Effects of Intensive Medical Therapy on Microemboli and Cardiovascular Risk in Asymptomatic Carotid Stenosis

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J. David Spence, MD; Victoria Coates, BA, HBSc; Hector Li, MD; Arturo Tamayo, MD; Claudio Muñoz, MD, PhD; Daniel G. Hackam, MD, PhD; Maria DiCicco, RVT; Janine DesRoches, RVT; Chrysi Bogiatzi, MD; Jonathan Klein, MD; Joaquim Madrenas, MD, PhD; Robert A. Hegele, MD

Objective: To assess the effect of more intensive medical therapy on the rate of transcranial Doppler (TCD) microemboli and cardiovascular events in patients with asymptomatic carotid stenosis (ACS).

Design: A prospective study.

Setting: A teaching hospital.

Patients: Four hundred sixty-eight patients with ACS greater than 60% by Doppler peak velocity.

Main Outcome Measures: We compared (1) the proportion of ACS patients who had microemboli on TCD, (2) cardiovascular events, (3) rate of carotid plaque progression, and (4) baseline medical therapy, before and since 2003.

Results: Among 468 ACS patients, 199 were enrolled between January 1, 2000, and December 31, 2002; and 269 were enrolled between January 1, 2003, and July 30, 2007. Microemboli were present in 12.6% before 2003 and 3.7% since 2003 ($P<.001$). The decline in microemboli coincided with better control of plasma lipids and slower progression of carotid total plaque area. Since 2003, there have been significantly fewer cardiovascular events among patients with ACS: 17.6% had stroke, death, myocardial infarction, or carotid endarterectomy for symptoms before 2003, vs 5.6% since 2003 ($P<.001$). The rate of carotid plaque progression in the first year of follow-up has declined from 69 mm^2 (SD, 96 mm^2) to 23 mm^2 (SD, 86 mm^2) ($P<.001$).

Conclusions: Cardiovascular events and microemboli on TCD have markedly declined with more intensive medical therapy. Less than 5% of patients with ACS now stand to benefit from revascularization; patients with ACS should receive intensive medical therapy and should only be considered for revascularization if they have microemboli on TCD.

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PATIENTS WITH ASYMPTOMATIC carotid stenosis (ACS) are at high risk of vascular disease, more so for myocardial infarction than for stroke.[1] Therefore, all patients with ACS warrant intensive medical therapy for atherosclerosis. Although clinical trials showed a statistically significant reduction of stroke with carotid endarterectomy in the past,[2] the absolute risk reduction was a modest 1% per year, with no benefit for women.[3] The resulting number needed to treat with endarterectomy to prevent 1 stroke in 2 years, 67 to 83, is thus very high.[4,5] Furthermore, the benefit of surgery in clinical trials was predicated on less intensive medical therapy than is now prevalent and on a low surgical risk of stroke or death of only 3%, which is seldom duplicated in real-world practice.[6] To date, the literature does not support arterial stenting in asymptomatic patients, because it carries a risk of complications of approximately 5% to 12%.[7-9] The most recent results show that carotid stenting carries a higher risk than endarterectomy in symptomatic carotid stenosis[10-12] and ACS.[12] Recently, Abbott and colleagues[13,14] have called for a halt to revascularization for ACS.

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In 1990, we began to measure carotid total plaque area, defined as the sum of the cross-sectional areas of all plaques measured in a longitudinal view in the common, internal, and external carotids on both sides.[15,16] In 2002, we showed that total plaque area is a strong predictor of stroke, death, and myocardial infarction. Specifically, after adjusting for age, sex, cholesterol, systolic blood pressure, pack-years of smoking, diabetes, total homocysteine, and treatment of lipids and hypertension, we observed that patients

Author Affiliations are listed at the end of this article.

in the top quartile of total plaque area had a 3.4 times higher risk of stroke, death, and myocardial infarction during 5 years. This finding has since been validated in the Tromsø Study.[17] Furthermore, patients with total plaque area progression in the first year despite treatment of traditional risk factors according to consensus guidelines had twice the risk of those events, even after adjustment for the same panel of risk factors.[16] This caused us to change the paradigm for patient treatment in our vascular clinics from treating risk factors to treating arteries. Therapy was intensified in patients with a high plaque burden and further intensified if the plaque was progressing despite achieving target levels of risk factors like blood pressure, smoking cessation, and low-density lipoprotein cholesterol. The explicit goal is to achieve plaque regression as opposed to merely attaining specified target levels of intermediate traits such as blood pressure or plasma lipoprotein profile.

Microemboli, as detected by transcranial Doppler (TCD) monitoring, were associated with increased risk of stroke among patients with symptomatic carotid stenosis,[18] and in a mixed population of patients with symptomatic and asymptomatic carotid stenosis.[19] In 2005 we reported[20] that among patients with ACS, TCD-detected microemboli were very useful in identifying patients who might be candidates for revascularization. Among the 90% of ACS patients who had no microemboli, the risk of stroke within 1 year was only 1% (95% confidence interval, 1.01-1.36). Patients with such a low risk would not stand to benefit from procedures, such as endarterectomy, which showed a real-world, 30-day risk of stroke or death of 4% to 7%,[6] or stenting, which showed stroke or death risks of approximately 5% to 12%.[8,21] On the other hand, the 10% of patients with microemboli had a stroke risk in the first year of 15.6% (95% confidence interval, 4.1-79), suggesting that they might be more optimal candidates for revascularization.

Finally, during a study of biological differences among ACS patients, we found, to our frustration, that in the past few years we became less able to find sufficient numbers of patients with microemboli on TCD to achieve the planned statistical power. We had observed in our earlier study[20] that among those with emboli at baseline, they were present in only 34% of patients after 1 year and only 9% after 2 years, suggesting that microemboli decline with medical therapy. We therefore hypothesized that the incidence of microemboli was reduced in ACS patients because of more intensive medical therapy in recent years and that this reduced incidence was coincident with instituting more aggressive medical therapy, probably through stabilization of carotid plaques. We also hypothesized that more intensive medical therapy may have reduced the risk of patients with microemboli and that the predictive value of microemboli may therefore have been reduced by more intensive medical therapy. We report herein the investigations undertaken to test those hypotheses.

METHODS

CLINICAL POPULATIONS

The study population was recruited beginning in 2000 for a prospective peer-reviewed study funded by the Heart and Stroke Foundation of Ontario to investigate whether TCD microemboli predicted cardiovascular risk in ACS. Patients consented to a protocol approved by the University of Western Ontario ethics review board. The initial results of the study, in the first 319 patients, were published in 2005.[16] Patients were included in the study if they had ACS of at least 60%, defined by peak velocities that qualified patients in our laboratory for the Asymptomatic Carotid Artery Surgery trial. Approximately one-third of the patients had been referred to J.D.S. at the Stroke Prevention Clinic at University Hospital in London, Ontario, Canada, because they had ACS detected by the referring physician (usually a bruit led to carotid ultrasonography). Asymptomatic carotid stenosis was detected in the remainder of patients in the course of routine carotid Doppler ultrasonography examinations when they came for measurement of carotid plaque area or for visits to our Stroke Prevention Clinic or Atherosclerosis Prevention Clinic.[22]

PLAQUE MEASUREMENT

All patients underwent a baseline measurement of total plaque area, with serial follow-up measurements at approximately annual intervals, as previously described.[16] Briefly, all plaques seen in the common, internal, and external carotids on both sides of the body were measured by duplex sonography by 2 sonographers (M.D. and J.D.; both are very experienced in measurement of total plaque area; M.D. invented plaque area measurement in our laboratory in 1990). Plaque was measured with an ATL/Phillips HDI 5000 duplex scanner with compound imaging (SonoCT; Philips, Andover, Massachusetts). The cross-sectional area of each plaque was measured in a longitudinal view in the plane where the plaque area was greatest; the total of the cross-sectional areas of all plaques was total plaque area. As previously reported,[16] the interobserver κ for plaque measurement was 0.85.

TRANSCRANIAL DOPPLER

The analyses presented in this article are based on the presence of microemboli at the baseline TCD study. All patients underwent a routine TCD study with a 2-MHz probe to identify intracranial stenosis. This was followed by monitoring of both middle cerebral arteries, preferably in the M1 segment, through a posterior or middle temporal window. Middle cerebral arteries were identified bilaterally within depths of insonation of 35 to 56 mm from the temporal window and monitored for up to 1 hour, using a head-fixation device. Because the headgear is somewhat uncomfortable and because some patients had difficulty lying still for long periods, monitoring was stopped after at least 40 minutes or if the test was positive (exhibiting >2 microemboli ipsilateral to the stenosed carotid artery). Two TCD machines were used to monitor patients: a Nicolet TC 4040 Pioneer for the first 150 patients and a PMD 100 (TCD 100 M) flow Trax Power M-Mode Doppler for the remainder. Microembolic signals were defined by unidirectionality, duration of shorter than 300 milliseconds, and intensity of more than 8 dB above the Doppler background, with adjustment of gain to enhance detection. The settings for microembolus detection were leading cols of 255 mm, trailing cols of 255 mm, a microemboli threshold of 9 mm, and rejection of 55 mm, corresponding to international consensus recommendations.[23] All sessions were recorded on the machine's hard drive for review and confirmation of microembolic signals noted during monitoring.

Intracranial stenosis was diagnosed if there was a stenosis of 50% or greater of a middle cerebral artery; this was defined by a peak systolic velocity of 150 cm/s, with a mean velocity of 100 cm/s in the absence of a generalized hyperdynamic state. Patients were categorized as having or not having intracranial stenosis.

Table 1. Baseline Characteristics of Patients With Asymptomatic Carotid Stenosis by Emboli Status

Characteristic	Mean (SD)		*P* Value[a]
	No Emboli	Microemboli	
Age, y	68.63 (9.02)	66.43 (8.10)	.37
SBP, mm Hg	148.05 (24.24)	148.82 (18.50)	.92
DBP, mm Hg	79.93 (11.60)	81.73 (13.61)	.62
Total plaque area, cm^2	2.84 (1.58)	3.30 (1.38)	.09
Carotid stenosis %[b]	114.00 (38.13)	127.97 (37.39)	.05
C-reactive protein, mg/L	6.45 (20.73)	4.98 (4.18)	.72
Total cholesterol, mg/dL	171 (41)	183 (39)	.10
Triglycerides, mg/dL	150 (119)	170 (103)	.33
HDL cholesterol, mg/dL	51 (18)	49 (15)	.60
LDL cholesterol, mg/dL	92 (36)	98 (35)	.28
Cholesterol to HDL ratio	3.62 (1.42)	3.94 (1.26)	.19
Total homocysteine, µmol/L	10.41 (7.32)	16.00 (9.77)	<.001
Serum vitamin B_{12}, pg/mL	724 (459)	697 (394)	.76
Smoking, pack-years	24.06 (24.76)	30.83 (30.55)	.21
Intracranial stenosis %	31 (46)	61 (50)	.01
Female sex, %	37.5	42.9	.54
Smokers, %	18.43	42.9	.001
Diabetes, %	17.8	25.7	.18
Angina, %	32.0	31.4	>.99
Claudication, %	15.8	34.3	.01
SBP <130 mm Hg, %	23.4	22.9	.57
DBP <85 mm Hg, %	80.1	71.8	.16
LDL cholesterol <69 mg/dL, %	27.5	17.6	.15
Cholesterol to HDL ratio <3.5, %	55.4	35.3	.02

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; HDL, LDL, and total cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and vitamin B_{12} to picomoles per liter, multiply by 0.7378.

[a] For continuous variables, analysis of variance was used, contrasting patients with and without microemboli. For categorical variables, the Fisher exact test was used (2-sided).

[b] Sum of the left and right internal carotid artery.

Table 2. Baseline Characteristics of Patients With Asymptomatic Carotid Stenosis by Time of Study Enrollment

Characteristic	Mean (SD) by Enrollment		*P* Value[a]
	Before 2003	Since 2003	
Age, y	70.11 (8.98)	69.39 (8.96)	.39
SBP, mm Hg	146.59 (23.82)	141.45 (19.58)	.01
DBP, mm Hg	74.57 (13.26)	74.06 (11.67)	.66
Total plaque area, cm^2	2.48 (1.29)	2.86 (1.65)	.008
Carotid stenosis %[b]	97.43 (36.27)	88.0 (44.80)	.46
C-reactive protein, mg/L	6.79 (20.15)	5.72 (19.36)	.66
Total cholesterol, mg/dL	179 (36)	166 (44)	.001
Triglycerides, mg/dL	165 (153)	141 (84)	.03
HDL cholesterol, mg/dL	52 (18)	50 (18)	.37
LDL cholesterol, mg/dL	94 (37)	50 (18)	.18
Cholesterol to HDL ratio	1.32 (0.10)	1.47 (0.09)	.31
Total homocysteine, µmol/L	11.28 (6.44)	10.07 (4.10)	.02
Serum vitamin B_{12}, pg/mL	676 (422)	485 (242)	.004
Smoking, pack-years	20.36 (24.22)	28.47 (25.70)	.005
Intracranial stenosis %	36 (48.2)	31 (46.2)	.27
Female sex, %	42.2	33.8	.04
Smokers, %	18.1	21.6	<.001
Diabetes, %	18.6	18.2	.51
Angina, %	33.2	32.0	.43
Claudication, %	25.1	11.9	<.001
SBP <130 mm Hg, %	22.6	25.1	.31
DBP <85 mm Hg, %	75.4	82.5	.04
LDL cholesterol <69 mg/dL, %	21.9	31.5	.02
Cholesterol to HDL ratio <3.5, %	50.8	55.8	.17

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; HDL, LDL, and total cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and vitamin B_{12} to picomoles per liter, multiply by 0.7378.

[a] For continuous variables, analysis of variance was used, contrasting patients with and without microemboli. For categorical variables, the Fisher exact test was used (2-sided).

[b] Sum of the left and right internal carotid artery.

EVENTS

Events were ascertained by a questionnaire at each annual visit, followed up by review of hospital records and/or contact with family physicians. The database was designed a priori to assess a composite end point of stroke, death, myocardial infarction, or carotid endarterectomy for development of symptomatic stenosis.

STATISTICAL ANALYSIS

Data were entered and analyzed in SPSS, version 16.0 (SPSS Inc, Chicago, Illinois). Analysis of variance was used to compare continuous variables across groups. The χ^2 and the Fisher exact tests were used to compare categorical variables across groups (microemboli positive vs negative; before vs after 2003). The log-rank test was used in Kaplan-Meier survival analyses. Binary logistic regression with conditional entry of covariates was used to adjust for age, sex, smoking, systolic blood pressure, cholesterol, and cholesterol to high-density lipoprotein ratio for comparisons of rates of microemboli and events across groups.

We analyzed the proportion of patients with ACS who had microemboli at their first TCD embolus detection test before and after 2003, by which time our change to more intensive medical therapy had been implemented. We also analyzed the event rate among patients with and without microemboli at baseline and analyzed the mean rate of plaque progression, comparing patients with and without microemboli, and compared the baseline medical therapy at the time of referral at these 2 times.

Sample size calculations show that we needed a total of 398 patients to ascertain a 50% reduction in cardiovascular events in the post-2003 compared with the pre-2003 period, given a cumulative event rate of 20%, power of 80%, and 2-tailed α level of .05.

INTENSIVE THERAPY

By 2003, we had implemented in our clinic a change of treating arteries, rather than simply treating risk factors. Our approach to intensive therapy for accelerated atherosclerosis has previously been described.[24] Therapy was intensified in patients with plaque progression despite routine therapy. This included (1) showing the plaque measurements and plaque images to the patients to impress on them that their plaque was progressing to motivate them to adhere to smoking cessation, exercise, medication, and a Mediterranean diet; (2) increasing the dose of statins to the maximum tolerated dose, regardless of low-density lipoprotein levels (eg, 80 mg of atorvastatin or

Table 3. Medical Therapy at the Time of Enrollment in the Study

Drug Class/Dose Category	% by Microemboli			% by Enrollment		
	No Emboli (n=431)	Microemboli (n=37)	*P* Value	Before 2003 (n=199)	Since 2003 (n=269)	*P* Value
Lipid-lowering	44.0	60.0	.13	44.1	59.2	.01
Statins	26.0	16.2	.13	13.6	33.8	<.001
Niacin	2.6	2.7	.76	2.0	3.0	.70
Ezetimibe	2.2	0.0	.66	0.0	2.9	.18
Fibrates	2.9	5.0	.47	3.2	2.9	.88
Antihypertensives	53.8	55.0	.92	44.1	58.3	.02
Hydrochlorothiazide	4.2	13.5	.01	8.0	2.6	.007
ACE inhibitor	16.0	3.5	.69	10.6	19.7	.007
ARB	2.3	0.0	.44	1.0	3.0	.15
Calcium-channel blocker	7.2	8.1	.84	4.5	9.3	.05
β-blocker	16.0	13.5	.69	9.0	20.0	.001
Aspirin	68.7	78.4	.22	68.8	69.9	.81
Clopidogrel	21.1	27.0	.40	12.6	28.3	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

40 mg of rosuvastatin); (3) in patients already at their maximum tolerated dose of statins, adding ezetimibe; (4) in those already taking maximum doses of statins and ezetimibe, adding niacin for patients who did not have diabetes or adding fibrates for diabetic patients or those unable to take niacin or slow-release niacin because of flushing; (5) ensuring that the patient was taking an angiotensin-converting enzyme inhibitor, or for those not able to take them because of cough or angioedema, ensuring that they were taking an angiotensin-receptor blocker; (6) optimizing blood pressure control by individualizing therapy according to the renin/aldosterone profile[24]; and (7) in some patients with insulin resistance (defined by a high fasting insulin level with normal serum glucose level), metformin or pioglitazone was added before the onset of diabetes.

RESULTS

There were 468 patients with ACS who underwent TCD embolus detection for the first time between 2000 and 2007; 199 were seen between January 1, 2000, and December 31, 2002 (referred to hereafter as *before 2003*), and 269 were seen between January 1, 2003, and June 30, 2007 (referred to hereafter as *since 2003*). The database was locked as of July 1, 2008, at which point all patients had at least 1 year of follow-up. Of the total, 7.4% had microemboli, 37.9% were female, 20% were smokers, 18.4% had diabetes, 32% had a history of angina, 11.2% had experienced a myocardial infarction, and 17.2% had intermittent claudication. Mean age was 69.73 years (standard deviation [SD], 8.96 years). Baseline characteristics of this group are presented in **Table 1** and **Table 2**, divided into those presenting before and after 2003 and with and without microemboli at baseline. The prevalence of microemboli was 12.6% before 2003 and 3.7% since 2003 ($P<.001$). After adjustment in binary logistic regression for age, sex, smoking, systolic blood pressure, serum cholesterol, and cholesterol to high-density lipoprotein cholesterol ratio, the difference remained significant ($P=.02$).

Patients with microemboli had significantly greater carotid stenosis on the index side compared with patients without microemboli: 84.19% vs 76.63% ($P=.006$). Plasma total homocysteine concentration was significantly higher among patients with microemboli (mean [SD], 16.0 [9.77] vs 10.41 [7.32] μmol/L). Those with microemboli were significantly more likely to be smokers and to have intermittent claudication; they were also more likely to have intracranial stenosis (Table 1).

Table 3 shows that since 2003, patients were significantly more likely to be taking statins, angiotensin-converting enzyme inhibitors, and clopidogrel at the time of their baseline TCD embolus detection. The medication profiles shown in Table 3 are of medication the patient was taking at the time of referral, after which their therapy was intensified. **Figure 1** shows that plasma lipid profiles improved steadily from 2000 to 2007. This resulted in a significant reduction in the rate of plaque progression. Before 2003, plaque progressed by a mean of 69 mm^2 (SD, 96 mm^2); since 2003, plaque progressed by only 23 mm^2 (86 mm^2; $P<.001$). The decline in plasma lipids and in plaque progression show that therapy during follow-up was more intensive after 2003.

Table 4 shows that patients with microemboli had significantly more cardiovascular events. Stroke, death, myocardial infarction, or carotid endarterectomy after development of symptoms occurred in 32.4% of patients with microemboli vs 8.6% of those free of microemboli ($P<.001$); this remained significant after adjustment in binary logistic regression for age, sex, smoking, systolic blood pressure, serum cholesterol, and cholesterol to high-density lipoprotein cholesterol ratio ($P=.05$). Stroke, death, or carotid endarterectomy after development of symptoms occurred in 32.4% of those with microemboli vs 6.5% of those without microemboli ($P<.001$); this remained significant in logistic regression as described above ($P<.001$). The proportion of patients with cardiovascular events has declined markedly with more intensive medical therapy, from 17.6% of patients enrolled before 2003 to 5.2% since 2003 ($P<.001$). This remained significant after adjustment in binary logistic regression as described above ($P=.003$).

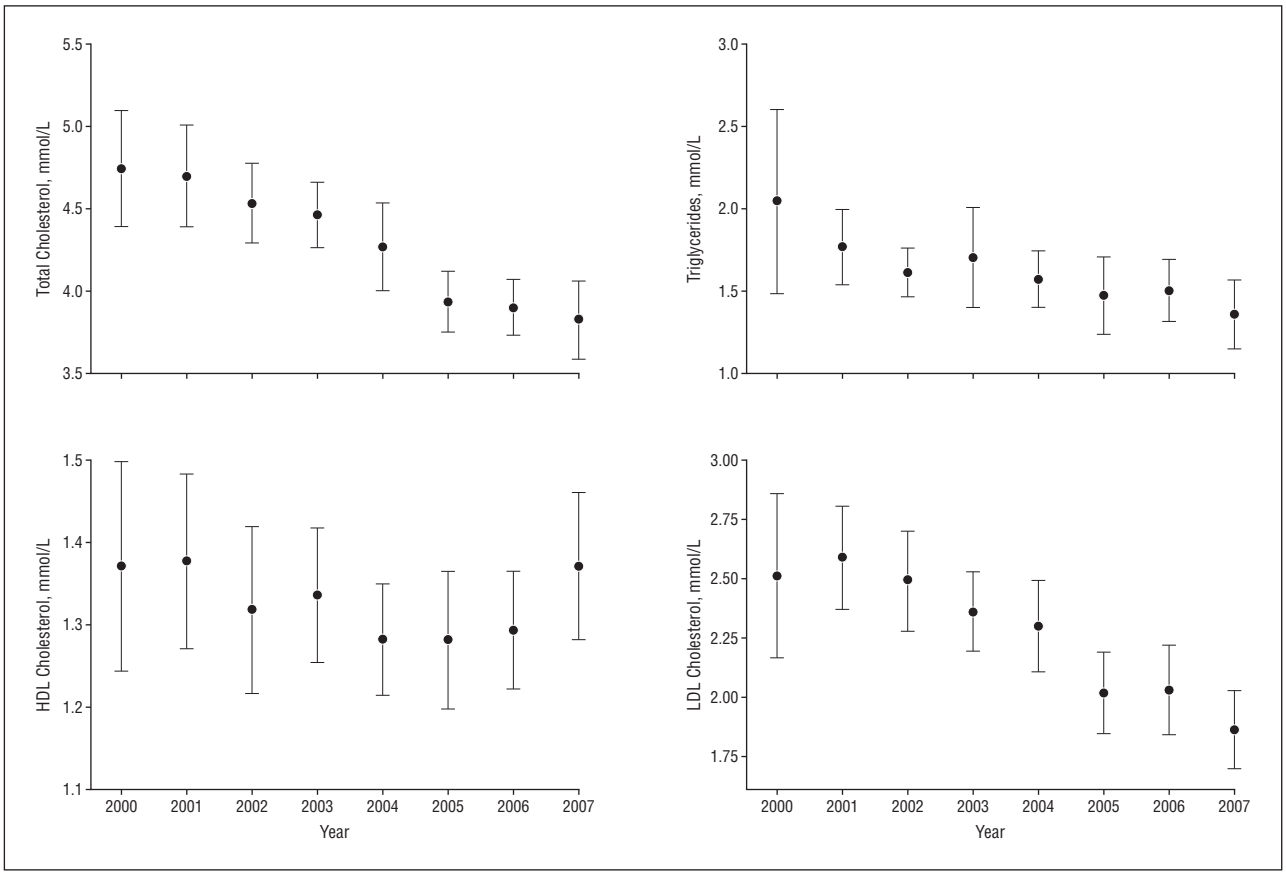

Figure 1. Levels of serum lipids by year of baseline. Error bars represent 95% confidence intervals. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

Table 4. Events in Patients With Asymptomatic Carotid Stenosis

Event	No. (%) by Microemboli			No. (%) by Enrollment		
	No Emboli (n=431)	Microemboli (n=37)	*P* Value	Before 2003 (n=199)	Since 2003 (n=269)	*P* Value[a]
Stroke						
In year 1	5 (1.4)	3 (10.3)	.02	6 (3.3)	2 (1)	.16
In year 2	5 (1.8)	5 (18.5)	.001	10 (5.5)	0	.01
MI						
In year 1	8 (2.2)	2 (6.9)	.16	9 (4.9)	1 (0.5)	.01
In year 2	5 (1.4)	1 (3.2)	.39	5 (2.7)	1 (0.5)	.10
Death						
In year 1	9 (2.8)	3 (10.3)	.07	8 (4.4)	4 (2.4)	.39
In year 2	6 (2.1)	1 (3.7)	.48	7 (3.8)	0	.04
CEA						
Year 1	5 (1.4)	4 (12.9)	.003	5 (2.7)	4 (1.9)	.74
Year 2	1 (0.3)	1 (3.7)	.15	2 (1.1)	0	.50
Stroke, death, or CEA in first 2 years	28 (6.5)	12 (32.4)	<.001	28 (14.1)	12 (4.5)	<.001
Stroke, death, MI, or CEA in first 2 years[b]	37 (8.6)	12 (32.4)	<.001	35 (17.6)	14 (5.2)	<.001

Abbreviations: CEA, carotid endarterectomy (after development of symptoms); MI, myocardial infarction.
[a] Fisher exact test, 2-sided.
[b] Includes only the first event.

Figure 2 shows the Kaplan-Meier survival plots for patients entering the study before and after 2003 and for patients with and without microemboli at baseline. Survival free of stroke, death, or myocardial infarction was significantly better for patients without microemboli and for patients who entered the study after 2003 (log-rank test, $P<.001$ for both analyses).

COMMENT

We found that patients with microemboli remain at a much higher risk, even with more intensive medical therapy, than those without. Table 4 shows that 32.4% of patients with microemboli had a stroke, myocardial infarc-

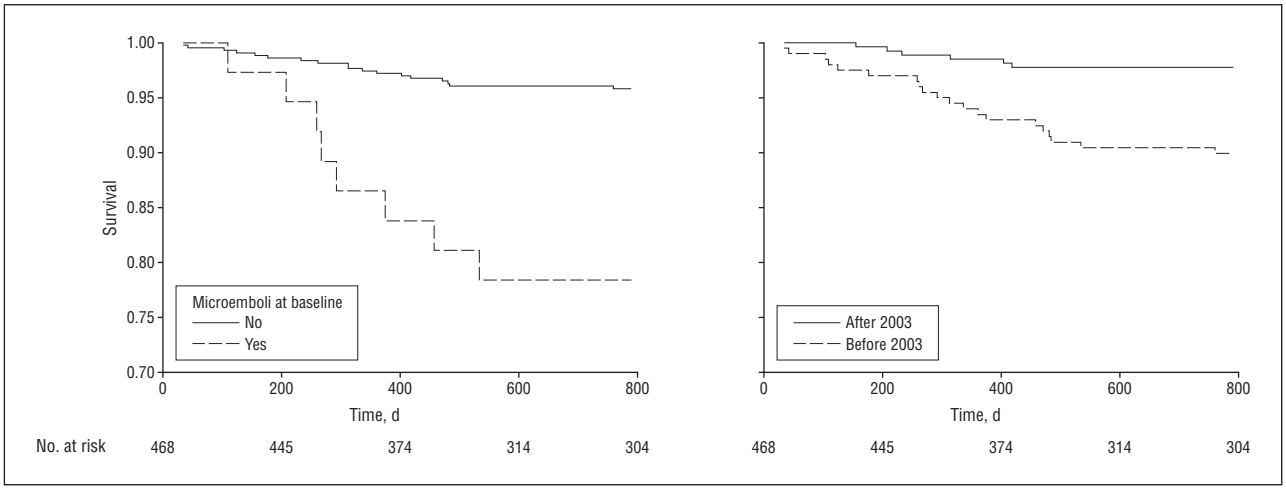

Figure 2. Kaplan-Meier survival plots by year of entry into the study and presence or absence of microemboli at baseline. Survival free of stroke, death, or myocardial infarction was significantly better for patients entering the study after 2003 and for patients without microemboli at baseline (log-rank test, $P<.001$ for both).

tion, required carotid endarterectomy because their carotid stenosis became symptomatic, or died in the first 2 years; these events occurred in only 8.6% of those without microemboli. However, the 1-year risk of stroke among patients with microemboli has declined from the 15.6% we reported earlier[20] to 10.3%. Risk among patients without microemboli remains low at 1.4%; it should be noted that this is lower than the risk of endarterectomy or stenting. Among patients enrolled since 2003, the rate of events was only 5.2% vs 17.6% of those enrolled between 2000 and 2003, when patients were receiving therapy based on consensus guidelines. These findings confirm that patients with carotid stenosis are at high risk and therefore may require more intensive medical therapy than consensus guidelines recommend and that more intensive medical therapy has markedly reduced not only microemboli, but also cardiovascular events.

Historically, it was thought that patients with ACS would benefit from revascularization if it could be done with a risk of 3% or less. This was based on the Asymptomatic Carotid Artery Surgery study and Asymptomatic Carotid Surgery Trial,[25] which were carried out largely before widespread use of statin drugs (particularly in patients without coronary artery disease). Our findings indicate that with more intensive medical therapy, the stroke risk in ACS and therefore the potential benefit of revascularization have markedly declined.

Hackam and Spence[26] recently calculated that intensive combination therapy could potentially reduce the risk of recurrent stroke by more than 90% in the highest-risk patients. As reported by Rothwell et al,[27] the age-adjusted incidence of stroke in Oxfordshire declined by 40% between 1981 and 2004, probably as the result of more intensive medical therapy, and stroke incidence has also been declining in Ontario, Canada, since the implementation of a provincial network of stroke-prevention clinics.[28] More recently, Rothwell et al[29] have shown that urgent treatment of patients with transient ischemic attacks has markedly reduced the risk of stroke.

The arguments against routine revascularization of patients with ACS have previously been reviewed.[4,7] Given our finding that intensive medical therapy has reduced the prevalence of microemboli to only 3.7% and markedly reduced cardiovascular events, particularly stroke, we suggest that such intensive medical therapy be regarded as the first line of therapy for patients with ACS. Given that with intensive medical therapy, the risk of stroke in patients without microemboli is less than the risk of endarterectomy or stenting, we think that revascularization should be considered only for the rare patients with microemboli. Revascularization would only be appropriate in patients without microemboli if it could be done with a risk of less than 1%.

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Author Affiliations: Stroke Prevention and Atherosclerosis Research Centre (Drs Spence, Tamayo, Muñoz, Hackam, Bogiatzi and Klein; and Mss Coates, DiCicco, and DesRoches), Immunology Laboratory (Dr Madrenas), and Blackburn Laboratory in Genetics of Atherosclerosis (Dr Hegele), Robarts Research Institute; and Schulich School of Medicine and Dentistry, University of Western Ontario (Drs Spence, Li, Hackam, Madrenas, Klein, and Hegele), London, Ontario, Canada; Brandon Regional Health Centre, Brandon, Manitoba, Canada (Dr Tamayo); and Medical School, Democritus University of Thrace, Alexandroupolis, Greece (Dr Bogiatzi).
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Correspondence: J. David Spence, MD, Stroke Prevention and Atherosclerosis Research Centre, 1400 Western Rd, London, ON N6G 2V2, Canada (dspence@robarts.ca).
Author Contributions: *Study concept and design:* Spence, Li, Madrenas, and Hegele. *Acquisition of data:* Spence, Coates, Li, Tamayo, Muñoz, Hackam, DiCicco, DesRoches, Bogiatzi, and Klein. *Analysis and interpretation of data:* Spence, Coates, Li, Hackam, and Hegele. *Drafting of the manuscript:* Spence, Coates, Tamayo, DiCicco, DesRoches, Bogiatzi, Klein, and Hegele. *Critical revision of the manuscript for important intellectual content:* Spence, Li, Muñoz, Hackam, Madrenas, and Hegele. *Statistical analysis:* Spence, Hackam, and Hegele. *Obtained funding:* Spence. *Administrative, technical, and material support:* Spence, Coates,

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