Progression of asymptomatic carotid stenosis: A natural history study in 1004 patients

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Purpose: **The purpose of this study was to delineate the natural history of the progression of asymptomatic carotid stenosis.**
Methods: **In a 10-year period, 1701 carotid arteries in 1004 patients who were asymptomatic were studied with serial duplex scans (mean follow-up period, 28 months; mean number of scans, 2.9/patient). At each visit, stenoses of the internal carotid artery (ICA) and the external carotid artery (ECA) were categorized as none (0 to 14%), mild (15% to 49%), moderate (50% to 79%), severe (80% to 99%), preocclusive, or occluded.** ***Progression*** **was defined as an increase in ICA stenosis to ≥50% for carotid arteries with a baseline of <50% or as an increase to a higher category of stenosis if the baseline stenosis was ≥50%. The Cox proportional hazards model was used for data analysis.**
Results: **The risk of progression of ICA stenosis increased steadily with time (annualized risk of progression, 9.3%). With multivariate modeling, the four most important variables that affected the progression ($P < .02$) were baseline ipsilateral ICA stenosis ≥50% (relative risk [RR], 3.34), baseline ipsilateral ECA stenosis ≥50% (RR, 1.51), baseline contralateral ICA stenosis ≥50% (RR, 1.41), and systolic pressure more than 160 mm Hg (RR, 1.37). Ipsilateral neurologic ischemic events (stroke/transient ischemic attack) occurred in association with 14.0% of the carotid arteries that were studied. The progression of ICA stenosis correlated with these events ($P < .001$), but baseline ICA stenosis was not a significant predictor.**
Conclusion: **In contrast to recently published studies, we found that the risk of progression of carotid stenosis is substantial and increases steadily with time. Baseline ICA stenosis was the most important predictor of the progression, but baseline ECA stenosis also was identified as an important independent predictor. Contralateral ICA stenosis and systolic hypertension were additional significant predictors. We found further that the progression of ICA stenosis correlated with ischemic neurologic events but not baseline stenosis. The data provide justification for the use of serial duplex scans to follow carotid stenosis and suggest that different follow-up intervals may be appropriate for different patient subgroups. (J Vasc Surg 1999;29:208-16.)**

Recent large trials in North America and Europe have defined the important role of carotid endarterectomy (CEA) in the treatment of symptomatic and asymptomatic carotid artery disease.[1-4] The studies have shown that the degree of carotid stenosis is a critical factor in decision making about the benefit of CEA.

On the basis of these and other studies, one might reasonably speculate that serial duplex scan surveillance of the carotid artery is an important tool, especially in patients who are asymptomatic and whose degree of stenosis does not initially warrant CEA. However, the natural history of the progression of carotid stenosis is not well defined, despite multiple studies that have directly or indirectly addressed the topic.[5-13] In fact, these studies have yielded conflicting conclusions about the value of serial duplex scan surveillance in patients who are asymptomatic, which range from a report that serial

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Table I. Velocity criteria and validation statistics

ICA/CCA PSV	*Inferred degree of stenosis*	*Sensitivity (%)*	*Specificity (%)*	*Kappa statistic (95% CI)*
0.1 to 1.4	None	95.6	99.2	
1.5 to 1.9	Mild (15% to 49%)	69.6	95.1	
2.0 to 3.9	Moderate (50% to 79%)	80.5	78.7	0.85
≥4.0, with ICA PSV <125 cm/s	Severe (80% to 99%)	95.3	82.8	(0.82 to 0.89)
≥4.0, with ICA PSV >125 cm/s	Preocclusive	85.1	87	
0 (no flow in ICA)	Occluded	90.9	89.3	

ICA, Internal carotid artery; *CCA,* common carotid artery; *PSV,* peak systolic velocity; *CI,* confidence interval.
Sensitivity, specificity, and kappa statistic were determined after review of 487 internal carotid arteries visualized in 248 consecutive carotid artery angiograms obtained in a 4-year period (October 1993 to June 1997). The angiographic data were compared with the respective duplex scan study results. For calculation of the kappa statistic, we used a customized computer program.[14]

duplex scan follow-up has minimal predictive power[5] to a recommendation for the aggressive application of serial surveillance.[8]

We undertook in this study to delineate the natural history of the progression of carotid stenosis as measured by means of duplex ultrasound scan in a large number of patients who were asymptomatic at the Pittsburgh Veterans Administration Medical Center and to define clinically useful predictors of progression. We also sought to determine the role and value of serial duplex scan surveillance in these patients.

PATIENTS AND METHODS

In the 10-year period from September 1988 to September 1997, the noninvasive vascular laboratory at the Pittsburgh Veterans Administration Medical Center performed 6775 carotid artery duplex scan studies in 4171 patients. We identified 1004 patients with the following characteristics: (1) asymptomatic at the time of the initial study, (2) at least one follow-up study more than 6 months after the baseline study, and (3) at least one carotid artery that had not undergone CEA. *Asymptomatic* was defined as the absence of transient ischemic attack, amaurosis fugax, or stroke in the 6-month interval before the baseline study. The initial patient referral to the laboratory was done by internists and surgeons for a large variety of indications. Although some of the follow-up studies were ordered by the patients' physicians, most were performed because the laboratory schedules routine follow-up appointments for all patients at intervals of 6 to 12 months. This is the result of a prospective strategy to track the clinical and ultrasound scan course of these patients.

The data on the carotid arteries that had undergone CEA before the baseline study were excluded from analysis. In addition, if a patient underwent CEA after the baseline study, then the stenosis data after the CEA were excluded from analysis. From the early 1990s, we had a policy of offering CEA to patients at good risk with severe (≥80%) stenosis. However, several asymptomatic severe lesions were followed among the patients who declined surgery or among those with significant medical risk factors.

At each visit to the vascular laboratory, a registered nurse obtained a detailed neurologic history and "yes/no" responses to questions about smoking, hypertension, hyperlipidemia, diabetes, angina, and myocardial infarction. The blood pressures in both arms were obtained, and a carotid artery duplex scan study (Accuson 128XP, Mountain View, Calif) was performed. The degree of internal carotid artery (ICA) stenosis was determined on the basis of velocity criteria that were validated at our institution by means of comparison with contrast angiography (Table I). With angiography as a gold standard, the sensitivity and specificity ranged from 70% to 99%. We found an excellent overall agreement between duplex scanning and angiography ($\kappa = 0.85$). The reproducibility of the duplex scan data was also excellent, as inferred from a 92% incidence rate of finding the same degree of stenosis among 48 studies that were repeated at intervals of less than 1 month. The ratio of external carotid artery (ECA) peak systolic velocity (PSV) to common carotid artery PSV was also recorded at each visit. The ECA/common carotid artery PSV ratio of 2.0 or more was used to determine ECA stenosis ≥50%.

We defined *progression* as an increase in ICA stenosis to ≥50% for carotid arteries with baseline stenosis <50% or as an increase to a higher category of stenosis if the baseline stenosis was ≥50%. Thus, a transition from the "none" category to the "mild" category was not considered to be progression, but all the other increases in stenosis category were considered to be progression.

The data initially were recorded in separate com-

Table II. Demographic and clinical features

Baseline patient characteristics (n = 1004 patients)	
Age (years)	65.5
Sex (% male)	98%
History of:	
Angina	33%
Myocardial infarction	35%
Current smoking	42%
Any smoking	90%
Hyperlipidemia	41%
Diabetes	31%
Hypertension	56%
Baseline distribution of ICA stenosis (n = 1701 ICAs)	
None	57%
Mild (15% to 49%)	18%
Moderate (50% to 79%)	14%
Severe (80% to 99%)	8%
Preocclusive	2%
Occluded	0%*

ICA, Internal carotid artery.
*Occluded internal carotid arteries were excluded from analysis (see Methods section).

puter files for each study with software from Life Sciences (Greenwich, Conn). These data then were extracted with a customized program written by one of the authors in QuickBasic (Microsoft, Redmond, Wash) and then transferred to Access (Microsoft), a relational database. In our analyses, we used Access for descriptive statistics, SAS (SAS Institute, Cary, NC) for the Cox proportional hazards model and the Kaplan-Meier method plots, and Excel (Microsoft) for the exponential curve fitting of the Kaplan-Meier method plots. Progression was considered to be a censoring event for the involved carotid artery, in the same way that death is treated in a mortality rate study. A carotid artery was considered to be withdrawn if the CEA was performed after the baseline study and at the point of the last serial duplex scan study. The Kaplan-Meier method plots were carried out to the time point when the standard error reached 10% of the value of the survival distribution function. Statistical significance was inferred at the .05 level.

RESULTS

The results are derived from the analysis of 1701 carotid arteries in 1004 patients. Table II shows the baseline demographic and clinical characteristics of the patients. The vast majority of the patients were men, as expected in a Veterans Administration hospital setting. The clinical risk factors for atherosclerosis were typical for patients followed in major vascular laboratories. Table II also shows the baseline distribution of ICA stenosis among the 1701 carotid arteries. The mean follow-up period of the patients was 28 months, and the mean number of scans per patient was 2.9.

The incidence rate of progression and the mean time to progression are shown in Table III for each category of baseline stenosis. The time-dependent risk of progression also was analyzed with the Kaplan-Meier method and the Cox proportional hazards model. The risk of progression among all the ICAs was found to increase steadily from the point of entry for as long as 7 years of follow-up. This is shown by the persistent negative slope of the solid line in Fig 1. These data closely follow an exponential curve (correlation coefficient, 0.99). The curve fitting shows an annualized progression rate of 9.3% of the at-risk population.

We first used the univariate proportional hazards model to analyze the predictive value of 18 variables available at the baseline study (Table IV). Of these variables, we found that seven had statistically significant effects on the time to progression. The seven variables were entered into a stepwise multivariate model, and four were found to retain an independent predictive value for the time to progression. These variables are indicated with boldface in Table IV. The Kaplan-Meier method curves for stratification with the two most important variables (baseline ipsilateral ICA stenosis ≥50% and baseline ipsilateral ECA stenosis ≥50%) are shown in Fig 1. Stratification with the other variables is not shown to maintain clarity of the figure.

The annualized risk of progression for the patient group that had none of the four risk factors was found to be 3.2% of the at-risk population, as determined from exponential curve fitting (correlation coefficient, 0.95). With this as a baseline risk, Table V shows the projected progression risks for all the possible combinations of the four variables identified in the multivariate model.

The incidence rates of the progression of carotid stenosis observed in this study are substantially higher than those reported in a recent study by Lewis et al.[5] Table VI shows a direct comparison of the progression incidence rate as a function of baseline carotid stenosis.

Of the 1701 carotid arteries that were studied, ipsilateral ischemic neurologic events (stroke, transient ischemic attack, amaurosis fugax) occurred in association with 14.0%. The frequency was significantly higher among carotid arteries that exhibited progression (21.0% vs 11.9%; $P < .001$). However, the event frequency was only marginally higher among the carotid arteries with baseline ICA stenosis ≥50%, and the difference was not significant (14.0% vs 13.9%; $P = .98$).

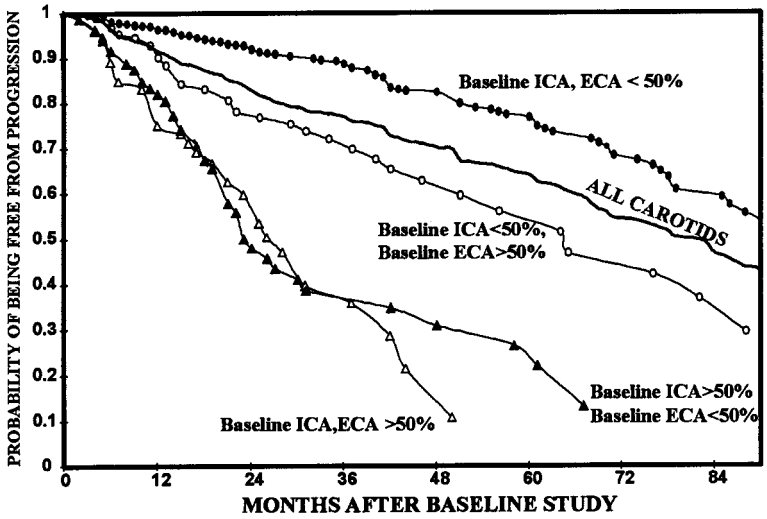

Fig 1. Kaplan-Meier method curves show probability of being free from progression as a function of time. *Solid line* incorporates all 1701 carotid arteries in study. Additional four curves are result of stratification of carotid arteries by two dichotomous variables (baseline ICA stenosis, ≥50%; baseline ECA stenosis, ≥50%).

DISCUSSION

This is the largest natural history study to date of the progression of carotid stenosis. We found that the risk of stenosis progression is substantial and steadily increases with time. In each year of follow-up, approximately 9.3% of the at-risk population exhibited progression. As indicated by the persistent negative slope of the solid line in Fig 1, this pattern of ongoing progression persisted to 7 years of follow-up.

Our data are sharply at odds with a recent large natural history study[5] derived from a secondary analysis of data from the Asymptomatic Cervical Bruit Study. From their analysis, Lewis et al[5] concluded that the predictive power of serial duplex scan is poor, and they suggested that its use could not be supported. They observed incidence rates of stenosis progression that were much lower than were observed in the current study (Table VI). One possible reason for this difference is that the patient cohort in the Lewis study was 60% female, in contrast with 98% male cohort in the current study of veteran patients. The male patients had a much higher risk for progression in our univariate analysis (Table II), but sex did not retain importance in the multivariate model. The failure of patient gender to retain predictive importance may be simply a result of the small number of women in our patient cohort, and it is possible that gender may play an important role in a cohort that consists of a significant proportion of women. Unfortunately, the Lewis paper did not report the effect of gender in their analysis.

The Lewis paper also found that the progression of carotid stenosis was not a predictor of ischemic neurologic events, but baseline stenosis was a predictor. Our data show the opposite. This distinction between the two studies is in part caused by the higher incidence rate of progression events that we observed in this study. However, another factor is the lower proportion of patients with advanced degrees of baseline stenosis in the current study. Such a distribution would be expected to reduce the importance of baseline stenosis and increase the importance of progression in the prediction of neurologic events.

Our strategy was to identify the variables available to the clinician at the baseline study that can be used to predict the risk of progression. After a preliminary univariate analysis, we identified four variables that had an independent predictive value in a multivariate model (Table IV).

Our finding that baseline ICA stenosis ≥50% is a strong predictor of progression is consistent with the data reported by Nehler et al.[9] In that analysis, an ICA PSV of more than 175 cm/s was a useful predictor of early stenosis progression. Our data also confirm the finding of Nehler et al[9] that systolic hypertension is a predictor of progression. Interestingly, we found that the presence of a systolic blood pressure of

Table III. Progression of stenosis by category of baseline stenosis

Baseline stenosis category	*N*	*Percent exhibiting progression*	*Mean time to progression (months)*
None	967	11.5	38.4
Mild	306	38.2	31
Moderate	246	43.5	20.6
Severe	144	26.6	21.1
Preocclusive	38	31.6	13.5
Occluded	0*	N/A	N/A
All categories	1701	22.6	28.7

*Occluded internal carotid arteries were excluded from analysis (see Methods section).

Table IV. Results of Cox proportional hazards model

	Univariate model				*Multivariate model*		
	P value	*Risk ratio**	*95% CI*	*Entered into multivariate model*	*P value*	*Risk ratio**	*95% CI*
Demographic variables							
Age (years)†	0	1.014†	1.00 to 1.03	yes	>.1		
Sex (male)	0	9.4	1.32 to 67.1	yes	>.1		
Race (nonwhite)	.19			no			
Clinical variables							
Angina	.1			no			
Blood pressure, systolic >160 mm Hg	**0**	**1.41**	**1.14 to 1.76**	**yes**	**0**	**1.37**	**1.05 to 1.78**
Blood pressure, diastolic >90 mm Hg	.55			no			
Diabetes	.1			no			
Hyperlipidemia	.1	1.23	1.00 to 1.52	yes	>.1		
Hypertension	.12			no			
Myocardial infarction	.18			no			
Obesity	.5			no			
Smoking status (current smoker)	.1			no			
Smoking status (never smoked)	.25			no			
Vertigo episodes	.58			no			
Duplex scan–related variables							
Baseline ICA stenosis ≥50%	**0**	**3.23**	**2.62 to 3.96**	**yes**	**0**	**3.34**	**2.46 to 4.53**
Baseline ECA stenosis ≥50%	**0**	**2.51**	**1.96 to 3.23**	**yes**	**0**	**1.51**	**1.11 to 2.04**
Baseline contralateral ICA ≥50%	**0**	**1.87**	**1.52 to 2.30**	**yes**	**0**	**1.41**	**1.07 to 1.85**
Side (left)	.13			no			

CI, Confidence interval; *ICA,* internal carotid artery; *ECA,* external carotid artery.
*Risk ratio is shown only for variables that have a statistically significant effect on probability of progression.
†All variables are dichotomous (no/yes) except age, which was analyzed as a continuous variable. Therefore, the risk ratio for age is the increased risk associated with a 1-year increase in age.
Boldfacing indicates variables that retained independent predictive value in the final multivariate model.

more than 160 mm Hg at the time of the baseline study was a useful predictor but that a history of hypertension was not in itself a significant predictor (Table IV). This suggests that inadequately controlled hypertension is the true risk factor—not the mere presence of the condition. However, our data do not allow us to definitively test this hypothesis.

We also identified contralateral ICA stenosis ≥50% and ipsilateral ECA stenosis ≥50% as significant risk factors (Table IV) for ICA stenosis progression. To our knowledge, this is the first report of the independent predictive importance of these factors.

The finding that baseline anatomic features (ipsilateral ICA and ECA stenosis, contralateral ICA stenosis) predict progression is intuitively logical because it implies that patients who have advanced atherosclerosis at the baseline are the ones in whom more stenosis is most likely to develop in the future. However, the identification of the magnitude of independent risk attributable to these factors has significant practical value in patient care. Furthermore, the finding that systolic blood pressure is a significant predictor raises the possibility that appropriate antihypertensive therapy can reduce the progression rates.

Table V. Annualized progression risk with all possible risk factor combinations

Ipsilateral ICA ≥ 50%	*Ipsilateral ECA ≥ 50%*	*Contralateral ICA ≥ 50%*	*SBP > 160 mm Hg*	*Projected annualized risk of progression (%)*
				3%
			X	4%
		X		5%
		X	X	6%
	X			5%
	X		X	7%
	X	X		7%
	X	X	X	9%
X				11%
X			X	15%
X		X		15%
X		X	X	21%
X	X			16%
X	X		X	22%
X	X	X		23%
X	X	X	X	32%

ICA, Internal carotid artery; *ECA,* external carotid artery; *SBP,* systolic blood pressure; *X,* indicates the presence of a given risk factor. Progression risks are rounded to the nearest integer.

This study does not directly address whether the early detection of the progression of carotid stenosis in patients who are asymptomatic leads to clinical benefits, such as reduction in stroke risk. However, we did find that the progression of ICA stenosis correlates with ipsilateral ischemic neurologic events but that baseline stenosis does not. Furthermore, other studies have shown that stroke reduction can be achieved with carotid endarterectomy in patients who are asymptomatic with hemodynamically significant stenosis.[2,4] Therefore, we propose that the early detection of the progression of carotid stenosis is clinically important. In this context, the status in any given patient of the four risk factors identified in this study can guide decisions about the frequency of serial duplex scan follow-up. The risks conferred by the variables are multiplicative, so that a patient who has all four risk factors would have nearly a 10-fold increase in risk as compared with a patient who has none of the risk factors. As shown in Table V, various combinations of the risk factors yield projected annualized progression risks that range from 3.2% (no risk factors) to 31.5% (all four risk factors present). We speculate that it is cost effective to assign patients to a 2-year follow-up if their annualized progression rate is 5% or less, to annual screening for the middle range of 6% to 20%, and to a 6-month follow-up for the high range of more than 20% annualized progression rate. However, these recommendations must be validated with further studies (preferably prospective) and by detailed cost analyses.

In addition to the risk of progression, another factor in the decision about the frequency of serial duplex scan evaluation is the time-dependent probability of an adverse neurologic event after disease progression has occurred. Further study and data accumulation will be needed to address this important issue.

Table VI. Incidence rates of progression of carotid stenosis as a function of baseline stenosis*

Baseline stenosis	*Lewis et al*[5]	*Muluk et al† (current study)*
None‡	3.25%	11.5%
Mild	19.5%	38.2%
Moderate	22.2%	43.5%
Severe§	9.7%	26.6%

*Definition of progression used in the current paper was applied to the data in Table II of reference 5.
†Values are derived from Table III.
‡The "0" and "1 to 15" categories in reference 5 were combined into the "none" category.
§The "severe" and "preocclusive" categories in the current manuscript were combined into the "severe" category.

CONCLUSION

In a large serial duplex scan study of veterans who were asymptomatic and who were followed up to 7 years after entry in the study, we found a 9.3% annual rate of progression of carotid stenosis. We identified four independent risk factors for the progression in a multivariate model. Three of these quantify the baseline degree of extracranial carotid atherosclerosis, and the fourth was systolic blood pressure of more than 160 mm Hg. The risk of pro-

gression varied by 10-fold depending on the absence or the presence of all four factors. These data may be useful in determining the frequency of serial duplex scan surveillance in different patient groups.

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DISCUSSION

Dr Mark A. Mattos (Springfield, Ill). With the advent of duplex scanning, an increasing number of patients who are asymptomatic with varying degrees of carotid artery disease are being identified. Clearly, as the asymptomatic carotid trials have shown us, not all asymptomatic internal carotid stenoses act in a similar manner, clinically or anatomically. Some patients will remain asymptomatic despite having carotid stenoses that undergo progression to a higher level of severity, and other patients will have ipsilateral neurologic symptoms with stenoses that do not progress to a higher degree of narrowing. Therefore, the key to proper evaluation and management of these ubiqutious lesions is to accurately determine their natural history. In doing so, one should be able to answer the following questions: What lesions will undergo progression to a higher level of severity? How frequently does it occur? To what severity? Does progression of disease predict the development of future ipsilateral neurologic events? What patients then should undergo operation, and who should be monitored with serial duplex scans?

Dr Muluk and associates present a large collection of data designed to answer the above questions. The authors' goals were to delineate the natural history of asymptomatic internal carotid artery stenosis, to identify the variables that would predict the progression of carotid artery stenosis, and to determine the role and value of duplex scan surveillance in these patients. On the basis of their interpretation of the data, we now know the following:

1. The progression of carotid disease increases over time, at the rate of approximately 9% per year, and by the 7th year of follow-up, more than one half of all patients at risk had had some degree of disease progression.
2. Certain risk factors are more likely to be associated with the progression of carotid stenosis. Individual factors or combinations of these four specific risk factors predicted a risk of disease progression that ranged from 3.2% to 32% annually.
3. Carotid arteries that exhibit progression of disease were associated with ipsilateral ischemic neurologic events to a much greater extent than arteries without disease progression (21% vs 12%, respectively).

However, although I applaud Dr Muluk for providing us with a fine presentation, I believe that many important questions remain unanswered or unaddressed, and I have concerns regarding the following issues.

First, Dr Muluk, I question whether or not patient selection bias has entered into your study. Only 24% of your study

population had a ≥50% internal carotid stenosis (presumably the subset of patients at highest risk for associated ischemic neurologic events and progression of carotid artery stenosis), which makes this a natural history study primarily of lesions with a ≤50% stenosis. During your study period, how many patients who were asymptomatic with a >50% internal carotid stenosis underwent prophylactic carotid endarterectomy and thus were excluded from the study population? Why did some patients undergo surgery although other patients with similar disease severity did not? Is it possible that the exclusion of this subset of patients who underwent carotid endarterectomy (who I assume had carotid artery stenosis of 50% to 99%) may have altered the natural history of your patient population, thereby resulting in a decreased incidence rate of ipsilateral neurologic ischemic events and disease progression rates? Could the authors comment on the implications that this would have on their conclusions?

Second, the authors provide an overall risk of disease progression of 9% per year and a development rate of ipsilateral neurologic symptoms associated with disease progression of 21% for the entire group of patients. However, I have concerns that these data may not be relevant or applicable to patients who are asymptomatic with different degrees of carotid disease. Therefore, I ask the authors to comment on the following questions:

1. Did the authors perform an analysis of the incidence rate of disease progression on the basis of the severity of baseline internal carotid stenosis?
2. Was there a correlation between the severity of baseline carotid stenosis and the incidence rate of carotid disease progression? That is, did a higher degree of internal carotid stenosis predict greater disease progression?
3. Was there a correlation between the severity of baseline carotid stenosis and the incidence rate of ipsilateral neurologic events? That is, did a higher degree of internal carotid stenosis predict a greater incidence rate of ipsilateral neurologic events?
4. What subgroup of patients with disease progression was associated with the highest incidence rate of ipsilateral neurological symptoms?

Third, the authors indicate that their results justify the use of serial duplex scanning to follow internal carotid stenosis. However, they do not provide any subset analysis of disease progression on the basis of severity of baseline carotid stenosis. Therefore, I ask the authors whether or not their results can provide answers to the following questions:

1. Which patients in your study population should receive serial duplex scan follow-up?
2. How frequently should these scans be performed? Would you determine your scanning frequency on the basis of the annual risk of disease progression or on the mean length of time to disease progression?
3. Have you performed any calculations regarding the number of strokes that might be prevented if such a duplex scan surveillance program is instituted for this patient population?

Fourth, the authors report that baseline ipsilateral external carotid artery stenosis >50% was predictive for progression of internal carotid stenosis. What validation criteria were used to determine a ≥50% stenosis of the external carotid artery? Can the authors provide sensitivity and specificity data regarding the accuracy of their duplex scan criteria for determining an external carotid artery stensosis >50%?

Dr Satish C. Muluk (Pittsburgh, Pa). I will try to answer the questions Dr Mattos raised as best I can. The first question related to the question of a possible selection bias. Admittedly, and I think this applies to any study of this sort, there is a certain bias because we are limited to the patients who are referred to our vascular laboratory. We certainly did not randomly select among all the veteran patients for this study.

On the other hand, the fact that most of our patients had initial degrees of stenosis <50% strengthens the manuscript in the sense that we are examining a population of patients who we would indeed consider for serial duplex scan surveillance. Certainly, the patients with more severe degrees of stenosis are less likely to need serial duplex scan surveillance. So, we think that actually is a strength of the study.

Certainly, patients did undergo prophylactic carotid endarterectomy, but our policy has been to do that only at the point at which severe stenosis has developed in the 80% to 99% range. Because of that, I do not think that policy would really affect our analysis of progression. It might affect the number of neurologic events that we pick up because we might prevent some of those events with prophylactic carotid endarterectomy. But, on the other hand, because we do not offer endarterectomy until the severe stage, it should not really affect our identification of progression, which I would point out is really the key focus of this paper.

It is true that these results may not be applicable to all the patients with carotid stenosis, but only in the sense that we are limited to the population of patients who were in the study—namely, the veteran patients. But that is an issue, of course, that is going to apply to any study, regardless of how large.

Dr Mattos also asked whether the incidence rate of disease progression is related to the severity of baseline stenosis. And, in fact, it is. One of the principal conclusions was that the increased level of baseline stenosis does correlate with the disease progression.

Another question was related to whether these results justified the use of serial duplex scanning. We certainly think that they do. The annualized risk of progression was quite high even in the unselected group of patients. And if various risk factors are present in different combinations, the risk increases as high as 30% or more per year with progression. Although we have not performed a detailed cost/benefit analysis yet, we are in the process of doing that. We believe that the frequency of progression is high enough, certainly, to warrant a serial duplex scan surveillance at least in certain subsets of patients.

We tried to avoid making specific recommendations from these data about the actual length or intervals of follow-up examination because we thought that would be

overreaching. Instead, we wanted to present the data to demonstrate that these risk factors do in fact correlate with the risk of progression.

The final question that Dr Mattos raised about the issue of statistics is quite valid. I would point out that the change in the statistics relates only to the calculation of the number of neurologic events, which was incorrect in the initial abstract, but that certainly does not affect the main conclusions of the paper, which all relate to the risk of progression. That is the main focus of the paper. And the programming error that led to that error in statistics does not affect the principal conclusions of the paper.

Dr Anthony M. Imparato (New York, NY). I enjoyed your paper and admire your interest in pursuing this subject. Because it is the progression of a pathologic process that we are trying to follow, I am surprised that you made no attempt to identify the specific characteristics of the plaque, which can be done noninvasively, at least to determine whether the plaques are echogenic or not. And I think the need for this is exemplified by the fact that your major parameter, which was predictive, was the degree of stenosis. We know that the incidence of secondary changes beyond neofibrous proliferation is the appearance of soft material in the plaque. So, I would ask whether you had made any attempt to determine that characteristic. And if not, I would urge you to add it to your protocol. Thank you.

Dr Muluk. I thank you for your comments. I think you make an important point, and it is something that we would like to go back and examine. It is difficult to extract those data because those data are available only in text format in our database and would require a fair amount of work to extract, but we are indeed planning to do just that.