factors nor in treatments other than the study medication (such as angiotensin-converting enzyme inhibitors, antiplatelet agents, or previous treatment with statins) between the 2 treatment groups. Baseline plaque volume (mean±SD) was 722.0±473.72 mm^3 for the placebo group and 689.53±409.99 mm^3 for the atorvastatin group (P=0.83); 3-month plaque volumes were 738.81±494.66 mm^3 on placebo and 599.29±355.19 mm^3 on atorvastatin.

TABLE 1. Baseline Characteristics of the Subjects

		Mean	SD	Significance
Age	Placebo	70.14	9.41	
	Atorvastatin	68.06	8.60	0.49
Total Cholesterol	Placebo	4.40	0.61	
	Atorvastatin	4.35	0.89	0.85
Triglycerides	Placebo	1.53	0.55	
	Atorvastatin	1.32	0.65	0.29
High-density lipoprotein	Placebo	1.22	0.36	
	Atorvastatin	1.47	0.45	0.08
Low-density lipoprotein	Placebo	2.51	0.72	
	Atorvastatin	2.29	0.78	0.38
Systolic blood pressure	Placebo	146.48	22.44	
	Atorvastatin	147.35	18.75	0.90
Diastolic blood pressure	Placebo	73.29	15.26	
	Atorvastatin	72.53	13.31	0.87
Sex	Placebo		15 male, 6 female	0.20
	Atorvastatin		9 male, 8 female	
Smoking	Placebo		13 no, 8 yes	
	Atorvastatin		13 no, 4 yes	0.27
Diabetes	Placebo		17 no, 4 yes	
	Atorvastatin		15 no, 2 yes	0.44

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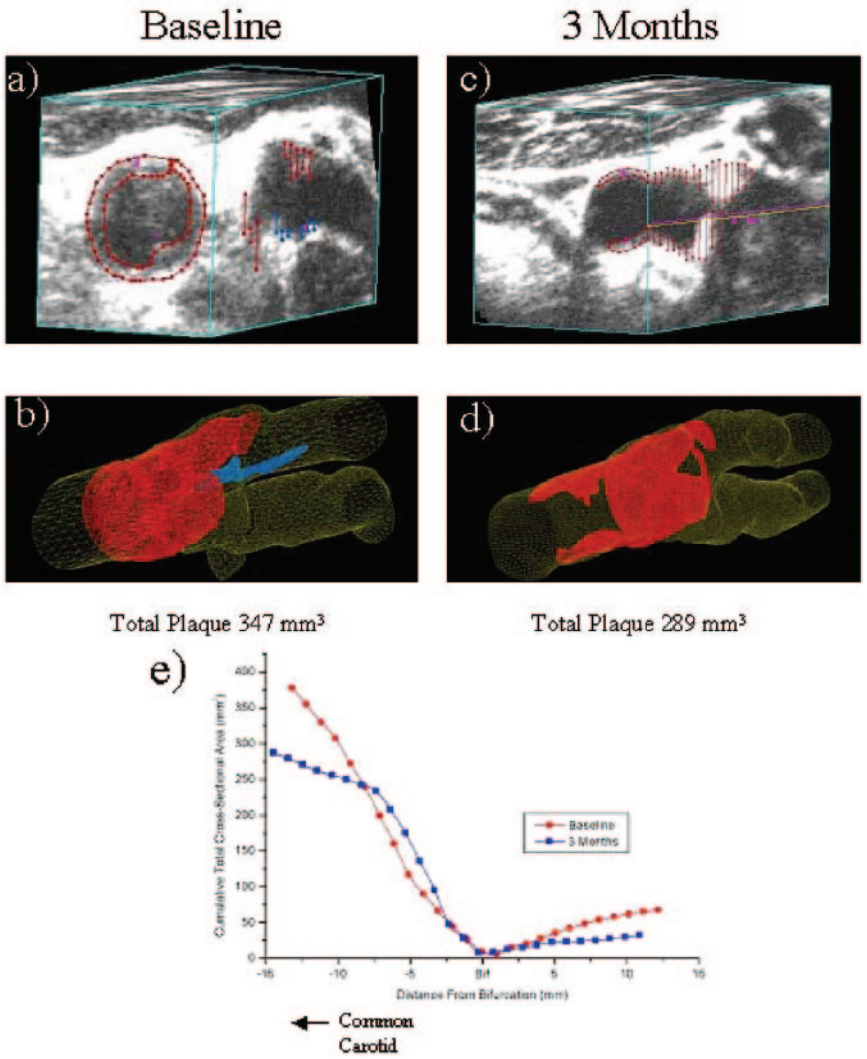

Figure 2. Comparison of plaque outlines and volumes for a patient on atorvastatin therapy. a, 3D US image showing a plaque outline in a transverse view for the baseline time point. b, Vessel wall (yellow) and plaques (red and blue) surfaces created with the contours in a; the total plaque volume was 347 mm^3. c, Plaque and vessel wall outlines at 3-month follow-up. d, Vessel wall and plaque surfaces for the 3-month follow-up using the outlines in c; the total plaque volume was 289 mm^3. e, Plot of plaque burden (plaque volume between the bifurcation and the given distance from the bifurcation) vs distance from the bifurcation showing where the plaque volume is changing in relation to the bifurcation point.

Figure 2 shows an example of plaque regression in a subject taking atorvastatin. Over 3 months, plaque volume increased on placebo by 16.81±74.10 mm^3, whereas on atorvastatin, there was significant regression of plaque by −90.25±85.12 mm^3 ($P<0.0001$; Figure 3). The operator variability was found to be 53 mm^3. Analysis of covariance gave essentially the same results; the estimated marginal means were: placebo progression 17.31±SE 17.20 mm^3 (95% CI, −17.6 to 52.23 mm^3) and atorvastatin −90.85±SE 19.12 mm^3 (95% CI, −160.39 to −55.93 mm^3; Figure 3; $P<0.0001$). (The SEs convert to SDs of 78.77, slightly smaller than the pooled variance of 80 used for the sample size estimates below.) Observed power was 0.98. There was no difference between the treatment groups with respect to plaque characteristics ($P=0.46$).

Sample Size Estimates

Table 2 shows sample size estimates for treatments with effect sizes compared with that of atorvastatin. Assuming that progression on placebo and regression on atorvastatin continue in a linear fashion, with equal variances (an SD of 80 mm^3, ie, slightly more than the average variance of the 2 groups), a treatment 25% as effective as atorvastatin would require 86 patients per group treated over 3 months, or 22 per group treated over 6 months to give a power of 90% to show a 2-tailed difference significant at the 0.05 level. Sample sizes using the results from the analysis of covariance were somewhat smaller.

The assumption of linear progression is consistent with our previous published experience with plaque area,[12] which bears a strong linear relationship to plaque volume ($R=0.93$).[21]

Discussion

We found that 3D US measurement of plaque progression demonstrated statistically significant effects of a highly efficacious therapy in a small sample over 3 months. This methodology promises to be extremely useful in evaluation of new therapies. A major advantage of 3D plaque measurement relates to the way that plaques grow. Plaque progresses along the vessel (in the axis of flow) 2.4× faster than it thickens[22] and also grows circumferentially. Therefore, methods that capture longitudinal and circumferential growth and regression of plaque are inherently more sensitive to change in plaque over time and with therapy than methods limited to measurement of change in thickness.

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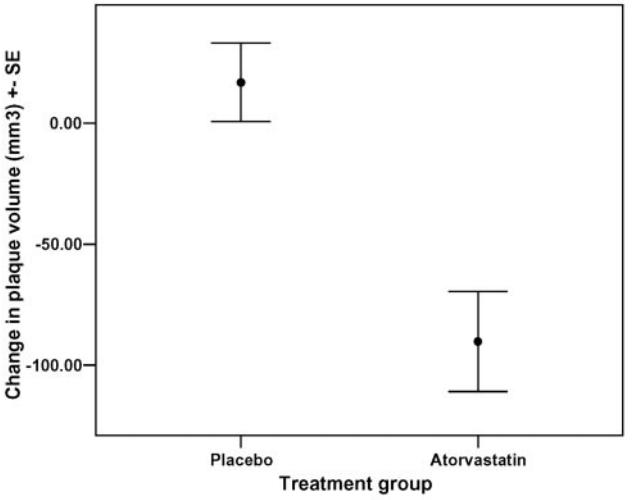

Figure 3. Mean change in plaque volume ±95% CIs from baseline to 3 months. Subjects taking placebo had progression, whereas those taking atorvastatin had significant regression of plaque in 3 months ($P<0.0001$).

By comparison, measurement of IMT requires much larger sample sizes for much longer times. Bots et al[23] reported that a treatment with an effect size of 30% would require 468 patients followed for 2 years to give a power of 80% to show an effect significant at the 0.05 level. A similar sample size (366 per group over 2 years) was calculated for the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE) trial comparing effects of ramipril and vitamin E on progression of IMT.[24] Newer methods of IMT measurement using automated edge detection[25] may reduce sample sizes by reducing variability of measurement[25] to as low as 68 per group followed for 1 year to give a 90% power of showing a 30% treatment effect (personal communication, Dr Jacques Barth, May 2004). However, there remain important differences in biology between IMT and plaque measurement. These have been discussed recently.[26] IMT represents mainly hypertensive medial hypertrophy, and only 15% to 17% of IMT is explained by traditional coronary risk factors;[27] in contrast, 52% of plaque is explained by these factors,[12,28] thus, treatments expected to affect atherosclerotic plaque should affect plaque volume more than IMT.[11]

TABLE 2. Range of Sample Sizes Required for Various Effect Sizes and Duration of Treatment

Power	Effect Size (% of atorva)	Regression in mm^3	Sample Size Per Group
To show treatment effect in 3 months; placebo progression 16.81±80 mm^3			
0.9	10%	−9	203
0.9	25%	−23	86
0.9	50%	−45	36
0.9	75%	−68	20
To show treatment effect in 6 months, placebo progression 33.62±80 mm^3/6 months			
0.9	10%	−18	51
0.9	25%	−45	22
0.9	50%	−90	9
0.9	75%	−135	6

Based on equal variances, with a SD of 80 mm^3, assuming linear progression on placebo and regression on active treatment; power of 90%, 2-sided significance 0.05; sample sizes for treatment efficacy compared with atorvastatin (eg 10% as effective as atorvastatin, 25% as effective, etc).

Measurement of coronary calcium as a means to study efficacy of antiatherosclerotic therapy has been reviewed recently.[29] The sample sizes required in the past have usually been ≈200 per group over a year;[30] however, recently, some studies have shown differences in effects of treatment with smaller samples and durations of therapy.[29] Again, the issue of biological differences among noninvasive phenotypes may be important; calcification may reflect different biological processes[31] and therefore respond to different therapies than measurement of plaque.[11,30]

Measurement of coronary plaque volume by intravascular US has also shown slowing of plaque progression with high-dose atorvastatin compared with pravastatin at a lower dose, but the sample size was 250 per group treated for 18 months.[10] Recently a recombinant ApoA1 Milano/phospholipid complex was shown to regress coronary plaque volume in ≈27 patients per group in 5 weeks.[4] Those results were very similar to ours; however, the much higher cost of IVUS (≈60-fold higher), combined with the risk of coronary angiography, makes carotid plaque volume measurement a much preferable approach to studying effects of therapy for atherosclerosis.

Interference with images by calcification, a concern commonly raised in relation to US measurements, was not a significant problem because several images were obtained at each visit using compound imaging with Sono-CT, which permitted images to be obtained that were not materially affected by the calcification. Calcification was not a reason for exclusion from the study nor the measurements.

We have shown previously that total carotid plaque area (the sum of cross-sectional areas of all plaques in the carotid arteries, measured in longitudinal views of each plaque) is a strong predictor of stroke, death, and myocardial infarction.[12] Patients in the top quartile of baseline plaque area have, after adjustment for age, sex, blood pressure, cholesterol, pack years of smoking, homocysteine, diabetes, and treatment of lipids and blood pressure, a relative risk of 3.4 for stroke, death, and myocardial infarction compared with patients in the lowest quartile of baseline plaque area. Patients with progression (≈45% of cases) had twice the risk of those with regression (35% of cases) or stable plaque (20% of cases).[12] Plaque volume and plaque area are closely related ($R=0.93$);[21] therefore, it is expected that plaque volume will also be a strong predictor of outcomes; long-term studies will be needed to confirm that.

Conclusions

Measurement of 3D plaque volume represents a powerful tool for measuring effects of new therapies on atherosclerosis in small numbers of patients treated for only 3 to 6 months. This technology promises to be very useful in investigation of new antiatherosclerotic therapies.

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