Carotid artery stenosis in patients with peripheral arterial disease: The SMART study

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Purpose: **The prevalence of asymptomatic internal carotid artery stenosis (ICAS) in patients with peripheral arterial disease (PAD) and characteristics that are associated with ICAS were studied.**

Methods: **We used data from the first 600 patients enrolled in the Second Manifestations of ARTerial disease (SMART) study, a single-center, prospective cohort study among patients referred with a manifestation of cardiovascular disease, diabetes mellitus, hypertension, or hyperlipidemia. Included in the analysis were 162 patients with PAD or a history of PAD, who were not known to have ICAS at the time of referral and who had no history of cerebrovascular symptoms or previous carotid endarterectomy. ICAS was detected with duplex scanning and defined as a peak systolic velocity more than 150 cm/s (diameter reduction 50% or higher) on at least one side. Cardiovascular risk factors were measured. Logistic regression analysis was performed to investigate associations between these characteristics and ICAS.**

Results: **The prevalence of previously unknown ICAS was 14%. A patient age of 67 years or older, body weight of 68 kg or less, and diastolic blood pressure of 75 mm Hg or lower were independently associated with ICAS.**

The prevalence of ICAS in patients with one of these characteristics (38% of the patients) was 8%, in those with two characteristics (21% of the patients) was 32%, and in those with three characteristics (6% of the patients) was 50%.

Conclusions: **The prevalence of ICAS increases as much as 50% in patients who have PAD and the risk indicators of an age of 67 years or older, a body weight of 68 kg or less, and a diastolic blood pressure of 75 mm Hg or lower, and, therefore, these characteristics may be used as a means of increasing the likelihood of detecting ICAS. (J Vasc Surg 1999;30:519-25.)**

Patients referred to the hospital with symptomatic peripheral arterial disease (PAD) often have symptomatic or asymptomatic manifestations of atherosclerosis elsewhere in the vascular system, because atherosclerosis is a generalized and progressive process. The risk of premature death in patients who have PAD is three times the risk in subjects without the disease.[1] Approximately 50% of the deaths are caused by myocardial ischemia, and 15% are caused by stroke.[2] The presence of co-existing cerebrocardiovascular disease increases mortality in patients who have PAD.[2-5]

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We investigated the prevalence of internal carotid artery stenosis (ICAS) in patients who had PAD and who were not yet known to have carotid disease and who never had sustained (transient) cerebral ischemia. We also investigated which patient characteristics were associated with the presence of ICAS.

PATIENTS AND METHODS

Patients. We used data from the first 600 patients enrolled in the Second Manifestations of ARTerial disease (SMART) study, a single-center, prospective cohort study of patients referred to the University Medical Center, Utrecht, The Netherlands, for the first time with a manifestation of cardiovascular disease (PAD, ICAS, abdominal aortic aneurysm, tran-

Table I. Definitions of enrollment diagnoses in the Second Manifestation of ARTerial disease (SMART) study

Enrollment diagnosis	*Definition*
Carotid stenosis	Symptomatic or asymptomatic internal carotid artery stenosis with a diameter reduction of ≥ 50% (peak systolic velocity ≥ 150 cm/s) on at least one side, measured with color Doppler-assisted duplex scanning
Peripheral arterial disease	Resting ABPI ≤ 0.90 or postexercise ABPI decreasing ≥ 20% in at least one leg, with signs of intermittent claudication, rest pain, or gangrene/ulcers
Abdominal aortic aneurysm	Distal aortic anteroposterior diameter ≥ 3 cm, measured with ultrasonography
Diabetic foot	Presence of tissue necrosis or ulceration at the foot in a patient who has diabetes mellitus
Transient ischemic attack or minor ischemic stroke	According to criteria established by the neurologist
Renal artery stenosis	Renal artery stenosis with a diameter reduction ≥ 50% on at least one side, measured with angiography, with hypertension or renal failure
Angina pectoris	Chest pain with or without documented ischemia on the ECG and with documented stenoses on the angiography (in practical terms, a patient with indication for percutaneous transluminal coronary angioplasty)
Myocardial infarction	At least two of the following: (1) chest pain for at least 20 minutes, not disappearing after administration of nitrates; (2) ST-elevation > 1 mm in two following leads or a left bundle branch block on the ECG; (3) CK level elevation of at least two times the normal value of CK and a MB-fraction > 5% of the total CK level
Hyperlipidemia	Total cholesterol ≥ 6.5 mmol/L, triglycerides ≥ 2.3 mmol/L, HDL cholesterol ≤ 1.0 mmol/L, or use of lipid-lowering drugs
Diabetes mellitus types 1 and 2	Fasting plasma glucose level ≥ 7.0 mmol/L, non-fasting serum glucose level ≥ 11.1 mmol/L, or use of oral antidiabetic drugs or insulin
Hypertension	Systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or use of antihypertensive drugs
Renal insufficiency	Plasma creatinine level > 120 μmol/L or microproteinuria > 3 mg per mmol creatinine

ABPI, Ankle brachial pressure index; *ECG,* electrocardiogram; *CK,* creatinine kinase; *MB,* myocardial band; *HDL,* high density lipoprotein.

sient ischemic attack or minor stroke, diabetic foot, angina pectoris, myocardial infarction, or renal artery stenosis) or marked risk factors for cardiovascular disease (hyperlipidemia, diabetes mellitus, hypertension, or renal insufficiency). Definitions of enrollment diagnoses in the SMART study are described in Table I. The main objectives of the SMART study are to determine the prevalence of additional vascular disease at other sites of the vascular bed and risk factors in patients who have a manifestation of vascular disease or risk factor and to study predictors for future cardiovascular events in these high-risk patients. Baseline examinations (including a questionnaire on cardiovascular disease; measurements of height, weight, and blood pressure; blood tests for glucose, lipid, creatinine, and homocysteine levels; urinary tests for microproteinuria; a resting 12-lead electrocardiogram; ultrasound scanning of the abdominal aorta, kidneys, and the carotid arteries; measurements of common carotid intima-media thickness and arterial stiffness; and ankle brachial pressure indices in rest and after exercise) were performed in all patients to confirm the referral diagnosis, to study atherosclerosis in other parts of the vascular system, and to screen for risk factors. The study was approved by the ethics committee of the University Medical Center, Utrecht, and written informed consent was obtained from all participants. Patients older than 79 years and those with a terminal malignancy were not enrolled.

Peripheral arterial disease. From the 600 patients participating in the SMART study, two patient groups were selected for the current study. The first group comprised patients referred because of symptomatic PAD, whose symptoms were confirmed by a vascular surgeon. The referral diagnosis of PAD was confirmed with a treadmill test to obtain resting and after-exercise ankle brachial pressure indices (ABPI) and was defined as a resting ABPI of 0.90 or less or a postexercise ABPI decreasing 20% or more in at least one leg.[6] The second group comprised patients who were referred because of another vascular disease or risk factor and also reported a history of PAD. All patients completed a questionnaire on their history of cardiovascular disease (based on the Rose questionnaire),[7] risk factors, and current drug use. A history of PAD was assessed on the basis of the answers to the Rose questionnaire, the question "Have you ever been treated for narrowing of the arteries in one or both legs (surgery or percutaneous transluminal angioplasty)?", and the disease history obtained by the vascular surgeon.

Patients with known carotid artery stenosis at the

Table II. Baseline characteristics of patients with peripheral arterial disease (n = 162)

	ICAS yes n = 23	*ICAS no n = 139*
Age (years)	68 (8)	59 (11)
Men (%)	61	65
Smoking, current or past (%)	83	87
Height (cm)	170 (8)	173 (9)
Weight (kg)	70 (12)	78 (15)
Body mass index (kg/m^2)	24 (3)	26 (4)
Systolic blood pressure (mm Hg)	151 (17)	148 (18)
Diastolic blood pressure (mm Hg)	74 (9)	80 (10)
Pulse pressure (mm Hg)	78 (16)	68 (16)
Antihypertensive drug use (%)	43	34
Total cholesterol (mmol/L)	6.4 (1.0)	5.9 (1.3)
Lipid-lowering drug use (%)	22	19
Glucose (mmol/L)	7.0 (2.4)	6.8 (2.6)
Insulin or blood sugar-lowering drug use (%)	26	19
Angina pectoris (%)	26	16
Myocardial infarction (%)	17	19
Ankle brachial pressure index*	0.63 (0.17)	0.70 (0.23)
History of abdominal aortic aneurysm (%)	9	8

Values are percentages or means, with standard deviation in parenthesis.
*Lowest ankle brachial pressure index of both legs.
ICAS, Internal carotid artery stenosis.

time of referral or a history of previous carotid endarterectomy, stroke, transient ischemic attack, or amaurosis fugax were excluded from the analysis.

Internal carotid artery stenosis. Color Doppler-assisted duplex scanning of the carotid arteries was performed to detect ICAS, which was determined by means of blood flow velocities. The duplex scans were performed by well-trained registered vascular technologists in a certified vascular laboratory. An ICAS was defined as a peak systolic velocity of more than 150 cm/s, corresponding with a diameter reduction of 50% or more on at least one side.[8,9]

Cardiovascular risk factors. The height of patients was measured without shoes by means of a fixed stadiometer, and their weight was measured without heavy clothing by means of standard scales. Body mass index was calculated as the ratio of weight to height squared (kg/m^2). Blood pressure was recorded noninvasively at the right brachial artery with a semiautomatic oscillometric device in supine position every 4 minutes for a total of 25 minutes. Mean blood pressure was calculated as the average of all obtained measurements. A venous blood sample was collected after an overnight fast of at least 8 hours. Plasma total cholesterol and glucose levels were measured with commercial enzymatic dry chemistry kits (Johnson and Johnson). Smoking habits, drug use, and history of angina pectoris, myocardial infarction, and abdominal aortic aneurysm were derived from the questionnaire and from the disease history obtained by the treating physician.

Data analysis. The prevalence of ICAS was determined in patients who had PAD without known cerebrovascular disease. Associations between patient characteristics and ICAS were evaluated by means of logistic regression analyses (SPSS for Windows 7.5, SPSS, Chicago, Ill) after continuous variables were divided in tertiles, because then the results may be interpreted more easily. Variables that had a significance level of 0.25 or less in the univariate analyses were sequentially entered into a multivariate model until no remaining candidate variable had a significance level of 0.10 or less.

The proportion of patients in whom the characteristics associated with ICAS were present and the prevalence of ICAS in these patients were calculated.

RESULTS

Of the 600 patients in the SMART cohort, 159 patients had PAD and 40 patients had a history of PAD. Of these, 30 patients were excluded because of known carotid artery stenosis, history of carotid endarterectomy, or cerebrovascular symptoms. In seven patients, duplex scanning was not performed because of logistic reasons. In total, 162 patients were included in the analysis. The baseline characteristics of the study population are presented in Table II. Twenty-three patients (14%) had an ICAS of 50% or greater on at least one side. Of these, 12 patients had an ICAS of 70% to 99% (two patients bilateral), and nine patients had an ICAS of 50% to

Table III. Associations between characteristics and internal carotid artery stenosis in patients with peripheral arterial disease, by means of univariate logistic regression analysis

	Odds ratio	*95% CI*	*P*
Age (years)			
≤ 54*	1.0		
55 to 66	10.0	1.2 to 83	.03
≥ 67	19.2	2.4 to 152	< .01
Sex (women = 0, men = 1)	0.8	0.3 to 2.0	.67
Smoking, past or current	0.7	0.2 to 2.3	.57
Height (cm)			
≤ 168	2.8	0.8 to 9.7	.11
169 to 177	2.7	0.8 to 9.2	.11
≥ 178*	1.0		
Weight (kg)			
≤ 68	3.3	1.2 to 9.5	.02
69 to 84	0.5	0.1 to 2.0	.29
≥ 85*	1.0		
Body mass index (kg/m^2)			
≤ 23	3.1	1.0 to 10.2	.06
24 to 26	1.8	0.5 to 6.7	.41
≥ 27*	1.0		
Systolic blood pressure (mm Hg)			
≤ 139*	1.0		
140 to 156	1.5	0.5 to 4.8	.50
≥ 157	1.6	0.5 to 4.7	.43
Diastolic blood pressure (mm Hg)			
≤ 75	4.1	1.3 to 13	.02
76 to 83	1.1	0.3 to 4.5	.93
≥ 84*	1.0		
Pulse pressure (mm Hg)			
≤ 59*	1.0		
60 to 73	3.0	0.6 to 15	.17
≥ 74	5.8	1.2 to 28	.03
Antihypertensive drug use	1.5	0.6 to 3.7	.37
Total cholesterol (mmol/L)			
≤ 5.4*	1.0		
5.5 to 6.5	1.4	0.4 to 4.6	.61
≥ 6.6	2.5	0.8 to 7.8	.11
Lipid-lowering drug use	1.2	0.4 to 3.6	.73
Glucose (mmol/L)			
≤ 5.4*	1.0		
5.5 to 6.5	0.7	0.2 to 2.1	.49
≥ 6.6	0.9	0.3 to 2.7	.87
Insulin or blood sugar-lowering drug use	1.5	0.6 to 4.3	.41
Ankle brachial pressure index†			
≤ 0.58	5.8	1.2 to 28	.03
0.59 to 0.78	5.3	1.1 to 26	.04
≥ 0.79*	1.0		
Angina pectoris	1.9	0.7 to 5.3	.23
Myocardial infarction	0.9	0.3 to 2.8	.82
History of abdominal aortic aneurysm	1.1	0.2 to 5.4	.90

*Reference group
†Lowest ankle brachial pressure index of both legs

69% (one patient bilateral) on at least one side. One patient had an occlusion of the right internal carotid artery and an ICAS of 70% to 99% on the left side, and another patient had an occlusion on the right side and a stenosis less than 30% on the left side.

Table IV. Characteristics independently associated with internal carotid artery stenosis in patients with peripheral arterial disease

	Odds ratio	*95% CI*	*P*
Age ≥ 67 years	3.2	1.1 to 8.8	.03
Weight ≤ 68 kg	4.3	1.5 to 12.2	.01
Diastolic blood pressure ≤ 75 mm Hg	3.0	1.1 to 9.6	.04

Table V. Prevalence of internal carotid artery stenosis in patients with peripheral arterial disease according to the number of risk indicators

*Number of risk indicators**	*Proportion of patients*	*Presence of ICAS*		*Prevalence†*
		yes	*no*	
0	35%	2	55	4%
1	38%	5	56	8%
2	21%	11	23	32%
3	6%	5	5	50%

*Age ≥ 67 years, body weight ≤ 68 kg, diastolic blood pressure ≤ 75 mm Hg
†Prevalence in total study population is 14%
ICAS, Internal carotid artery stenosis.

Results of the univariate logistic regression analysis are shown in Table III. Older age, shorter height, lower weight, lower body mass index, lower diastolic blood pressure, higher pulse pressure, higher total cholesterol level, presence of angina pectoris, and lower ankle brachial pressure index were associated with ICAS of 50% or greater at a significance level of 0.25 or less. Being thin appeared to be highly associated with ICAS. In stepwise multivariate logistic regression analysis, age, body weight, and diastolic blood pressure remained independently associated with ICAS (Table IV). Adjusting for the use of antihypertensive drugs did not alter the results.

The prevalence of ICAS increased from 14% (prevalence in all patients studied) to 32% and 50%, respectively, in patients who had two (21% of the patients) or three (6% of the patients) of the characteristics described in Table III (Table V). The prevalence decreased to 4% and 8%, respectively, in patients with no or only one of these characteristics.

DISCUSSION

The prevalence of ICAS of 50% or greater was 14% in our study population and was independently associated with age, low body weight, and low diastolic blood pressure. In patients with none of these characteristics, the prevalence of ICAS was just 4%. However, the prevalence becomes markedly higher in patients with two or three characteristics: 32% and 50%, respectively. These observations may be used to increase the chance of detecting an ICAS in patients who have PAD without known cerebrovascular disease.

Results of other studies showed prevalences of ICAS from 14% to 28% in patients who had PAD.[10-15] The wide range of prevalence of carotid artery stenosis reported can be explained by the different definitions and methods used by the investigators to define the study population and the degree of carotid stenosis. The duplex scan criteria used for grading carotid stenosis are especially different.

We did not have information on the presence of carotid bruit. Although a carotid bruit does not have a high sensitivity, it is significantly associated with ICAS of 50% or greater.[11-13] Using information on carotid bruit might increase the prevalence of ICAS.[16] Adequate assessment of bruits, however, demands trained and experienced personnel.

Aside from age, low body weight and low diastolic blood pressure were associated independently with ICAS. As a result of the cross-sectional design of this study, these parameters have to be regarded as markers for the presence of ICAS and not as risk factors for ICAS. The observed high systolic and low diastolic blood pressure and, therefore, high pulse pressure may be the result rather than the cause of the disease process. A more atherosclerotic vascular system results in stiffer arteries, and such stiffening, through a variety of mechanisms, tends to raise systolic blood pressure and lower the diastolic blood pressure.[17-21] In our study, systolic blood pressure and pulse pressure were positively associated with ICAS, but did not reach statistical significance in multivariate analysis, indicating that diastolic blood pressure is a better predictor.[20,21] Obesity is generally accepted as a risk factor for cardiovascular disease. Surprisingly, in this study low body weight was independently associated with the presence of ICAS. Several studies reported an inverse relationship between short stature and cardiovascular morbidity and mortality,[21-24] although the evidence is not consistent.[25,26] Most of these studies are focused on body height, whereas in our study, low body weight was a marker of ICAS independent from height. Other studies showed a less pronounced or even an inverse relationship between body mass index and (cardiovascular) mortality in elderly people.[26,29]

Other investigators found indicators such as age,[13,15] carotid bruit,[11,13,14] and more severe PAD[11,13] to be associated with ICAS. Klop et al reported that none of the risk factors they investigated (age, gender, history of hypertension, cardiac disease, diabetes mellitus, hypercholesterolemia, smoking, and severity of PAD) in 416 patients who had PAD or abdominal aortic aneurysm had a significant relationship with ICAS.[10] Unfortunately, in these studies, risk factor assessment was based on questionnaires rather than direct measurement. Some investigators recommended that all patients who have PAD should undergo duplex scanning of the carotid arteries, because limiting screening to patients with characteristics associated with ICAS would exclude too many patients with stenosis.[11,13,14] Ahn et al concluded that routine carotid screening in patients who have PAD can be limited to patients older than 68 years.[15] The clinical consequences of detecting an asymptomatic ICAS, however, are still limited. Investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reported a benefit from carotid endarterectomy in asymptomatic patients who had an ICAS that was greater than 60%.[31] This benefit, however, has to be interpreted with caution, and the indication for surgery of asymptomatic ICAS is still a matter of debate.[32-37] Moreover, widespread duplex screening may result in unnecessary angiography, which in turn may cause cerebrovascular or other complications.[38] Medical treatment remains the sensible alternative for patients who have asymptomatic carotid stenosis.[36,39] Results are awaited from the ongoing Asymptomatic Carotid Surgery Trial (ACST)[40,41] or similar trials. Meanwhile, to prevent widespread screening, the characteristics we found to be associated with ICAS, ie, age, low body weight, and low diastolic blood pressure, may be used in screening programs to increase the likelihood of the presence of an ICAS in patients who have PAD. These patients may then be entered in one of the ongoing asymptomatic carotid endarterectomy trials.

REFERENCES

1. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
2. Dormandy J, Mahir M, Ascady G, Balsano F, De Leeuw P, Blombery P, et al. Fate of the patient with chronic leg ischaemia. J Cardiovasc Surg 1989;30:50-7.
3. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and aging process: A review. J Clin Epidemiol 1992;45:529-42.
4. Balkau B, Vray M, Eschwege E. Epidemiology of peripheral arterial disease. J Cardiovasc Pharmacol 1994;23(Suppl 3):S8-S16.

5. Ogren M, Hedblad B, Isacsson SO, Janzon L, Jungquist G, Lindell SE. Ten year cerebrovascular morbidity and mortality in 68 year old men with asymptomatic carotid stenosis. BMJ 1995;310:1294-8.
6. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-92.
7. Rose GA, Blackburn H. Cardiovascular survey methods. Geneve: World Health Organisation; 1968.
8. van Leersum M, van Leeuwen MS, van der Schouw YT, Mali WP, Eikelboom BC. New duplex threshold values for angiographically determined stenosis in the internal carotid artery in the light of the NASCET and ECST [abstract]. Cardiovasc Intervent Radiol 1995;18:62.
9. Elgersma OEH, van Leersum M, Buijs PC, van Leeuwen MS, van de Schouw YT, Eikelboom BC, et al. Changes over time in optimal duplex threshold for the identification of patients eligible for carotid endarterectomy. Stroke 1998;29:2352-6.
10. Klop RBJ, Eikelboom BC, Taks ACJM. Screening of the internal carotid arteries in patients with peripheral vascular disease by colour-flow duplex scanning. Eur J Vasc Surg 1991;5:41-5.
11. Gentile AT, Taylor LM, Moneta GL, Porter JM. Prevalence of asymptomatic carotid stenosis in patients undergoing intrainguinal bypass surgery. Arch Surg 1995;130:900-4.
12. Alexandrova NA, Gibson WC, Norris JW, Maggisano R. Carotid artery stenosis in peripheral vascular disease. J Vasc Surg 1996;23:645-9.
13. Marek J, Mills JL, Harvich J, Cui H, Fujitani RM. Utility of routine carotid duplex screening in patients who have claudication. J Vasc Surg 1996;24:572-9.
14. de Virgilio C, Toosie K, Arnell T, Lewis RJ, Donayre CE, Baker JD, et al. Asymptomatic carotid artery stenosis screening in patients with lower extremity atherosclerosis: A prospective study. Ann Vasc Surg 1997;11:374-7.
15. Ahn SS, Baker JD, Walden K, Moore WS. Which asymptomatic patients should undergo routine screening carotid duplex scan? Am J Surg 1991;162:180-4.
16. Sauve JS, Thorpe KE, Sackett DL, Taylor W, Barnett HJ, Haynes RB, et al. Can bruits distinguish high-grade from moderate symptomatic carotid stenosis? The North American Symptomatic Carotid Endarterectomy Trial. Ann Intern Med 1994;120:633-7.
17. Safar ME, Siche JP, Mallion JM, London GM. Arterial mechanics predict cardiovascular risk in hypertension. J Hypertens 1997;15:1605-11.
18. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308-15.
19. Sleight P. Blood pressures, hearts, and U-shaped curves. Lancet 1988;1:235.
20. Witteman JCM, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, et al. A J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. Lancet 1994;343:504-7.
21. Bots ML, Witteman JCM, Hofman A, de Jong PTVM, Grobbee DE. Low diastolic blood pressure and atherosclerosis in elderly subjects. Arch Intern Med 1996;156:843-8.
22. Palmer JR, Rosenberg L, Shapiro S. Stature and the risk of myocardial infarction in women. Am J Epidemiol 1990; 132:27-32.
23. Yarnell JWG, Limb ES, Layzell JM, Baker IA. Height: A risk marker for ischaemic heart disease: Prospective results from the Caerphilly and Speedwell Heart Disease Studies. Eur Heart J 1992;13:1602-5.
24. Hebert PR, Rich-Edwards JW, Manson JE, Ridker PM, Cook NR, O'Connor GT, et al. Height and incidence of cardiovascular disease in male physicians. Circulation 1993;88:1437-43.
25. Kannam JP, Levy D, Larson M, Wilson PWF. Short stature and risk for mortality and cardiovascular disease events. The Framingham Heart Study. Circulation 1994;90:2241-7.
26. Liao Y, McGee DL, Cao G, Cooper RS. Short stature and risk of mortality and cardiovascular disease: Negative findings from the NHANES I Epidemiologic Follow-Up Study. J Am Coll Cardiol 1996;27:678-82.
27. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body mass index and mortality. N Engl J Med 1998;338:1-7.
28. Diehr P, Bild DE, Harris TB, Duxbury A, Siscovick D, Rossi M. Body mass index and mortality in nonsmoking older adults: The Cardiovascular Health Study. Am J Public Health 1998;88:623-9.
29. Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L. Body mass index and mortality among nonsmoking older persons. The Framingham Heart Study. JAMA 1988;259:1520-4.
30. Kinney EL, Caldwell JW. Relationship between body weight and mortality in men aged 75 years and older. South Med J 1990;83:1256-8.
31. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid stenosis. JAMA 1995;271:1421-8.
32. Brott T, Toole J. Medical compared with surgical treatment of asymptomatic carotid artery stenosis. Ann Intern Med 1995;123:720-2.
33. Barnett HJM, Meldrum HE, Eliasziw M. The dilemma of surgical treatment for patients with asymptomatic carotid disease. Ann Intern Med 1995;123:723-5.
34. Warlow C. Endarterectomy for asymptomatic carotid stenosis? Lancet 1995;345:1254-5.
35. Hennerici M, Daffertshofer M, Meairs S. Concerns about generalisation of premature ACAS recommendations for carotid endarterectomy. Lancet 1995;345:1041.
36. Benavente O, Moher D, Pham B. Carotid endarterectomy for asymptomatic carotid stenosis: A meta-analysis. BMJ 1998;317:1477-80.
37. Warlow C. Carotid endarterectomy for asymptomatic carotid stenosis. BMJ 1998;317:1468.
38. Hankey GJ, Warlow CP, Sellar RJ. Cerebral angiographic risk in mild cerebrovascular disease. Stroke 1990;21:209-22.
39. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.
40. Halliday AW, Thomas D, Mansfield A. The Asymptomatic Carotid Surgery Trial (ACST). Rationale and design. Eur J Vasc Surg 1994;8:703-10.
41. Chaturvedi S, Halliday A. Is another clinical trial warranted regarding endarterectomy for asymptomatic carotid stenosis? Cerebrovasc Dis 1998;8:210-3.

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