11-1-2005

Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis who do not warrant endarterectomy or stenting

J. David Spence
Robarts Research Institute, jdspence@uwo.ca

Arturo Tamayo
Robarts Research Institute

Stephen P. Lownie
Western University

Wai P. Ng
Western University

Gary G. Ferguson
Western University

Absence of Microemboli on Transcranial Doppler Identifies Low-Risk Patients With Asymptomatic Carotid Stenosis

J. David Spence, MD; Arturo Tamayo, MD; Stephen P. Lownie, MD; Wai P. Ng, MD; Gary G. Ferguson, MD, PhD

Background and Purpose—Carotid endarterectomy clearly benefits patients with symptomatic severe stenosis (SCS), but the risk of stroke is so low for asymptomatic patients (ACS) that the number needed to treat is very high. We studied transcranial Doppler (TCD) embolus detection as a method for identifying patients at higher risk who would have a lower number needed to treat.

Methods—Patients with carotid stenosis of ≥60% by Doppler ultrasound who had never been symptomatic (81%) or had been asymptomatic for at least 18 months (19%) were studied with TCD embolus detection for up to 1 hour on 2 occasions a week apart; patients were followed for 2 years.

Results—319 patients were studied, age (standard deviation) 69.68 (9.12) years; 32 (10%) had microemboli at baseline (TCD+). Events were more likely to occur in the first year. Patients with microemboli were much more likely to have microemboli 1 year later (34.4 versus 1.4%; $P<0.0001$) and were more likely to have a stroke during the first year of follow-up (15.6%, 95% CI, 4.1 to 79; versus 1%, 95% CI, 1.01 to 1.36; $P<0.0001$).

Conclusions—Our findings indicate that TCD− ACS will not benefit from endarterectomy or stenting unless it can be done with a risk <1%; TCD+ may benefit as much as SCS if their surgical risk is not higher. These findings suggest that ACS should be managed medically with delay of surgery or stenting until the occurrence of symptoms or emboli. **(*Stroke*. 2005;36:2373-2378.)**

Key Words: asymptomatic carotid stenosis ■ endarterectomy ■ transcranial Doppler ■ ulcer ■ ultrasound ■ unstable plaque

Carotid endarterectomy is clearly beneficial for patients with severe (>70%) symptomatic stenosis,[1] but patients with moderate or asymptomatic stenosis are at lower risk and will benefit less from endarterectomy.[2] The Asymptomatic Carotid Artery Surgery (ACAS) trial[3] showed a statistically significant benefit of surgery for patients with asymptomatic stenosis >60%, but the number needed to treat to prevent one event in 2 years was very high, approximately 67.[4] As in the European Asymptomatic Carotid Surgery Trial (ACST) trial reported recently,[5] there was no benefit of surgery for the first 4 years and no benefit in women.[6] Furthermore, the surgical risk in ACAS and ACST (a 3% risk of morbidity or mortality) was substantially lower than in average practice. Such complication rates are seldom seen outside highly selective clinical trials. In a large regional survey of Medicare records, endarterectomy carried a 5.2% 30-day rate of stroke or death, so that in ≈60% of states, there was no benefit of endarterectomy for asymptomatic patients.[7]

Carotid stenting carries a substantial risk: in the CAVATAS trial,[8] the risk of stenting was 10%, and in SAPPHIRE, in which two thirds of patients were asymptomatic, the procedural risk of stenting with distal protection was 5%, with a 1-year event rate of 10%.[9]

It would therefore be useful to have methods for determining which patients with asymptomatic stenosis have a level of risk higher than that of surgery or stenting. One approach to identifying high-risk patients is transcranial Doppler detection of microemboli. Two small studies[10,11] in mixed populations (ACS and SCS) have suggested that microemboli detected by transcranial Doppler are associated with a higher risk of stroke. In this article, we report the results of follow-up for 2 years with respect to the presence of microemboli on transcranial Doppler in patients with asymptomatic carotid stenosis.

Methods

Patient Population

Consecutive patients with internal carotid stenosis ≥60%, based on a peak velocity ≥170 cm/s, a cutoff equivalent to that based on peak frequency shift established for our laboratory in the ACAS trial,[3] were included in the study. The patients were referred for asymptomatic stenosis or were identified during annual follow-up in the

Received February 26, 2005; final revision received July 5, 2005; accepted August 6, 2005.

From the Stroke Prevention & Atherosclerosis Research Centre (J.D.S., A.T.), Robarts Research Institute, and the London Health Sciences Centre (J.D.S., S.P.L., W.P.N., G.G.F.), University of Western Ontario, London, Canada; currently at the University of Manitoba (A.T.), Winnipeg, Canada.

Correspondence to J. David Spence, Stroke Prevention & Atherosclerosis Research Centre, 1400 Western Rd, London, Ontario, Canada N6G 2V2. E-mail dspence@robarts.ca

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000185922.49809.46**

Stroke Prevention Clinic of the London Health Sciences Centre. Some had experienced previous transient ischemic attack (TIA) but had been asymptomatic for at least 18 months, which placed them at a low risk similar to that of never symptomatic.[12]

Transcranial Doppler

All patients underwent a routine transcranial Doppler study (TCD) 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 between 35 to 56 mm from the temporal window and monitored for up to 1 hour on 2 occasions a week apart using a Spencer Mark 500 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 more than 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 for the remainder, a PMD 100 (TCD 100 mol/L) flow Trax Power M-Mode Doppler. Microembolic signals were defined by unidirectionality, duration of $<$300 ms, and intensity of $>$8 dB above the Doppler background, with adjustment of gain to enhance detection; settings for microemboli detection were: leading cols 255 mm, trailing cols 255 mm, microemboli-threshold 9 mm, and rejection 55 mm, corresponding to international consensus recommendations.[13] All monitoring was performed and analyzed by the same observer (AT). All sessions were recorded on the hard drive for review and confirmation of microembolic signals noted during monitoring. TCD monitoring was repeated annually. Figure 1 shows an example of a microembolic event.

Risk Factors

Age and sex were self-reported by the patients and supported by hospital records. Pack-years of smoking were defined as number of packs per day of cigarettes smoked multiplied by the number of years smoked. Blood pressure was measured in both arms recumbent with an automated device (Dinamapp), and the pressure in the arm with the higher pressure was recorded as baseline blood pressure.

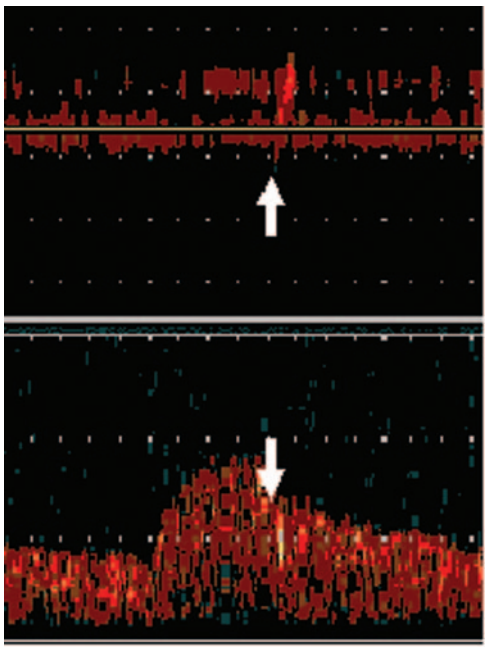

Figure 1. Microembolic signal on transcranial Doppler. (A) M-mode recording; the arrow points to an image of a microembolus; (B) the Doppler velocity envelope; the arrow points to the high-intensity transit signal created by the microembolus.

Biochemical and Genetic Determinations

After a 12-hour fast, blood was taken for biochemical determinations. Plasma total homocysteine (tHcy) was measured by high-performance liquid chromatography.[14,15] Plasma triglycerides and total and high-density lipoprotein cholesterol were determined as described.[14–17]

Blinding and Ascertainment

Ascertainment of events and follow-up embolus detection at yearly intervals were conducted blind to the microembolic status at baseline. Events were ascertained initially from interviews at annual follow-up or at earlier visits in the case of TIA or stroke and verified from review of hospital records. Strokes were defined as focal central nervous system deficits lasting more than 24 hours, with other causes excluded clinically and by computed tomography or magnetic resonance imaging. In the case of deaths outside the hospital, information was obtained from family members and from the referring physician.

Statistical Methods

Data were recorded in an Excel spreadsheet, which was converted to SPSS files for analysis in SPSS PC+ version 12. Analysis of variance was used to compare groups with respect to continuous variables; χ^2 was used to compare groups with respect to categorical variables. Kaplan-Meier survival analysis was performed and the log-rank statistic computed to compare event-free survival between TCD+ and TCD− cases. Point estimates and variances are provided as mean (SD). All probability values are 2-sided. Relative risk and 95% CI were computed for stroke at 1 year by microembolic status.

Results

There were 319 patients enrolled, mean age 69.65 (SD 8.83) years; 37.6% were female; 32 (10%) had microemboli at baseline (TCD+). Emboli were bilateral in one case; in all others, the emboli were present on the side of the index stenosis (the more severe stenosis if bilateral). Contralateral occlusion of the internal carotid was present on the left in 7.4% and on the right in 5.2% of cases; there was no stenosis on the right in 15% or on the left in 9.8% of cases. Fifty-nine (18.5%) had a remote TIA (ie, at least 18 months before they entered the study); these were not differently distributed among those with and without microemboli (P=0.26). Ten patients (4.1%) withdrew from the study; of these, only one had an event. In addition to those enrolled, 39 others were screened; 32 were excluded because of lack of temporal windows for transcranial Doppler and 7 were excluded because of atrial fibrillation.

During the first year 11 (3.4%) died, 8 (2.5%) had a stroke, 8 (2.5%) had TIAs, and 13 (4.1%) had a myocardial infarction. Causes of death were: 3 myocardial infarction, 3 sudden death, 2 stroke, one lung cancer, one renal failure, and one pulmonary hypertension. Five (1.6%) patients underwent endarterectomy because of the onset postenrollment of TIAs; of these, 4 had microemboli at baseline. Microemboli were present in 32 (10%) of patients at baseline. For the 2-year follow-up, 210 patients were available, because 62 had not yet completed 2 years of follow-up, 11 had died, and 36 had missed and rescheduled appointments after the 2-year point had passed. During year 2, 8 (2.5%) died, 7 (2.2%) had a myocardial infarction (MI), 5 (1.6%) had endarterectomy, 2 (0.6%) had a stroke, and one (0.3%) had a TIA. Causes of death were: 4 myocardial infarction, 2 congestive heart failure, one gastric cancer, and one pneumonia. In all, 53

TABLE 1. Baseline Characteristics of the Study Population by Microembolic Status: TCD+ vs TCD−

Baseline Characteristic, mean±SD	Embolic Status at Baseline: TCD−, n=287	Embolic Status at Baseline: TCD+, n=32	*P* Value (ANOVA)
Age, y	69.68±8.99	69.41±7.38	0.87
Systolic blood pressure, mm Hg	145.4±22.25	144.6±21.12	0.83
Diastolic blood pressure, mm Hg	73.7±11.98	73.4±14.86	0.91
Total cholesterol, mmol/L	4.61±1.02	4.58±0.92	0.91
Triglycerides, mmol/L	1.79±1.52	1.78±0.91	0.98
High-density lipoprotein cholesterol, mmol/L	1.34±0.49	1.29±0.39	0.62
Total homocysteine, μmol/L	10.1±4.53	16.20±10.07	<0.0001

Categorical Variables

Baseline Characteristic	Embolic Status at Baseline: TCD−, n=287	Embolic Status at Baseline: TCD+, n=32	Exact Significance χ^2
Male	62.7%	59.4%	0.43
Smoking	16.7%	37.5%	0.017
Diabetes	17.8%	28.1%	0.12
Claudication	20.6%	37.5%	0.029
Myocardial infarction	21.6%	21.9%	0.56
Angina	38%	34.4%	0.42
Previous TIA	19.2%	12.5%	0.26

ANOVA indicates analysis of variance.

(16.6%) patients had stroke, death, MI, or endarterectomy. Table 1 shows the baseline characteristics of the population; Table 2 shows results after 1 and 2 years of follow-up by the presence or absence of microemboli at baseline.

At 1 year of follow-up, microemboli were present in only 1.4% of those who were TCD− at baseline versus 34.4% of those who were TCD+ at baseline ($P<0.0001$); at 2 years, microemboli were present in only 1% of baseline TCD− versus 9.4% of baseline TCD+ ($P=0.004$).

Ten patients went on to endarterectomy because they became symptomatic (TIAs); these patients were significantly more likely to be TCD+ (Table 2). None of the events was a postoperative event.

Patients with microemboli were somewhat but not significantly more likely to be taking aspirin, angiotensin-converting enzyme inhibitors, statins, or clopidogrel (Table 3).

Degree of stenosis at baseline was not a predictor of events, perhaps because the severity of stenosis was not widely distributed: the mean severity was 79±14%.

There were no significant differences in traditional risk factors except for smoking, which was more prevalent among patients with microemboli at baseline. Plasma total homocysteine was significantly higher among patients with microemboli. Among TCD+, the relative risk was 15.6% (odds ratio,

TABLE 2. Emboli, Events, and Endarterectomy During the First and Second Year of Follow-Up by the Presence or Absence of Microemboli at Baseline

	Year 1			Year 2		
	Emboli at Baseline			Emboli at Baseline		
Event, n (%)	TCD−	TCD+	*P* Value	TCD−	TCD+	*P* Value*
	287	32		205	5	
Emboli at follow-up	4 1.4%	11 34.4%	<0.0001	3 1.0%	3 9.4%	0.004
TIA	4	4		1	0	
	1.4%	12.5%	0.004	0.3%	0%	0.90
Death	7	4		6	2	
	2.4%	12.5%	0.017	2.1%	6.3%	0.19
MI	10	3		5	2	
	3.5%	9.4%	0.13	1.7%	6.3%	0.15
Stroke	3	5		2	0	
	1.0%	15.6%	<0.0001	0.7%	0%	0.81
Endarterectomy	3	2		2	3	
	1.9%	6.3%	0.08	0.7%	9.4%	0.008

*P values are from χ^2 analysis.

TABLE 3. Medical Therapy at Baseline in Patients With and Without Emboli

Medication	Embolic Status: TCD+	Embolic Status: TCD−	*P* Value
ACE inhibitor	62.5%	47.8%	0.083
Aspirin	81.3%	66.3%	0.061
Clopidogrel	28.1%	19.2%	0.17
Statin	78.1%	71.7%	0.30
B vitamins	71.9%	59.8%	0.13

17.9): 15.6% (95% CI, 4.1 to 79) had a stroke in the first year versus 1% among TCD− (95% CI, 1.01 to 1.36; $P<0.0001$). In Cox regression, after adjustment for age, sex, cholesterol, and smoking, the difference was not significant ($P=0.38$). Only 2 strokes occurred in year 2, both among TCD− ($P=0.81$).

Figure 2 shows a Kaplan-Meier plot of survival free of stroke among patients with microemboli compared with those with no microemboli at baseline (log rank $P<0.0001$).

There were 8 strokes during the first year of follow-up; all but one were large-artery infarcts. Five occurred among patients with emboli at baseline and 3 among those without emboli at baseline ($P<0.0001$). One of the strokes among patients without baseline microemboli occurred in year 2, after the patient had become positive for microemboli. Among those with microemboli, all but one stroke were ipsilateral to the baseline microemboli; the exception was attributed to atrial fibrillation. Three of the ipsilateral strokes were preceded by TIAs ipsilateral to the microemboli (2 retinal, 1 hemispheric). None of the strokes was fatal, but 4 were disabling.

Discussion

We found that among patients without microemboli at baseline, only 1% had a stroke in the first year, meaning that they would only stand to benefit from either endarterectomy or stenting if it could be done with a risk of <1%. The confidence limits were very tight around the negative estimate, so it can be stated confidently that TCD− would be better off with intensive medical management and delay of surgery or stenting until the occurrence of symptoms or emboli. The numbers of strokes were small and the confidence limits wider around the positive estimate, so that although TCD+ had a 15.6-fold increase in risk of stroke and would be more likely to benefit, this hypothesis should be tested in clinical trials. Although it may seem obvious that they would benefit, the possibility that they may have a higher risk during surgery or stenting should be kept in mind. That the difference was not significant in Cox regression is probably not relevant to clinical decision-making, because age and sex are not treatable, and decisions about revascularization are made about individuals, not groups.

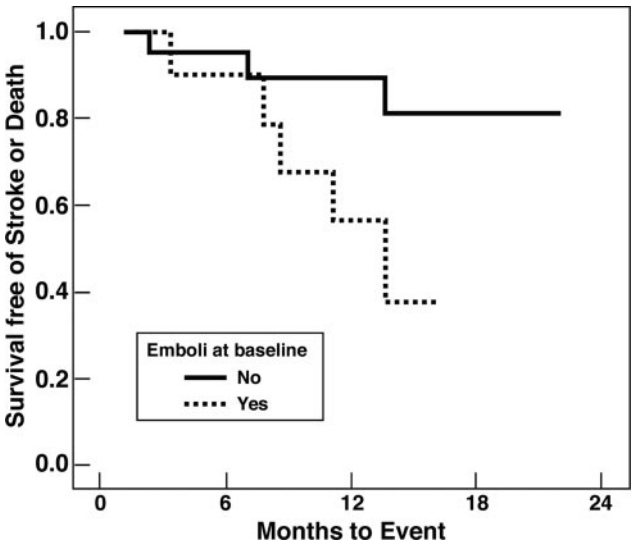

Figure 2. Survival free of stroke or death by microembolic status at baseline. A Kaplan-Meier plot shows that patients with microemboli at baseline were more likely to experience a stroke or death during 2 years of follow-up; most of the events occurred soon after the microemboli were detected. Log rank $P<0.0001$.

The presence of microemboli was not an independent predictor of MI or death, suggesting that the association with stroke was indeed likely to have been causal rather than confounded by some other unmeasured risk factor, in which case it would probably have predicted MI as well as stroke.

Although we did not study symptomatic patients, it seems likely that TCD embolus detection would also be helpful in deciding which patients with moderate symptomatic carotid stenosis (50% to 70%), a group with a risk intermediate between that of severe symptomatic and severe asymptomatic stenosis, might benefit more from endarterectomy. A recent study by Markus and McKinnon supports that hypothesis.[18]

We also confirmed that patients with asymptomatic carotid stenosis are at very high risk, not only of stroke, but also of death or MI: in the first year, 11 died, 8 had a stroke, and 13 had a MI. In the second year, 8 died, 2 had a stroke, and 7 had a MI. It is important to recognize that MI is more common than stroke in these patients and that intensive medical therapy is indicated in such patients. Indeed, these events occurred despite intensive medical therapy: the patients were all followed in our Stroke Prevention Clinic and were advised to take a Mediterranean diet (high in whole grains, fruits, vegetables, and beneficial oils, and low in cholesterol and animal fat), quit smoking, exercise, take aspirin or clopidogrel; most were prescribed statins with or without fibrates, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers if they were unable to take ACE inhibitors), and vitamins to reduce levels of total homocysteine. Patients with microemboli had been taking somewhat more intensive medical therapy (Table 3), so their higher risk cannot be explained by lack of medical therapy. It seems likely that the decline in events and microemboli from baseline to 2 years was related to plaque stabilization with medical therapy, as discussed subsequently.

It is interesting that our patients had a lower risk overall, 1.6% per year, than did patients in the medical arm of the ACAS trial (2% per year).[3] This may be explained by the effect of more intensive medical therapy and in that way reflects the decline in stroke apparently resulting from treatment of risk factors in the Oxfordshire studies recently reported by Rothwell et al.[19] Also of interest, we found even greater risk of stroke for patients with microemboli than did Markus et al in a smaller mixed population of symptomatic and asymptomatic cases.[11] It seems likely that this is based on a lower rate of events for asymptomatic patients without emboli and probably also on the shorter duration of monitoring in some cases because of discomfort. Similarly, our TCD+ had a higher risk than those described by Abbott et al, who repeated the TCD embolus detection on a 6-month basis.[20]

Performing endarterectomy with a complication rate of <3% is a tall order. It was achieved in the ACAS trial[3] and again in ACST.[5] The results of the latter trial were similar to those in ACAS and, in combination with Toole's subsequent call for population screening,[21] are bound to encourage even more inappropriate endarterectomy. It should be noted that although in ACAS there was a significant reduction of ipsilateral stroke, ACST showed, rather than a reduction of ipsilateral stroke, a reduction of the total of strokes on either side, a result that throws into doubt the benefit of surgery. Rothwell has reviewed some of the problems of applying to patients in actual practice the results of randomized trials,[22] and Rothwell and Goldstein have recently questioned the benefit of endarterectomy for asymptomatic patients, particularly in women.[23]

Even more worrisome is the widespread and growing tendency for cardiologists to stent asymptomatic carotid arteries despite the absence of any randomized, controlled trial evidence that carotid stenting is as safe as the <3% benchmark for complications of endarterectomy. The CAVATAS investigators asserted that angioplasty was as safe as endarterectomy, but as we pointed out[24] it was only as safe as bad endarterectomy: the surgical complication rate of 9.9% was slightly exceeded by the 10% complication rate of angioplasty.[24] Stenting is safer with distal protective devices that trap plaque fragments, but the recent results of the SAPPHIRE study indicate that in patients at high risk of surgery with >50% symptomatic or >80% ACS at high risk of surgery, surgical risk was 10% versus 5% for stenting with distal protection.[9] The 1-year rate of death, stroke, or MI was 12.2% with stenting versus 20.1% with endarterectomy, but there was no significant reduction of stroke alone. Because carotid stenting would not be expected to reduce the risk of MI, any benefit of stenting is questionable. Two thirds of patients in that trial were asymptomatic; our results make it clear that most of them could not have benefited from stenting.

The much higher levels of plasma total homocysteine in patients with microemboli suggest that homocysteine may have a role in aggravating plaque instability or in activating thrombi on the surface of rough plaques.[25–27]

Conclusions

Our results suggest that a policy of waiting until microemboli or symptoms occur would be preferable to immediate endarterectomy or stenting in patients with asymptomatic stenosis. Among patients with asymptomatic carotid stenosis, the absence of microemboli detected by TCD was associated with such a low risk of stroke (1%), with such tight 95% confidence limits (1.01 to 1.36) that such patients could not be expected to benefit from endarterectomy or stenting unless it could be done with a risk <1%. Most of the events occurred in the first year. Those with microemboli had a 15.6-fold increase in the risk of stroke over 1 year and thus represent a group who may benefit from intervention as much as do symptomatic patients, assuming that their surgical risk is not higher. Because the confidence limits were wide (4 to 79), this hypothesis should be tested in randomized, controlled trials.

Acknowledgments

J.D.S. conceived of the study, obtained funding, supervised the conduct of the study, engaged the enthusiasm of surgical colleagues for referral of patients, performed the statistical analyses, and wrote all drafts of the manuscript. A.T. recruited patients, performed the transcranial Doppler examinations, performed the data entry, and participated in revisions of the manuscript. W.P.N., S.P.L. and G.G.F. were involved in the design of the study, recruited patients, followed patients for end points, and participated in revisions of the manuscript. The study was funded by the Heart & Stroke Foundation of Ontario grant no. NA 4990.

References

1. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ. Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.
2. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. *Lancet*. 1999;353:2105–2110.
3. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;272:1421–1428.
4. Barnett HJM, Meldrum HE, Eliasziw M. The appropriate use of carotid endarterectomy. *CMAJ*. 2002;166:1169–1179.
5. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. MRS Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.
6. Rothwell PM. ACST. Which subgroups will benefit most from carotid endarterectomy? *Lancet*. 2004;364:1122–1123.
7. Kresowik TF, Bratzler D, Karp HR, Hemann RA, Hendel ME, Grund SL, Brenton M, Ellerbeck EF, Nilasena DS. Multistate utilization, processes, and outcomes of carotid endarterectomy. *J Vasc Surg*. 2001;33:227–234.
8. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357:1729–1737.
9. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501.
10. Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J, Steinmetz H. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. *Stroke*. 1995;26:2184–2186.
11. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 1999;30:1440–1443.
12. Barnett HJM, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe carotid stenosis. *N Engl J Med*. 1998;339:1415–1425.
13. Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke*. 1998;29:725–729.
14. Spence JD, Barnett PA, Marian AJ, Freeman D, Malinow MR, Hegele RA. Plasma homocyst(e)ine, but not MTHFR genotype, is associated with variation in carotid plaque area. *Stroke*. 1999;30:969–973.
15. Spence JD, Barnett PA, Bulman DE, Hegele RA. An approach to ascertain probands with a non traditional risk factor for carotid atherosclerosis. *Atherosclerosis*. 1999;144:429–434.
16. Hegele RA, Ban MR, Anderson CM, Spence JD. Infection-susceptibility alleles of mannose-binding lectin are associated with increased carotid plaque area. *J Invest Med*. 2003;48:198–202.
17. Spence JD, Ban MR, Hegele RA. Lipoprotein lipase (LPL) gene variation and progression of carotid artery plaque. *Stroke*. 2003;34:1178–1182.

18. Markus HS, Mackinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005;36:971–975.
19. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PA, Dennis MS, Warlow CP, Bamford JM, Anslow P. Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004. *Lancet*. 2004;363: 1925–1933.
20. Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. *Stroke*. 2005;36:1128–1133.
21. Toole JF. Surgery for carotid artery stenosis. *BMJ*. 2004;329:635–636.
22. Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet*. 1995;345:1616–1619.
23. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke*. 2004;35: 2425–2427.
24. Spence D, Eliasziw M. Endarterectomy or angioplasty for treatment of carotid stenosis? *Lancet*. 2001;357:1722–1723.
25. Quere I, Perneger TV, Zittoun J, Bellet H, Gris JC, Daures JP, Schved JF, Mercier E, Laroche JP, Dauzat M, Bounameaux H, Janbon C, de Moerloose P. Red blood cell methylfolate and plasma homocysteine as risk factors for venous thromboembolism: a matched case–control study. *Lancet*. 2002;359:747–752.
26. Signorello MG, Pascale R, Leoncini G. Effect of homocysteine on arachidonic acid release in human platelets. *Eur J Clin Invest*. 2002;32: 279–284.
27. Sauls DL, Wolberg AS, Hoffman M. Elevated plasma homocysteine leads to alterations in fibrin clot structure and stability: implications for the mechanism of thrombosis in hyperhomocysteinemia. *J Thromb Haemost*. 2003;1:300–306.