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Original Investigation

Risk of Stroke at the Time of Carotid Occlusion

Catherine Yang, BHSc; Chrysi Bogiatzi, MD; J. David Spence, MD

IMPORTANCE Many patients with asymptomatic carotid stenosis are offered carotid stenting for the prevention of carotid occlusion. However, this treatment may be inappropriate if the risk of stroke is low at the time of occlusion and with intensive medical therapy.

OBJECTIVES To determine the risk resulting from progression to occlusion among patients with asymptomatic carotid stenosis and to assess the role of severity of carotid stenosis or the presence of contralateral occlusion as factors that may predict the risk of stroke or death after occlusion of a previously asymptomatic carotid stenosis.

DESIGN, SETTING, AND PARTICIPANTS We conducted a retrospective analysis of data collected from patients at the Stroke Prevention Clinic of Victoria Hospital from January 1, 1990 (when annual surveillance with carotid ultrasonography first began), through December 31, 1995, or the Stroke Prevention at University Hospital from January 1, 1995, through December 31, 2012. The last date of follow-up was August 26, 2014.

EXPOSURES A new carotid occlusion during annual monitoring with carotid duplex ultrasonography (index occlusion).

MAIN OUTCOMES AND MEASURES Ipsilateral stroke or transient ischemic attack, death from ipsilateral stroke, or death from unknown cause.

RESULTS Among 3681 patients in our clinic database with data on sequential annual carotid ultrasonographic examinations during the study period, 316 (8.6%) were asymptomatic before an index occlusion that occurred during observation. Most of the new occlusions (254 of 316 [80.4%]) occurred before 2002, when medical therapy was less intensive; the frequency decreased by quartile of years ($P < .001$, χ^2 test). Only 1 patient (0.3%) had a stroke at the time of the occlusion, and only 3 patients (0.9%) had an ipsilateral stroke during follow-up (all before 2005). In Kaplan-Meier survival analyses, neither severity of stenosis ($P = .80$, log-rank test) nor contralateral occlusion ($P = .73$) predicted the risk of ipsilateral stroke or transient ischemic attack, death from stroke, or death from unknown cause at a mean (SD) follow-up of 2.56 (3.64) years. In Cox proportional hazards regression analyses, only age ($P = .02$), sex ($P = .01$), and carotid plaque burden ($P = .006$) significantly predicted risk of those events.

CONCLUSIONS AND RELEVANCE The risk of progression to carotid occlusion is well below the risk of carotid stenting or endarterectomy and has decreased markedly with more intensive medical therapy. Preventing carotid occlusion may not be a valid indication for stenting.

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Increasing evidence indicates that with modern intensive medical therapy most patients (90%) with asymptomatic carotid stenosis (ACS) are more likely to be harmed than to benefit from carotid endarterectomy or carotid stenting.¹⁻³ Unfortunately, many patients, particularly in the United States, undergo such procedures. In the United States, more than 90% of carotid intervention is for asymptomatic stenosis⁴; in Denmark, the rate is 0%.⁵ Such a wide range of practice brings into question the advisability, and even the ethics, of routine intervention for ACS.

Some or much of this intervention is performed with the objective of preventing carotid occlusion, the underlying assumption being that carotid occlusion would carry a high risk of stroke. However, this approach to routine intervention in ACS, which may be based on analogy to coronary occlusion, ignores the substantial protection offered by the circle of Willis.

Carotid endarterectomy and carotid stenting should probably be conducted to prevent emboli, rather than to increase blood flow to the brain.⁶ The circle of Willis is usually effective at maintaining blood flow in the face of unilateral carotid occlusion and is often protective even in the face of bilateral carotid occlusion.

Some interventionalists may invoke severity of stenosis or the presence of contralateral carotid occlusion as reasons to perform carotid stenting or endarterectomy. We therefore sought to determine the risk resulting from progression to occlusion among patients with ACS and to assess the role of severity of carotid stenosis or the presence of contralateral occlusion as factors that may predict the risk of stroke or death after occlusion of a previous ACS. We also evaluated the frequency of index occlusion over time. Our hypotheses were that the risk of stroke at the time of carotid occlusion was low and that the frequency of index carotid occlusion was decreasing over time, after implementation in our clinic (in 2002-2003) of more intensive medical therapy based on plaque measurement.^{2,7}

Methods

Data Sources

We conducted a retrospective analysis of data collected from all patients at the Stroke Prevention Clinic of Victoria Hospital from January 1, 1990 (when annual surveillance with carotid ultrasonography first began), through December 31, 1995, or the Stroke Prevention Clinic at University Hospital from January 1, 1995, through December 31, 2012. The last date of follow-up was August 26, 2014. The protocol was approved by the Western University Human Subjects Ethics Review Board. Data were from the electronic medical record of the patients' physician and anonymized before analyses were performed.

Cases were identified by first listing all patients in the database with a carotid occlusion and then searching their clinic file to determine whether a prior carotid ultrasonographic examination was on record that did not reveal occlusion on that side and office visits going back at least 18 months before the index occlusion. The date of the first ultrasonographic examination revealing new occlusion was recorded as the time of the index occlusion. Eligible patients were asymptomatic before

the index occlusion. *Asymptomatic* was defined as not having had a neurologic event (transient ischemic attack [TIA] or stroke) in the carotid territory within 18 months before the index occlusion based on the rate of decrease in symptoms among symptomatic patients randomized to surgery in the North American Symptomatic Carotid Endarterectomy Trial.⁸

Outcomes

Events recorded were TIA, stroke, and death. Outcomes were ascertained by clinic notes and hospital records. Cause of death was ascertained from hospital records or faxed from family physicians' offices or, if the family physician was no longer in practice, from family members (if they were confident that they knew the cause of death). Cause of death was recorded as unknown if it could not be determined. A TIA was defined as an episode of focal neurologic symptoms diagnosed by a stroke neurologist as being caused by cerebral ischemia, with symptoms persisting less than 24 hours and no corresponding lesion seen on brain imaging. A stroke was an episode of focal neurologic dysfunction caused by cerebral ischemia, with symptoms and signs persisting 24 hours or longer or symptoms and signs persisting less than 24 hours with a corresponding infarction seen on brain imaging.

The TIA and stroke events were classified as ipsilateral or contralateral to the side of the index occlusion and by their stroke subtype (large artery atherosclerosis, cardioembolic, small vessel disease, other rare or unusual causes, and undetermined), using the SPARKLE (Subtypes of Ischaemic Stroke Classification System) classification.⁹

The primary outcome was a combination of ipsilateral stroke, ipsilateral TIA, or death from ipsilateral stroke or unknown cause. The decision to include TIA in the primary outcome was based on the concept that the occurrence of TIAs would likely lead to intervention. A secondary outcome was combined ipsilateral stroke, death from ipsilateral stroke, or death from unknown cause. Among this patient population, 48 became symptomatic during follow-up and had carotid intervention.

Stenosis Severity

Stenosis was measured by carotid Doppler peak velocity. We used cutoffs for levels of percent stenosis that were validated for our laboratory from angiography in the Asymptomatic Carotid Surgery Trial (ACST)¹⁰ and in angiograms from 100 patients (200 carotid arteries) followed up in our ultrasonography laboratory during the North American Symptomatic Carotid Endarterectomy Trial study,⁸ with the percentage of angiographic stenosis measured in the central radiology laboratory of that trial.

Plaque Measurement

As described previously,¹¹ carotid total plaque area was measured using a high-resolution duplex ultrasonographic scanner. Plaque was defined as a local thickening of the intima greater than 1 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 sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as the total plaque area.

Statistical Analysis

Data were analyzed with SPSS statistical software, version 22.0 (SPSS Inc). Continuous variables were assessed by analysis of variance and categorical variables by χ^2 analyses. Kaplan-Meier survival analyses were conducted to evaluate the effects of various features of the carotid artery disease on event-free survival assessing log-rank probabilities, and Cox proportional hazards regression analyses (backward Wald) were performed to assess effects of covariates on event-free survival.

Results

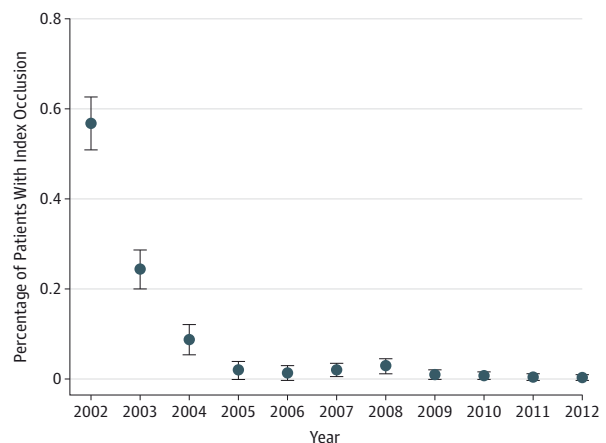
Among 3681 patients in our clinic database with data on sequential annual carotid ultrasonographic examinations during the study period, 316 (8.6%) were asymptomatic before an index occlusion that occurred during observation. Results are presented for those patients. Mean (SD) age was 66.4 (10.5) years, 225 (71.2%) were men, 246 (77.8%) were hypertensive, and 216 (68.4%) had hyperlipidemia. The mean (SD) duration of patient follow-up was 2.56 (3.64) years (maximum, 20.22 years). Prior asymptomatic occlusion on the contralateral side was present in 10 patients. Three of the patients with index occlusions had no significant plaque or stenosis before the occlusion, suggesting that the occlusion may have been due to dissection or embolism.

Most of the index occlusions occurred before the initiation of more intensive therapy based on plaque measurement^{2,7} (eTable 1 in the Supplement), the implementation of which began in 2002 and was in effect after 2003. By quartile of years

of index occlusion, 254 occurred before 2002, 39 in 2002-2007, 16 in 2007-2010, and 7 after 2010 ($P < .001$, χ^2 test). Figure 1 shows the proportion of patients in the database with index occlusions by year.

At baseline before the index occlusion, 42 patients (13.3%) had a previous myocardial infarction, 69 (20.6%) had diabetes mellitus, 69 (21.8%) still smoked, 167 (52.8%) had quit smoking, and 38 (12.0%) had never smoked. The mean (SD) smoking burden was 26.81 (23.11) pack-years. Baseline characteristics of the patients are presented by stenosis groups in Table 1 and by the presence of prior occlusion of the contralateral internal carotid artery in eTable 2 in the Supplement. Patients with

Figure 1. Percentage of Patients in the Clinic With New Index Occlusion by Year



Among 3681 patients in the database, the percentage of patients who progressed to occlusion was much higher before 2002; the frequency decreased markedly after implementation in 2002-2003 of more intensive therapy based on plaque measurements. Error bars indicate 95% CI.

Table 1. Baseline Characteristics of the Study Population by Stenosis Groups^a

Characteristic	Stenosis, %				P Value
	<60 (n = 159)	60-80 (n = 80)	81-90 (n = 19)	>90 (n = 58)	
Age, y	65.60 (11.62)	67.00 (9.00)	67.05 (10.08)	66.88 (10.08)	.60 ^b
Blood pressure, mm Hg					
Systolic	148 (24)	148 (24)	147.63 (24.10)	152.83 (25.08)	.16 ^b
Diastolic	80 (14)	77 (12)	78 (8)	79 (16)	.51 ^b
Total plaque area, cm ²	3.42 (1.72)	4.46 (1.87)	4.49 (1.82)	5.52 (2.09)	<.05 ^b
Cholesterol, mg/dL					
Total	176 (49)	169 (42)	163 (58)	152 (46)	.03 ^b
HDLc	48 (14)	45 (14)	44 (21)	43 (16)	.16 ^b
LDLc	98 (43)	93 (38)	86 (35)	79 (34)	.39 ^b
Triglycerides, mg/dL	158 (146)	165 (125)	164 (108)	146 (95)	.90 ^b
Total homocysteine, mg/L	1.41 (0.47)	1.79 (1.01)	1.29 (0.37)	1.47 (0.51)	.13 ^b
No. (%) of patients					
Male	111 (69.8)	61 (76.3)	14 (73.7)	39 (67.2)	.65 ^c
Smoking	39 (24.5)	47 (15.0)	4 (21.1)	69 (21.8)	.22 ^c
Diabetes mellitus	23 (14.5)	16 (22.5)	7 (36.8)	65 (20.6)	.02 ^c
Claudication	16 (10.1)	10 (12.5)	2 (10.5)	36 (11.4)	.87 ^c
Myocardial infarction	21 (13.2)	13 (16.3)	2 (10.5)	42 (13.3)	.76 ^c

Abbreviations: HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol, HDLc, and LDLc values to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and homocysteine to micromoles per liter, multiply by 7.397.

^a Data are presented as mean (SD) unless otherwise indicated.

^b P values determined by analysis of variance.

^c P values determined by χ^2 test.

more severe stenosis were more likely to have diabetes ($P = .02$) and more likely to have a lower (with treatment) level of low-density lipoprotein cholesterol ($P = .03$). No significant differences were found in baseline characteristics of patients with prior contralateral occlusion.

Only 1 patient (0.32%) had an ipsilateral stroke at the time of the occlusion, and only 3 patients (0.9%) had an ipsilateral stroke during follow-up. During follow-up after the index occlusion, 71 patients died; the mean (SD) time of death was 7.2 (4.9) years after the occlusion. **Table 2** lists the causes of death. Cause of death was unknown in 16 patients because it was not in the hospital record, the family physician had died or retired from practice, or family members

could not be contacted or were unsure of the cause of death at the time we conducted the analyses.

For the purpose of the Kaplan-Meier survival analyses, we assumed that all deaths of unknown cause were stroke deaths; despite this conservative assumption, neither percent stenosis of the index artery before occlusion nor previous contralateral occlusion predicted survival free of ipsilateral stroke or TIA, death from any stroke, or death from unknown cause. **Figure 2** shows survival free of those events by groups of percent stenosis (<60%, 60%-80%, 81%-90%, and >90%); no significant difference was found ($P = .80$). There was also no significant difference in event-free survival by prior contralateral occlusion ($P = .73$, log-rank test; eFigure in the Supplement). However, as shown in **Figure 3**, carotid plaque burden measured as total plaque area significantly predicted reduced event-free survival ($P = .006$).

Occurrence of the secondary outcome (survival free of ipsilateral stroke, death from ipsilateral stroke, or death from unknown cause) was similar for contralateral occlusion ($P = .30$) and the stenosis groups ($P = .20$). Outcome for stroke or death was also similar for the stenosis groups ($P = .60$) and contralateral occlusion ($P = .17$). Survival free of ipsilateral stroke could not be computed because there was only 1 case.

The results of Cox proportional hazards regression analysis (backward Wald) are provided in eTable 3 in the Supplement. With age, sex, diabetes, stenosis groups, contralateral occlusion, and total plaque area as covariates, the only significant predictors of the primary outcome were age ($P = .02$), male sex ($P = .01$), and total plaque area ($P = .006$).

Table 2. Causes of Death

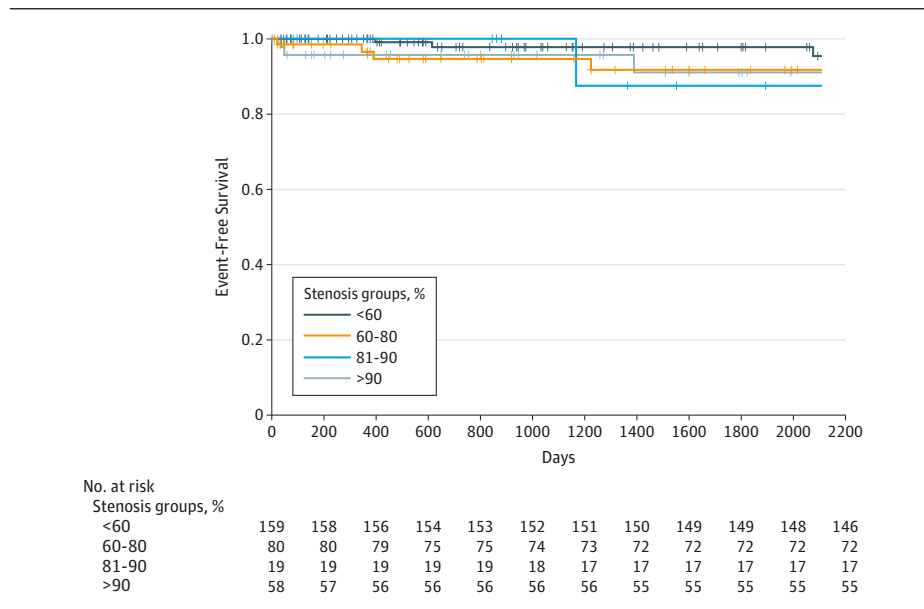
Cause of Death	No. (%) of Patients (N = 71)
Cancer	9 (12.7)
COPD	2 (2.8)
Sudden death or cardiac arrest	8 (11.3)
Congestive heart failure	5 (7.0)
Intracranial hemorrhage	1 (1.4)
Myocardial infarction	11 (15.5)
Pulmonary embolism	1 (1.4)
Sepsis (eg, pneumonia, aspiration, other infection)	8 (11.3)
Renal failure	2 (2.8)
Stroke	1 (1.4)
Parkinson disease	3 (4.2)
Other hemorrhage	2 (2.8)
Mesenteric ischemia	1 (1.4)
Complications from ileostomy	1 (1.4)
Unknown	16 (22.5)

Abbreviation: COPD, chronic obstructive pulmonary disease.

Discussion

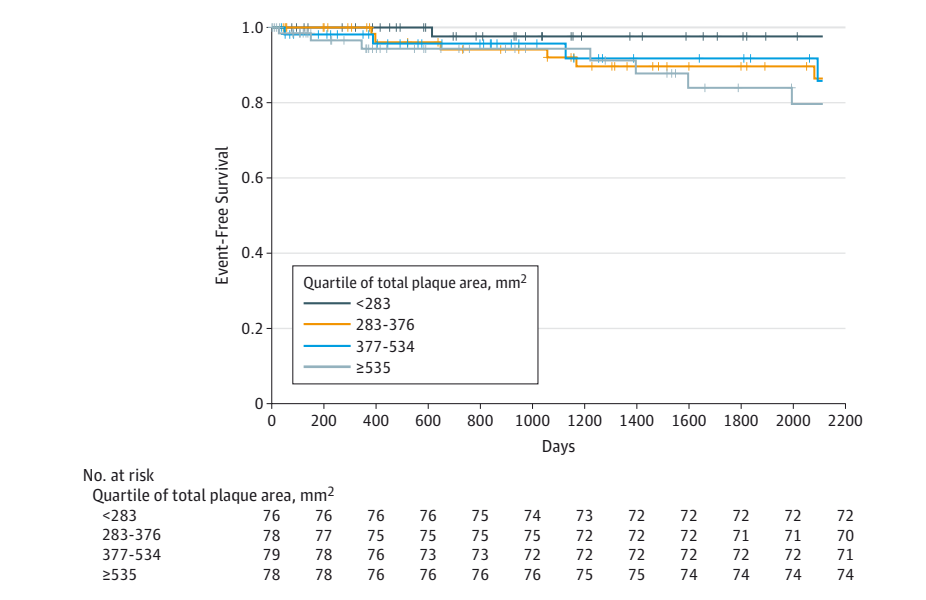
In our stroke prevention clinic and premature atherosclerosis clinic, high-risk patients with vascular disease undergo

Figure 2. Event-Free Survival by Groups of Percent Stenosis of the Index Carotid Artery



In Kaplan-Meier analysis, survival after the index carotid occlusion free of ipsilateral stroke or transient ischemic attack, death from ipsilateral stroke, or death from unknown cause was not predicted ($P = .80$, log-rank test) by severity of stenosis before the index occlusion by groups (<60%, 60%-80%, 81%-90%, and >90%). Plots were truncated at 2000 days because of low numbers surviving after that time, but the P values from log-rank tests are for the entire follow-up period.

Figure 3. Event-Free Survival by Quartile of Carotid Plaque Burden



In Kaplan-Meier analysis, survival free of ipsilateral stroke or transient ischemic attack, death from ipsilateral stroke, or death from unknown cause was significantly predicted ($P = .006$, log-rank test) by quartile of carotid plaque burden (total plaque area) at the time of the occlusion (<283 mm², 283-377 mm², 377-535 mm², and ≥ 535 mm²). Plots were truncated at 2000 days because of low numbers surviving after that time, but the P values from log-rank tests are for the entire follow-up period.

annual carotid ultrasonographic examinations to quantify their carotid plaque burden for the purpose of “treating arteries instead of risk factors.”^{7(p 1193)} We took advantage of that circumstance to analyze the risk of stroke at the time of a de novo carotid occlusion. We found that among patients with asymptomatic carotid disease, only 1 of 316 (0.3%) had a stroke at the time of a new carotid occlusion. Neither severity of stenosis of the index artery before occlusion nor the presence of a prior contralateral carotid occlusion predicted the risk of events during follow-up after the occlusion.

Among patients receiving intensive medical therapy, the risk of stroke at the time of a carotid occlusion is thus much lower than the risk of intervention. Even in the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST),¹² the 30-day risk of stroke or death for asymptomatic patients was 2.5% for stenting and 1.4% for endarterectomy; the 4-year risk was 4.5% for stenting and 2.7% for endarterectomy. In real-world practice, the risk is much higher: Wang et al⁴ reported that in Medicare patients the 1-year risk of stroke or death was 16.7% for stenting and 11.0% for endarterectomy. More recently, Jalbert et al¹³ found that among Medicare patients subjected to carotid stenting, the 30-day rate of death was 1.7%, the risk of stroke or TIA was 3.3%, and the risk of myocardial infarction was 2.5%. During a mean follow-up time of 2 years, mortality was 27.7% among asymptomatic patients. The CREST-2 trial¹⁴ is under way with a contemporaneous medical therapy arm; the corresponding European trial does not have a medical arm. Given the marked decrease in the risk of asymptomatic stenosis since 2005, it is not legitimate to use the event rate in the medical arm of studies conducted more than a decade ago to justify routine intervention based on the risks in the CREST trial, which had no medical arm.¹⁵

Patients with carotid stenosis are at high risk of death, but as indicated in Table 2, most of the deaths are not from stroke. Carotid stenting or endarterectomy can therefore not be expected to improve those outcomes.

Spence et al¹¹ reported in 2002 that carotid plaque burden, measured as total plaque area, was a strong predictor of cardiovascular events, after adjustment for coronary risk factors, and others have found that total plaque area is a stronger predictor of myocardial infarction^{16,17} or stroke¹⁸ than carotid intima media thickness. Our finding that carotid plaque burden was a stronger predictor of cardiovascular events than stenosis confirms our previous report in 2004.¹⁹ The burden of carotid atherosclerosis predicts outcome more strongly than the percent stenosis.

Few previous studies^{20,21} have investigated the neurologic consequences of progression to internal carotid occlusion, and to our knowledge, only 1 previous study⁵ focusing solely on carotid occlusion in asymptomatic patients has been conducted. Naylor et al⁵ analyzed the consequences of new occlusion in the ACST: “for every 700 asymptomatic patients with a 70-99% asymptomatic stenosis treated medically, seven will occlude their carotid artery each year, but only 1 of the 700 will suffer an ipsilateral stroke.”^{5(p 636)} This result validates our findings.

This study has some limitations. We did not perform brain imaging unless patients had a stroke, so we cannot state the frequency of silent infarction. We also did not investigate the adequacy of collateral circulation, including the patency of the ipsilateral external carotid artery. Furthermore, we did not study patients who became symptomatic and had intervention for that reason. It is also possible that some patients who did not return for follow-up may have had events that were missed because they went to a different hospital; however, our hospital is the only tertiary care hospital and the designated regional stroke hospital in Southwestern Ontario (the region from which patients were referred). Patients who did not respond to notification of follow-up appointments (or their family or family physician) were called to determine their status.

Spence et al²² found in 2005 that among patients with ACS, the absence of microemboli detected by transcranial Doppler ultrasonography was associated with such a low risk of stroke

(1%) and such a tight 95% CI (1.01-1.36) that such patients could not be expected to benefit from endarterectomy or stenting unless it could be performed with a risk less than 1%. Most of the events occurred in the first year.²² Microemboli were present in 12.6% of patients before 2003; then with more intensive therapy as described in eTable 1 in the Supplement, the prevalence of microemboli decreased to 3.7% of patients with ACS,² suggesting stabilization of plaque. The annual rate of ipsilateral stroke associated with ACS has decreased to less than 1% during the past 20 years.^{3,23} Therefore, most patients with ACS would be better served by intensive medical therapy than by carotid endarterectomy or carotid stenting.⁶ Naylor et al⁵ calculated that even assuming an operative risk of zero, 93% of endarterectomies would have been unnecessary, even in the historical studies that are used to justify intervention.

Progression of stenosis, although often touted as a reason for intervention, is of limited use in identifying patients who should have intervention.^{5,6} Although Hirt²⁴ reported that progression of stenosis was predictive of events in the ACST, both Spence et al⁶ and Naylor et al⁵ pointed out that the proportion of patients was very small: "Among the 1469 patients in the study, there were events in only 50 (3.4%), among the 117 (8%) of patients with progression by ≥ 2 grades of stenosis. It must also be understood that the ACST trial was conducted before the widespread implementation of

intensive medical therapy that has diminished the stroke risk picture markedly."^{24(p 655)}

The small proportion of patients with ACS (approximately 10%) who could benefit from endarterectomy can be identified by the presence of microemboli on transcranial Doppler ultrasonography^{2,22,25} or reduced cerebrovascular reserve,²⁶ and a number of other modalities are being studied that may slightly increase this proportion. Other methods for identifying high-risk asymptomatic stenosis that are in development include ulceration on 3-dimensional ultrasonography,²⁷ echolucency,^{28,29} plaque texture, intra-plaque hemorrhage on magnetic resonance imaging, neovascularity on contrast ultrasonography of carotid plaques, and plaque inflammation on positron emission tomography with fluorodeoxyglucose.^{6,30}

Conclusions

The risk of ipsilateral stroke at the time of carotid occlusion was well below the risk of carotid stenting or carotid endarterectomy, and the percent stenosis or contralateral occlusion did not identify patients who would benefit from intervention. Preventing carotid occlusion may not be a valid indication for intervention.

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Study concept and design: Bogiatzi, Spence.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yang, Spence.

Critical revision of the manuscript for important intellectual content: Bogiatzi.

Statistical analysis: All authors.

Administrative, technical, or material support: Bogiatzi, Spence.

Study supervision: Bogiatzi, Spence.

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