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Carotid plaque area: A tool for targeting and evaluating vascular preventive therapy

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Carotid Plaque Area

A Tool for Targeting and Evaluating Vascular Preventive Therapy

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Background and Purpose—Carotid plaque area measured by ultrasound (cross-sectional area of longitudinal views of all plaques seen) was studied as a way of identifying patients at increased risk of stroke, myocardial infarction, and vascular death.

Methods—Patients from an atherosclerosis prevention clinic were followed up annually for up to 5 years (mean, 2.5 ± 1.3 years) with baseline and follow-up measurements recorded. Plaque area progression (or regression) was defined as an increase (or decrease) of ≥ 0.05 cm² from baseline.

Results—Carotid plaque areas from 1686 patients were categorized into 4 quartile ranges: 0.00 to 0.11 cm² (n=422), 0.12 to 0.45 cm² (n=424), 0.46 to 1.18 cm² (n=421), and 1.19 to 6.73 cm² (n=419). The combined 5-year risk of stroke, myocardial infarction, and vascular death increased by quartile of plaque area: 5.6%, 10.7%, 13.9%, and 19.5%, respectively ($P < 0.001$) after adjustment for all baseline patient characteristics. A total of 1085 patients had ≥ 1 annual carotid plaque area measurements: 685 (63.1%) had carotid plaque progression, 306 (28.2%) had plaque regression, and 176 (16.2%) had no change in carotid plaque area over the period of follow-up. The 5-year adjusted risk of combined outcome was 9.4%, 7.6%, and 15.7% for patients with carotid plaque area regression, no change, and progression, respectively ($P = 0.003$).

Conclusions—Carotid plaque area and progression of plaque identified high-risk patients. Plaque measurement may be useful for targeting preventive therapy and evaluating new treatments and response to therapy and may improve cost-effectiveness of secondary preventive treatment. (*Stroke*. 2002;33:2916-2922.)

Key Words: atherosclerosis ■ cerebrovascular disorders ■ risk ■ stroke prevention ■ ultrasonography

A worldwide epidemic of cardiovascular and cerebrovascular disease is anticipated.¹ Faced with an increasing number of patients at high risk of vascular events, it will be necessary to improve methods for identifying which patients require aggressive medical therapy. One approach is to target therapy using traditional risk factors with instruments such as Sheffield tables.² It has also been suggested that physicians use absolute risk reductions for making treatment decisions.³ For making decisions about resource allocation, the number of patients that need to be treated to prevent an additional event can be used.⁴ Risk-based guidelines do not obviate the need to set treatment thresholds,⁵ but they are helpful in deciding which patients require aggressive management.⁶

Estimating risk on the basis of factors such as age, sex, blood pressure, smoking, and lipid levels is imperfect. These Framingham risk factors explain only half of the variance in coronary risk.⁷ Waiting until patients have symptomatic vascular disease is also problematic because about half of patients who experience a stroke or myocardial infarction

have no warning symptoms. It would be desirable, therefore, to have noninvasive methods for identifying patients at higher risk by the presence of preclinical atherosclerosis. Simon and others^{2,8,9} have suggested that methods such as intimal-medial thickness (IMT), plaque in extracoronary arteries, coronary calcification, wall rigidity in aorta and peripheral arteries, and abnormal endothelium-dependent vasodilation and blood rheology may optimize the management of hypertension. Noninvasive detection of atherosclerosis should ideally involve methods that are safe, inexpensive, noninvasive, reliable, and reproducible. Additionally, their results should correlate with the extent of atherosclerotic disease and have high positive and negative predictive value for clinical events.¹⁰

For the past 7 years, measurements of carotid plaque area at the patients' first visit and at follow-up visits have been recorded at the Atherosclerosis Prevention Clinic and have been used to determine the effectiveness of different therapies. Patients whose carotid atherosclerosis was progressing despite control of traditional risk factors were investigated for

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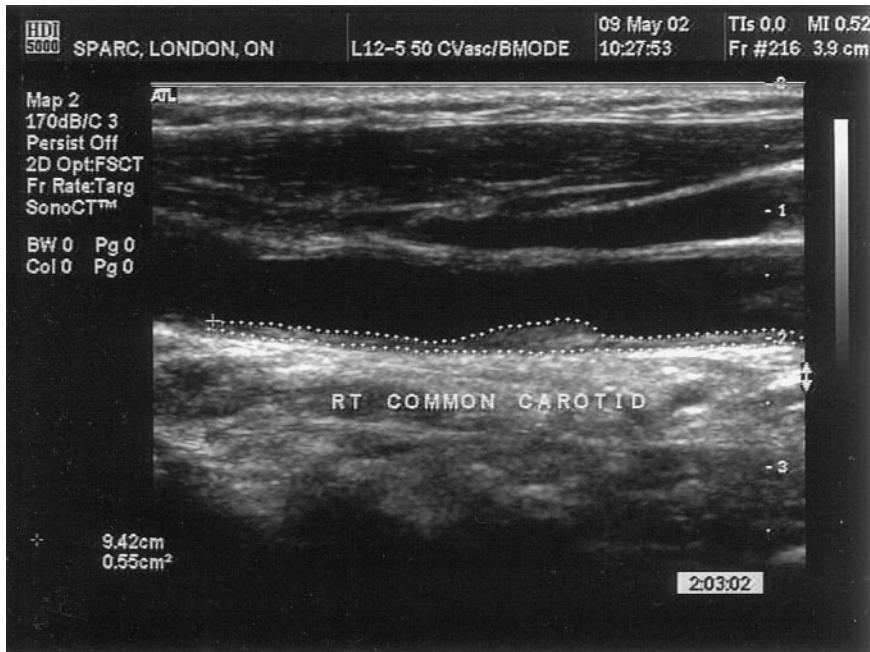


Figure 1. Measurement of carotid plaque area. Each plaque was measured in a longitudinal view in the plane in which the plaque is maximal. Image was frozen and magnified on the screen, and a cursor was traced around the perimeter of the cross section. Microprocessor in the duplex scanner displays cross-sectional area of plaque (cm^2). Plaque shown is in the right common carotid artery and measures 0.55 cm^2 .

new risk factors, including plasma homocysteine and lipoprotein(a). The relationship between cardiovascular reactivity to mental stress and carotid plaque area has been previously reported.¹¹ Recently, it was reported that among patients whose plaque was progressing rapidly despite treatment of traditional risk factors, vitamin therapy for homocysteine halted the progression of carotid atherosclerosis.¹² Measurement of carotid plaque, combined with multiple regression modeling using traditional risk factors, has been used to define the quantitative trait “unexplained atherosclerosis” for genetic research.^{13,14}

The primary aim of the present study was to examine the relationship between baseline carotid plaque area and the subsequent risk of the combined outcome of stroke, myocardial infarction, and vascular death in this patient population. The effect of carotid plaque progression (or regression) on subsequent risk was a secondary aim.

Subjects and Methods

The patients for the present study were being followed up in the Premature Atherosclerosis Clinic and the Stroke Prevention Clinic of the University Campus of the London Health Sciences Center (London, Canada). Patients in the Premature Atherosclerosis Clinic were referred because of vascular disease not explained by usual risk factors such as age or because of a strong family history of vascular disease. Those referred to the Stroke Prevention Clinic were referred mainly because of a stroke or a transient ischemic attack and in some cases because of asymptomatic carotid stenosis.

Carotid plaque area was measured as described previously¹¹ with a high-resolution duplex ultrasound scanner (initially an ATL Mark 9, more recently an ATL 5000 HDI, Advanced Technology Laboratories). Plaque was defined as a local thickening of the intima $>1 \text{ mm}$ in thickness. Measurements were made in magnified longitudinal views of each plaque seen in the right and left common, internal, and external carotid arteries. The plane in which the measurement of each plaque was made was chosen by panning around the artery until the view showing the largest extent of that plaque was obtained. The image was then frozen and magnified, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The microprocessor in the scanner then

displayed the cross-sectional area of the plaque (Figure 1). The operator then moved on to the next plaque and repeated the process until all visible plaques were measured. The sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as total plaque area. Intraobserver reliability (intra-class correlation) was 0.94 for repeated measurements.¹¹ For the purpose of demonstrating generalizability of our results to other ultrasound laboratories and clinics, we carried out a study of interobserver reliability in which plaque area measurements in 25 patients were repeated a week apart by 2 technicians using 2 different machines. The senior technologist, who has been carrying out these measurements for 8 years and who performed all the measurements on which this article was based, used a new, high-resolution TL HDI 5000 scanner; the junior technologist, who has been doing such measurements for 1 year, used an ATL Mark 9 duplex scanner. The reliability (intraclass correlation) was 0.85, with the senior technician using the higher-resolution machine systematically measuring more plaque. Outcome events of stroke and myocardial infarction were ascertained first by a questionnaire at the patients’ annual visits and second by inspection of hospital charts for any admissions. Deaths were confirmed by death certificates either from the hospital charts or faxed from family physicians’ offices. In 2 cases, family physicians had retired, and records were unavailable; in those cases, cause of death was reported by the widow. (Both were sudden deaths classified as cardiovascular death.) Determination of outcomes was not blinded in a small number of cases (ie, some strokes evaluated by J.D.S.), but in most cases, outcomes occurred in settings other than the clinic. Because of the long length of follow-up, patients included in the present study were followed up in 2 studies to which they gave informed consent, depending on when they were first seen; protocol review numbers from the University of Western Ontario Ethics Review Board were 02391 and 07270. Only patients for whom complete data were available were included in the present study.

Statistical Analyses

Associations between baseline risk factors and the level of carotid plaque area were assessed through analysis of variance for continuous variables and a χ^2 test for dichotomous variables. The 5-year risks of combined outcome of stroke, myocardial infarction, and vascular death were estimated from discrete-time event-free survival curves with a complementary log-log regression model,¹⁵ which was also used to adjust for all the baseline characteristics listed in Table 1. The corrected-group-prognosis method was used to compute

TABLE 1. Baseline Patient Characteristics by Quartile of Carotid Plaque Area (cm²)

Patient Characteristic	0.00–0.11 (n=422)	0.12–0.45 (n=424)	0.46–1.18 (n=421)	1.19–6.73 (n=419)	P Value
Age, y	43.5	53.7	61.7	68.9	<0.001
Body mass index, kg/m ²	26.6	27.6	27.8	27.7	0.06
Pack-years of smoking	6.3	9.7	14.1	20.1	<0.001
Systolic pressure, mm Hg	129.2	135.3	144.1	150.4	<0.001
Diastolic pressure, mm Hg	79.8	80.6	80.5	79.6	0.52
Cholesterol, mmol/L	5.16	5.33	5.24	4.90	<0.001
Triglycerides, mmol/L	1.71	2.03	1.86	1.84	0.001
HDL, mmol/L	1.23	1.24	1.33	1.28	<0.001
Homocysteine, μmol/L	11.31	11.87	12.97	14.94	<0.001
Male sex	44.8	49.1	50.4	67.5	<0.001
Diabetes mellitus	1.7	4.9	10.4	18.6	<0.001
On lipid-lowering drugs*	19.7	38.4	59.6	73.5	<0.001
On antihypertensive drugs*	37.7	51.9	62.7	74.9	<0.001

Data in the upper portion of the table are mean values and in the lower portion are percentages.
*at the time of referral to the clinic.

adjusted risk estimates and adjusted event-free survival curves.¹⁶ The 5-year risks of stroke alone and of combined stroke and myocardial infarction were estimated with the same approach. The effect of plaque progression (and regression) on the risk of the combined outcome was analyzed as a time-dependent covariate, also after adjustment for all baseline characteristics. The relationships between baseline characteristics and plaque progression were assessed with a complementary log-log regression model. All statistical analyses were carried out with SAS 8.0 (SAS Institute Inc).

Results

A total of 1686 patients with a baseline carotid plaque area measurement were categorized into 4 ranges of carotid plaque area corresponding approximately to quartile cut points: 0.00

to 0.11 cm² (n=422), 0.12 to 0.45 cm² (n=424), 0.46 to 1.18 cm² (n=421), and 1.19 to 6.73 cm² (n=419). The mean±SD plaque area of each quartile was 0.03±0.04, 0.27±0.09, 0.78±0.21, and 2.33±1.05 cm², respectively.

Baseline patient characteristics are shown in Table 1. Carotid plaque area was strongly related to age. A mean difference of 25.4 years was observed between the age of subjects in the fourth and first quartiles. The striking relationship between age and carotid plaque area is illustrated in Figure 2, showing a marked increase between 45 and 70 years of age and a leveling after 70 years of age. Except for diastolic blood pressure and body mass index, all other

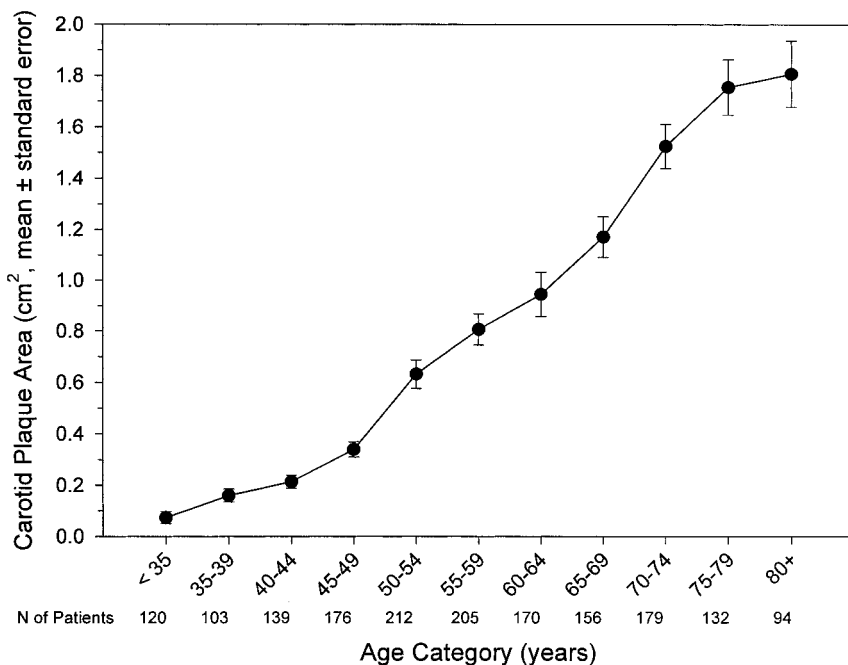


Figure 2. Increase in carotid plaque area with age. Some measurable plaque is present in most patients >45 years of age. Rapid increase in plaque area between 60 and 75 years of age may be associated with the impairment of mitochondrial function or loss of ability to handle oxidative stress. Apparent leveling off after 75 years of age may represent a survivor effect (ie, those with rapid progression may not survive to older age).

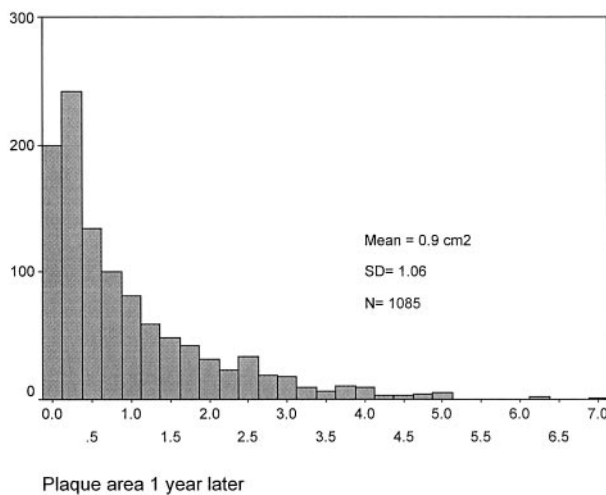
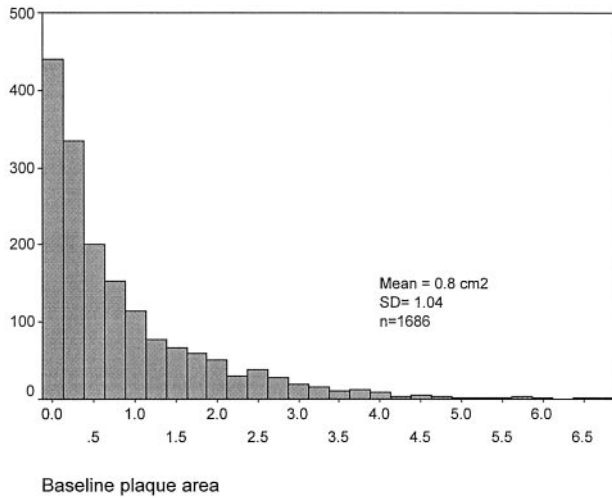


Figure 3. Distribution of plaque area at baseline and after 1 year. At baseline, 209 patients had no measurable plaque, and 22.6% of patients had <0.1 cm²; after 1 year, only 75 had no measurable plaque, and 15.7% had <0.1 cm². Distribution is heavily weighted to low plaque areas, with few patients having >3 cm² of total plaque area.

baseline characteristics in Table 1 were significantly associated with increased plaque area.

At baseline, 209 patients had no measurable plaque; after 1 year, only 75 had no measurable plaque. The distributions of plaque area at baseline and after 1 year are shown in Figure 3.

A total of 45 strokes, 94 myocardial infarctions, and 41 deaths (27 vascular, 12 cancer, and 2 other) occurred during a mean follow-up of 2.5±1.3 years (range, 0.1 to 5 years). The combined 5-year risk of stroke, myocardial infarction, and vascular death increased with increasing levels of plaque area (3-*df* likelihood ratio test, *P*<0.001; Table 2 and Figure 4). The increase in risk by plaque area quartile was weakly confounded by other baseline characteristics (as assessed by the small change between the adjusted and unadjusted relative risks) but remained statistically significant after adjustment (Table 2). Subjects in the highest quartile of plaque area were 3.5 times (95% CI, 1.8 to 6.7; *P*<0.001) more likely to have had a stroke, myocardial infarction, or vascular death

TABLE 2. Unadjusted and Adjusted 5-Year Risks and Relative Risks of Combined Outcome of Stroke, Myocardial Infarction, and Vascular Death by Quartile of Carotid Plaque Area (cm²)

Plaque Area	5-Year Risk (%)	Relative Risk (95% CI)	<i>P</i> Value
Unadjusted			
0.00–0.11	6.3	1.0*	
0.12–0.45	11.3	1.8 (1.1 to 3.0)	0.03
0.46–1.18	13.2	2.1 (1.2 to 3.5)	0.004
1.19–6.73	19.1	3.0 (1.8 to 4.9)	<0.001
Adjusted†			
0.00–0.11	5.6	1.0*	
0.12–0.45	10.7	1.9 (1.1 to 3.3)	0.02
0.46–1.18	13.9	2.5 (1.4 to 4.4)	0.001
1.19–6.73	19.5	3.5 (1.8 to 6.7)	<0.001

*Reference category.

†Adjusted for all baseline patient characteristics listed in Table 1.

than patients in the lowest quartile. Outcomes of stroke alone and of combined stroke and myocardial infarction yielded similar patterns of results (Table 3).

A total of 1085 patients had ≥1 annual carotid plaque area measurements. Plaque area progression (or regression) was

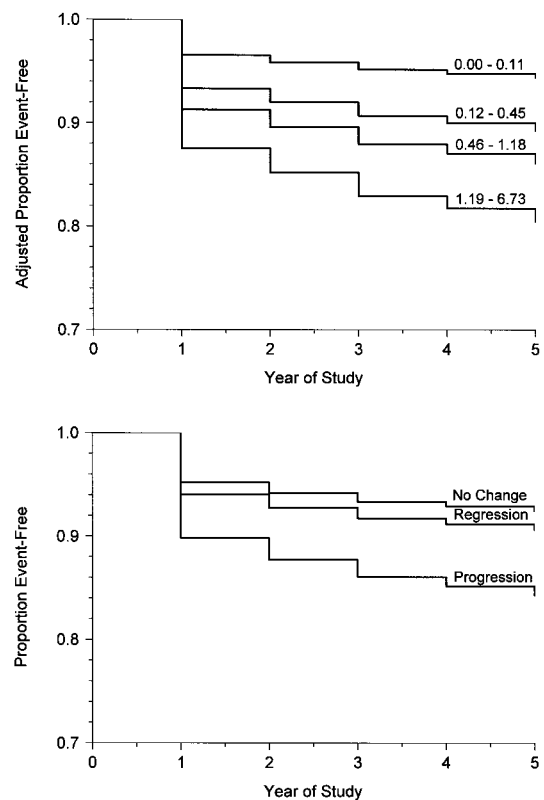


Figure 4. Risk-factor-adjusted event-free survival from stroke, myocardial infarction, and vascular death by quartiles of carotid plaque area (top; cm²) and by status of carotid plaque area progression or regression during follow-up (bottom). Plaque area regression was defined as a decrease of ≥0.05 cm² from baseline; progression was defined as an increase of ≥0.05 cm² from baseline; and no change was defined as either an increase or decrease of no more than 0.049 cm². Survival was adjusted for all baseline patient characteristics listed in Table 1.

TABLE 3. Adjusted 5-Year Risks and Relative Risks of Stroke Alone and of Stroke and Myocardial Infarction by Quartile of Carotid Plaque Area (cm²)

Plaque Area	5-Year Risk (%)	Relative Risk (95% CI)	P Value
Stroke Alone			
0.00–0.11	1.6	1.0†	
0.12–0.45	2.3	1.4 (0.4 to 4.6)	0.58
0.46–1.18	3.9	2.4 (0.7 to 7.6)	0.14
1.19–6.73	4.0	2.4 (0.7 to 8.8)	0.17
Stroke and MI			
0.00–0.11	4.8	1.0†	
0.12–0.45	9.3	1.9 (1.1 to 3.4)	0.02
0.46–1.18	12.3	2.5 (1.4 to 4.7)	0.001
1.19–6.73	14.0	2.9 (1.4 to 5.8)	0.002

*Adjusted for all baseline patient characteristics listed in Table 1.

†Reference category.

defined as an increase (or decrease) of $0. \geq 05$ cm² from baseline. This value corresponded to approximately the median change in carotid plaque area from baseline. Of the 1085 patients, 685 (63.1%) had carotid plaque progression, 306 (28.2%) had plaque regression, and 176 (16.2%) had no change in carotid plaque area over the period of follow-up. The occurrence of progression or regression of plaque area was associated with the combined outcome (2-*df* likelihood ratio test, $P=0.003$; Figure 4) after adjustment for all baseline characteristics listed in Table 1. The combined 5-year adjusted risk of stroke, myocardial infarction, and vascular death was 9.4% for patients with carotid plaque area regression, 7.6% for patients with no change in plaque area, and 15.7% for patients with plaque area progression. Patients who progressed were 2.1 times (95% CI, 1.2 to 3.6; $P=0.005$) more likely to have had a stroke, myocardial infarction, or vascular death than patients who had no change in plaque area. Among all the baseline characteristics, only increased age, higher cholesterol level, and male sex were statistically significant predictors of plaque progression, although the relative risks were all close to unity (Table 4).

TABLE 4. Adjusted Relative Risks of Plaque Progression

Patient Characteristic	Relative Risk (95% CI)	P Value
Age (per 10 years)	1.1 (1.1 to 1.2)	<0.001
Body mass index (per 10 kg/m ²)	0.9 (0.7 to 1.0)	0.12
Smoking (per 10 pack-years)	1.0 (1.0 to 1.1)	0.64
Systolic pressure (per 10 mm Hg)	1.0 (1.0 to 1.1)	0.28
Diastolic pressure (per 10 mm Hg)	0.9 (0.9 to 1.0)	0.11
Cholesterol (per 1 mmol/L)	1.1 (1.1 to 1.2)	0.001
Triglycerides (per 1 mmol/L)	1.0 (0.9 to 1.1)	0.95
HDL (per 1 mmol/L)	0.8 (0.6 to 1.0)	0.06
Homocysteine (per 5 μ mol/L)	1.0 (1.0 to 1.1)	0.48
Female sex	0.8 (0.7 to 0.9)	0.03
Diabetes mellitus	1.1 (0.8 to 1.4)	0.60
On lipid-lowering drugs*	1.1 (0.9 to 1.3)	0.21
On antihypertensive drugs*	1.2 (1.0 to 1.4)	0.08

*At the time of referral to the clinic.

Discussion

The results of the present study demonstrated that baseline carotid plaque area was a strong risk factor for the combined outcome of stroke, myocardial infarction, and vascular death and for the combined outcome of stroke and myocardial infarction. Measuring carotid plaque area adds to the arsenal of tools for identifying high-risk patients and is useful for targeting aggressive preventive therapy and testing new therapies. The fact that plaque progression also predicted outcome indicated that measurement of plaque in follow-up may be used to determine the effectiveness of therapy.

We speculate that the trend to better outcomes in patients with stable plaque than in those with regression may be explained by carotid endarterectomy, which often results in large reductions in plaque burden. Carotid endarterectomy patients are at high risk for death or myocardial infarction, even though endarterectomy significantly reduces risk of stroke.

It may seem unusual that adjustment for age, sex, systolic blood pressure, serum cholesterol, and pack-years of smoking did not diminish the predictive value of plaque area measurement. This can be understood in light of previous studies showing that Framingham risk factors explain only half of coronary risk and our previous studies showing that traditional risk factors explain only half of carotid plaque. In a multiple regression model with all the risk factors mentioned above, in addition to treatment of blood pressure and lipids, the R^2 for plaque area was only 0.51.¹³

High-risk patients benefit more from treatment, so the ability to identify them prospectively should make aggressive preventive therapy more cost-effective. For example, the number needed to treat to prevent 1 myocardial infarction in 10 years for young overweight women with moderate hypertension would be 500 to 800, whereas for elderly men with isolated systolic hypertension, it would be <50.¹⁷

Alternative noninvasive indexes include coronary plaque calcification by CT, measurement of IMT, and measurement of carotid stenosis by Doppler ultrasound. The latter approach may be intuitively attractive but is limited because of the phenomenon of compensatory enlargement. As plaque develops, the artery enlarges to accommodate the plaque, so stenosis is a late event likely resulting from plaque rupture with scarring.¹⁸ Smoking, blood pressure, and serum cholesterol are much more weakly associated with carotid stenosis than with risk. Smoking, for example, increases the odds ratio for stenosis only to 1.08 (95% CI, 1.03 to 1.16),¹⁹ whereas smoking increases risk of stroke 6-fold.²⁰

Measuring plaque as a continuous variable appears to be more powerful than simply detecting the presence or absence of plaque at extracoronary sites or counting the number of sites involved. Simon et al⁹ found that although extracoronary plaque was a more powerful predictor of coronary risk than coronary calcification by CT, the odds ratio for patients with plaque at 3 sites versus none was only 2.37 (95% CI, 1.08 to 5.21), whereas that between grade 3 and 0 of coronary calcification was 1.79 (95% CI, 0.94 to 3.40).

Ease of measurement and low cost are important advantages compared with measuring IMT. Because the magnitude of the quantity being measured is much greater relative to the

resolution of the ultrasound scanner, the reliability of the measurements is much greater. Additionally, no special equipment or software is required, and the time to perform the measurements only adds about 25% to the time of a routine carotid ultrasound examination. With the advent of 3-dimensional measurement of carotid plaque volume,²¹ the examination has become even easier to perform, requiring only 2 minutes a side for data acquisition.

Carotid IMT, which predicts stroke more strongly than myocardial infarction,²² is an indirect method of assessing atherosclerosis, which is mainly an intimal process. Because IMT represents largely medial hypertrophy related to hypertension^{23,24} and a substantial proportion of strokes are due to hypertensive small-vessel disease, it is not surprising that IMT predicts stroke more strongly than myocardial infarction, whereas we found the opposite for plaque area, as shown in Table 3.

Adams et al¹⁰ found that IMT was weakly associated with coronary atherosclerosis. They pointed out that in early disease, the media accounts for ≈80% and the intima for only 20% of IMT. Direct measurement of the atherosclerotic plaque itself, without inclusion of the media, should be a more specific approach to predicting atherosclerosis risk. Indeed, this has been the case in studies in Britain²⁵ and in Canada.²⁶ Like IMT,²⁷ carotid plaque increases with age, as shown in Figure 2, but the quantity of plaque area levels off at about 75 years of age, perhaps because people with rapid progression of plaque do not survive to old age.

We have adopted regression of plaque as the therapeutic goal in our clinic. We have found that follow-up measurements of plaque can determine whether therapy is successful or whether more intensive investigation and treatment of new risk factors such as homocysteine and lipoprotein(a) may be required for patients whose plaque is progressing rapidly despite active treatment of the usual risk factors.¹¹ Showing patients the pictures and measurements of their plaque progression often seems to help motivate them to implement lifestyle changes such as smoking cessation and dietary change. Conversely, plaque regression validates and encourages persistence with successful lifestyle changes.

We have used the results of the present study in scheduling patient follow-up visits. Patients with regression in successive years are given more lengthy follow-up appointments, commonly at 2 to 3 years and as long as 5 years. Conversely, patients whose plaque area is progressing rapidly despite aggressive therapy are brought back to the clinic sooner for more intensive investigation, including enrollment in research protocols in which we look for such emerging risk factors as lipoprotein(a) and *Chlamydia pneumoniae* and draw blood for DNA extraction for candidate gene studies.

Measurement of plaque progression is a very powerful method to evaluate new therapies. Only 50 patients per group were required to show the effectiveness of vitamin therapy for homocysteine on the rate of plaque progression.¹¹ This provides a very efficient approach to testing new therapies, particularly when other intermediate end points are lacking. This approach will be particularly useful for treatments such as acyl-CoA:cholesterol acyltransferase inhibitors, which are antiatherosclerotic in animals^{28,29} but for which the cost of

drug development in patients would be prohibitive without the ability to measure effects on atherosclerosis. We have come to believe that trying to treat atherosclerotic patients without knowing how their arteries are doing is rather similar to trying to treat hypertension without measuring blood pressure or trying to treat dyslipidemia without measuring follow-up lipid levels. Simon et al⁸ have discussed a similar approach.

Conclusions

The results of the present study lead to the hypothesis that ultrasound-based management of vascular patients may improve the cost-utility of preventive therapy by permitting expensive therapies to be targeted on patients with a low number needed to treat and providing feedback on the success of therapy. This hypothesis needs to be tested in a randomized, controlled trial. One approach would be to use cluster randomization of physician or clinic practices to usual care versus care based on ultrasound evaluation, with cost-utility as the primary outcome. Furthermore, because the quantity of baseline plaque and rate of progression predict outcomes, plaque measurement represents a way to efficiently evaluate new therapies with much smaller sample sizes than would be required for studies based on clinical events. For new therapies that have been shown to be antiatherosclerotic in animal studies but do not have other intermediate outcomes such as effects on plasma lipids, plaque measurement would permit dose-finding studies and provide preliminary evidence of efficacy, which could lead to human studies that could not otherwise be contemplated.

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