Carotid ultrasound findings as a predictor of long-term survival after abdominal aortic aneurysm repair: A 14-year prospective study

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Purpose: **Several factors have been related to long-term survival after open abdominal aortic aneurysm (AAA) repair. The effect of carotid stenosis on outcome has not yet been examined. We performed an open prospective study to evaluate the prognostic significance of carotid stenosis on long-term survival of patients who had undergone elective operative repair of AAA.**

Methods: **Two hundred eight patients who underwent elective open AAA repair in our department between March 1987 and December 2001 were included in the study. All patients were evaluated preoperatively with color duplex ultrasound (US) scanning of the carotid arteries, and were followed up with clinical examination and carotid duplex US scanning 1 month after the operation and every 6 months thereafter. Median duration of follow-up was 50 months (range, 5-181 months). Cardiovascular morbidity and mortality, as well as all causes of mortality, were recorded and analyzed with regard to traditional risk factors and carotid US findings.**

Results: **Twenty-seven fatal and 46 nonfatal cardiovascular events were recorded. Both univariate and multivariate analysis showed that carotid stenosis 50% or greater and echolucent plaque were significantly associated with cardiovascular mortality and morbidity. Carotid stenosis was a stronger predictor of cardiovascular death than was ankle/brachial index. Age, hypercholesterolemia, coronary artery disease, and diabetes mellitus were also associated with higher mortality and morbidity from cardiovascular causes.**

Conclusion: **Patients electively operated on for AAA repair and with stenosis 50% or greater and echolucent plaque at duplex US scanning are at significantly increased risk for cardiovascular mortality and morbidity. Carotid US can therefore be used to select a subgroup of patients with AAA who might benefit from medical intervention, including antiplatelet and lipid-lowering agents. (J Vasc Surg 2003;38:1220-5.)**

Abdominal aortic aneurysm (AAA) is a degenerative disorder that traditionally has been attributed to atherosclerotic disease. The atherosclerotic cause of AAA is supported by clinical, pathologic, and experimental data. Patients with peripheral arterial occlusive disease have a high prevalence of AAA,[1-5] atherosclerotic changes are consistently found in the aneurysm sac, and atherosclerotic diet has resulted in aneurysm formation in an experimental model.[6] On the other hand, in many patients with extensive atherosclerosis of the aorta, aneurysm never develops, and their risk factor profile is different from that of patients with AAA.[7-10] In addition, noncardiovascular diseases, such as inguinal hernia and chronic obstructive pulmonary disease, are frequently present in patients with AAA, signifying that connective tissue disorders may have a role in AAA formation.[11,12] On the basis of these observations, it has been suggested that AAA may be divided into two pathologic entities: one with primarily atherosclerotic origin and a predominantly nonatherosclerotic subtype.[13] Although such classification may be of little value with regard to surgical treatment, these AAA subtypes may be associated with different long-term prognosis after surgical repair.

Two methods have been suggested for differentiation between atherosclerotic and nonatherosclerotic AAA: ankle/brachial index (ABI), with a value of 0.90 separating the two groups, and degree of internal carotid artery (ICA) stenosis, with 50% as the cutoff point.[13] ABI is also an important prognostic indicator,[14] whereas the prognostic significance of carotid stenosis in patients with AAA has not been examined yet. To evaluate the effect of carotid stenosis on long-term survival after elective open AAA repair, we performed an open prospective study.

METHODS

Two hundred eight patients who underwent elective open AAA repair in our department between March 1987

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Competition of interest: none.

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Table I. Baseline characteristics

Characteristic	*n*	*%*
Age (y)		
Median	69	
Range	49-80	
Gender (M/F)	192/16	92/8
Coronary artery disease	87	42
Diabetes mellitus	75	36
Hypertension	144	69
Hypercholesterolemia	95	46
History of smoking	148	71

and December 2001 were included in the study. The study was approved by the hospital ethics committee, and informed consent was obtained from each patient. To ensure adequacy of follow-up, only patients residing in Athens were selected to participate in the study. Indication for surgery was AAA diameter at least 5 cm. At entry into the study a complete medical history was taken and risk factors were recorded (Table I), including age, gender, coronary artery disease (CAD; angina pectoris, myocardial infarction (MI), coronary artery bypass grafting, percutaneous transluminal coronary angioplasty), diabetes mellitus (controlled with diet, oral hypoglycemic agents, or insulin; fasting glucose level >7 mmol/L), hypercholesterolemia (total cholesterol >5.2 mmol/L), hypertension (blood pressure >160 mm Hg systolic or 95 mm Hg diastolic), and smoking history (current or past).

Apart from routine preoperative evaluation, baseline assessment included measurement of ankle/brachial systolic pressure index and color duplex US scanning of the carotid arteries. Systolic blood pressure in both arms and ankles was measured with a handheld Doppler scanning device (8 MHz; Huntleigh Doppler, Cardiff, Wales) and a standard mercury sphygmomanometer. A single measurement by an experienced examiner was considered sufficient in each patient. The lower of the right and left index values was used for analysis. ABI could not be calculated in one patient, because of incompressible arterial walls.

Color duplex US scans of the carotid arteries were obtained with an ATL Interspec Apogee scanner with a 7.5 MHz probe (Advanced Technology Laboratories, Bothel, Wash). All scanning was performed by the same examiner. The most severe stenosis in either ICA was used for analysis. The US characteristics of the plaque were also recorded, with plaque classified into five categories.[15,16] Intraobserver variability of plaque characterization in our laboratory is good, as previously reported.[17]

All patients were followed up with clinical examination and carotid duplex US scanning 1 month after the operation and every 6 months thereafter. Cardiovascular morbidity and mortality, and all-cause mortality were recorded and analyzed with regard to traditional risk factors, ABI, and carotid US findings. Criteria used to define cardiovascular events were adapted from those proposed by the American Heart Association.[18,19] The effect of these variables on cardiovascular morbidity and mortality, as well as all-cause mortality, was assessed with the Kaplan-Meier method. Curves depicting event-free survival were drawn for each variable and compared with the log-rank test. Continuous variables such as age and ABI were converted into dichotomous variables, with cutoff points of 70 years and 0.90, respectively. Graded parameters with more than two categories, such as carotid stenosis and plaque type, were also transformed into dichotomous variables. In the case of carotid stenosis, a cutoff point of 50% was used, whereas in the case of plaque type, types I and II were combined (low echogenicity group) and compared with combined types III and IV (high echogenicity group). After determining univariate associations, multivariate (Cox regression) analysis was used to determine independence of associations. Plaque type was entered in the multivariate model as a dummy parameter, with three values: 0, no assessable plaque; 1, echolucent plaque; and 2, echogenic plaque. $P < .05$ was considered statistically significant in all tests.

RESULTS

At entry into the study, 156 patients (75%) had carotid stenosis less than 50% and 52 patients (25%) had stenosis 50% or greater. Carotid stenosis ranged from 0% to 70%, and was asymptomatic in all patients. Thirty-one plaques (15%) were uniformly echolucent (type I), 48 (23%) were predominantly echolucent (type II), 46 (22%) were predominantly echogenic (type III), and 39 (19%) were uniformly echogenic (type IV); we did not encounter any type V plaque (plaque that cannot be classified because of heavy calcification and acoustic shadows). The remaining 44 patients (21%) did not have any assessable carotid plaque. Median ABI was 0.96 (range, 0.45-1.35).

Two patients (1%) died within 30 days of surgery, of multiple organ failure and acute renal failure, respectively. The remaining 206 patients were followed up for a median of 50 months (range, 5-181 months), for total follow-up of 869 patient-years. Eleven patients (5.3%) were lost to follow-up.

Forty-eight deaths were recorded during follow-up. Twenty-seven patients died of cardiovascular events (21, cardiac disease; 6, stroke). On the basis of diagnostic criteria for acute cardiovascular events,[17,18] 3 patients had definite fatal MI, verified at autopsy; 8 patients had definite fatal MI diagnosed with electrocardiography and abnormal cardiac enzyme concentrations; 6 patients had definite sudden death due to coronary heart disease, as demonstrated by severe cardiac symptoms and absence of nonatherosclerotic disease; and 4 patients had definite fatal coronary heart disease, according to the death certificate and supported by a history of MI and absence of nonatherosclerotic disease. Diagnosis of fatal stroke was verified in all patients at physical examination, and was supported by CT findings in four patients.

Cumulative freedom from death due to cardiovascular events at 8 years after AAA repair was 77%. Kaplan-Meier analysis with the log-rank test (Fig 1) showed that cumulative freedom from cardiovascular death was significantly lower in patients with carotid stenosis 50% or greater (58%

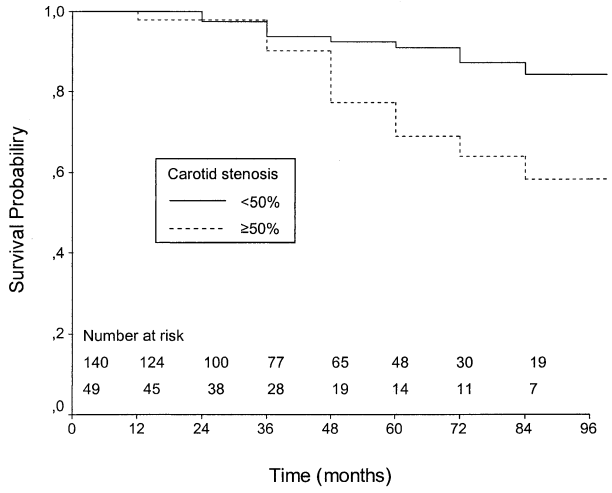

Fig 1. Cumulative freedom from death from cardiovascular causes, relative to degree of carotid stenosis.

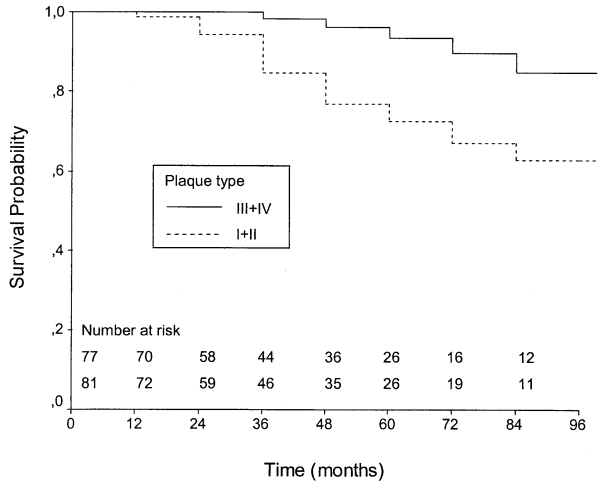

Fig 2. Cumulative freedom from death from cardiovascular causes, relative to type of carotid plaque as noted at ultrasonography.

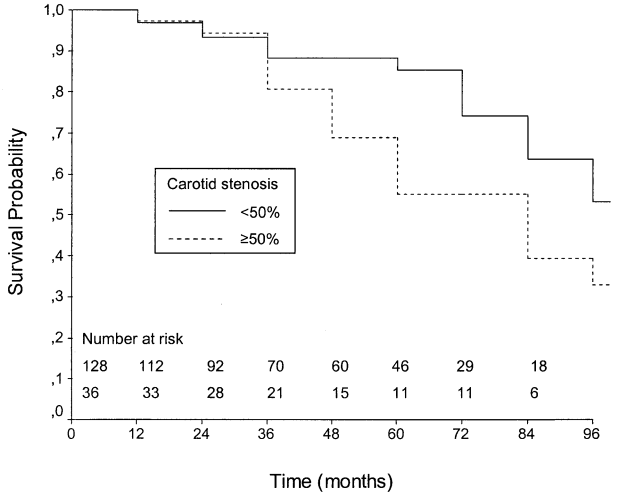

Fig 3. Cumulative freedom from cardiovascular morbidity, relative to degree of carotid stenosis.

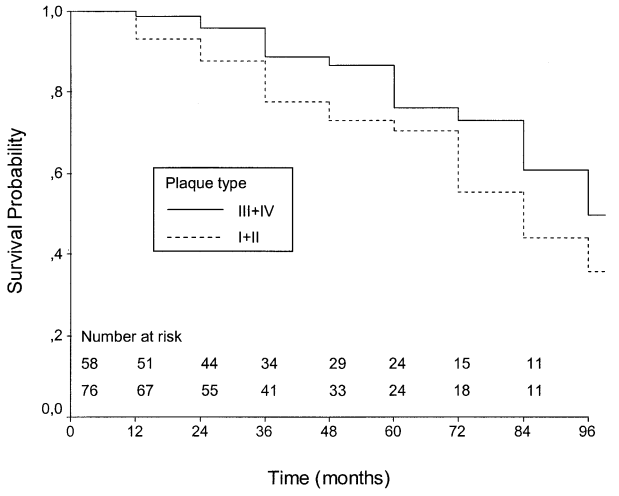

Fig 4. Cumulative freedom from cardiovascular morbidity, relative to type of carotid plaque as noted at ultrasonography.

at 8 years) than in patients with carotid stenosis less than 50% (84%; $P = .007$). Cumulative freedom from cardiovascular death was also significantly lower in patients with echolucent plaque (63% vs 85%; $P = .03$; Fig 2), patients with ABI less than 0.90 (65% vs 89%; $P = .008$), patients 70 years or older (45% vs 93%; $P < .0001$), and patients with known CAD (64% vs 88%; $P = .03$), diabetes mellitus (65% vs 82%; $P < .05$), or hypercholesterolemia (66% vs 85%; $P < .05$). Gender, smoking, and hypertension were not significantly associated with cardiovascular mortality after AAA repair.

Forty-six patients had at least one nonfatal cardiovascular event during follow-up, resulting in cumulative freedom from cardiovascular morbidity of 50% at 8 years of follow-up. Thirty-one of these patients had nonfatal MI, 7 had nonfatal stroke, 4 had transient ischemic attack, and 4 patients had both MI and stroke. Diagnosis was verified in all cases according to hospital records. Univariate analysis showed that cumulative freedom from cardiovascular morbidity was significantly lower in patients with carotid stenosis 50% or greater (31% vs 58% at 8 years; $P = .002$; Fig 3) and in those with echolucent plaque (40% vs 50%; $P < .005$; Fig 4). Cumulative freedom from nonfatal cardiovascular events was also significantly lower in patients with known CAD (41% vs 57%; $P = .01$), diabetes mellitus (30% vs 57%; $P < .05$), hypercholesterolemia (35% vs 60%; $P = .05$), hypertension (44% vs 76%; $P < .05$), and ABI less than .90 (39% vs 59%; $P < .01$), and in patients aged 70 years or older (39% vs 56%; $P = .0001$). Gender and smoking were not significantly associated with cardiovascular morbidity after AAA repair.

Table II. Results of Cox regression analysis with mortality from cardiovascular causes as dependent variable

Variable	*Significance*	*Hazard ratio*	*95% confidence interval*
Age*	<.0001	1.27	1.17-1.39
Coronary artery disease	.03	2.93	1.12-7.66
Diabetes mellitus	.03	2.60	1.10-6.14
Hypercholesterolemia	.003	4.64	1.71-12.59
Ankle/brachial index	<.05	2.81	1.02-7.75
Carotid stenosis	.01	3.61	1.28-10.14
Plaque type†	.03	3.83	1.17-12.53

* Age used as continuous variable.
†Echolucent vs echogenic.

Table III. Results of Cox regression analysis with cardiovascular morbidity as dependent variable

Variable	*Significance*	*Hazard ratio*	*95% confidence interval*
Age*	<.0001	1.15	1.08-1.23
Coronary artery disease	.005	2.65	1.34-5.22
Diabetes mellitus	.002	2.77	1.45-5.31
Hypercholesterolemia	.0001	4.31	2.13-8.74
Hypertension	.02	3.12	1.24-7.83
Ankle/brachial index	.07	1.89	0.95-3.74
Carotid stenosis	.0007	4.04	1.81-9.03
Plaque type†	.008	2.82	1.31-6.10

*Age used as continuous variable.
†Echolucent vs echogenic.

All parameters found to be of prognostic significance in univariate analysis were entered into a multivariate model (Cox regression analysis), to assess independence of associations. The results of the analysis verified that the degree of carotid stenosis and the US characteristics of the carotid plaque were independently associated with cardiovascular mortality (Table II) and morbidity (Table III). Age, CAD, diabetes mellitus, hypercholesterolemia, and ABI were also significant, independent predictors of death due to cardiovascular causes. In particular, age was the most significant predictor of long-term cardiovascular mortality, with each year of age adding a 27% probability of death from cardiovascular cause. Hypercholesterolemia was the second most significant risk factor, associated with a more than fourfold increase in probability of cardiovascular death. Echolucent plaque (hazard ratio [HR], 3.83), carotid stenosis 50% or greater (HR, 3.61), known CAD (HR, 2.93), ABI less than 0.90 (HR, 2.81), and diabetes mellitus (HR, 2.60) followed in descending order. Age was the most significant independent predictor of cardiovascular morbidity (HR, 1.15), followed by hypercholesterolemia (HR, 4.31), carotid stenosis 50% or greater (HR, 4.04), hypertension (HR, 3.12), echolucent plaque (HR, 2.82), diabetes mellitus (HR, 2.77), and history of CAD (HR, 2.65). ABI, on the other hand, lost its independent prognostic significance when entered in the multivariate model.

There were 21 deaths from noncardiovascular causes: 14 patients died of cancer, 2 died of renal failure, 1 died of chronic obstructive pulmonary disease, 1 died of pulmonary infection, and 3 died of unknown cause. Univariate analysis showed that of the recorded risk factors only age 70 years or older was significantly associated with mortality from noncardiovascular causes ($P < .0005$).

Overall survival at 8 years of follow-up was 60%, as calculated by life-table analysis, and was significantly affected by carotid stenosis 50% or greater (42% vs 67%; $P < .01$), age 70 years or older (24% vs 81%; $P < .0001$), known CAD (50% vs 68%; $P < .01$), and ABI < .90 (46% vs 73%; $P < .05$). At multivariate analysis, however, none of these risk factors proved to be independently associated with all-cause mortality, except for age (HR, 1.21; 95% confidence interval [CI], 1.14-1.28).

DISCUSSION

Age, CAD, hypertension, chronic renal failure and previous history of cerebrovascular events are among the most commonly cited factors related to long-term survival after elective AAA repair.[20-27] However, there is unanimity only regarding the predictive value of age, and no consensus regarding the prognostic value of other major risk factors, including hypertension and even CAD.[21-24] The inability of several studies to determine the negative influence of well-established atherosclerotic risk factors on survival has been attributed to many reasons, such as small number of patients, short follow-up, or inadequate preoperative detection of CAD.[22] Apart from these possible explanations, we believe that the inclusion of deaths not related to complications of atherosclerosis in the outcome measures reduces the ability of a study to detect the deleterious effect of atherosclerotic risk factors. In line with this, cancer was the principal cause of late mortality after successful AAA repair in some studies.[20-22] For these reasons, in the present study we chose to focus on mortality due to cardiovascular events.

The most important finding is that color duplex US scanning of the carotid arteries can be used to predict long-term mortality due to cardiovascular events in patients undergoing elective AAA repair. Simons et al[13] showed that common carotid intima-media thickness (IMT) can be used to differentiate between two groups of patients with AAA, that is, one with IMT greater than 0.90 mm, which is more likely to be associated with ABI 0.90 or less and ICA stenosis 50% or greater, and another group with IMT 0.90 mm or less, which is more likely associated with ABI greater than 0.90 and ICA stenosis less than 50%. Examination of long-term outcome in these subgroups of patients was beyond the scope of our study. Recently Powell et al[14] examined the prognostic value of ABI in patients with AAA. A clear association was found between ABI and worse survival, with the all-cause mortality risk increasing by 25% per 0.2 unit decrease in ABI. Lower ABI was also strongly associated with cardiovascular death, with an increase of 28% in cardiovascular mortality per 0.2 unit decrease in ABI.

In accord with these findings, ABI was a significant predictor of long-term cardiovascular mortality in our study. Patients with ABI less than 0.90 had a 2.8-fold increased risk for long-term cardiovascular death compared with patients with ABI 0.90 or greater (HR, 2.81; 95% CI, 1.02-7.75). However, ICA stenosis 50% or greater was a stronger predictor of cardiovascular mortality, associated with a 3.6-fold increased incidence of cardiovascular death (HR, 3.61; 95% CI, 1.28-10.14). These findings suggest that carotid stenosis might be a better indicator than ABI of generalized atherosclerosis in patients with AAA.

The most commonly used indicator of widespread atherosclerosis is no doubt the common carotid IMT. Numerous studies have shown that increased IMT of the carotid artery is associated with atherosclerosis at other sites of the arterial system,[28] and some studies have also shown an association between IMT and risk for MI or stroke.[29-31] With regard to carotid stenosis, Rosfors et al[32] showed that IMT of the common carotid artery (CCA) is correlated with presence of stenosis in the left carotid bifurcation, and Zureik et al[33] recently reported that CCA-lumen diameter, but not CCA-IMT, is independently associated with aortic stiffness. These findings suggest that, in addition to IMT, carotid stenosis may be used as a surrogate marker of generalized atherosclerosis.

One of the advantages of duplex US scanning is that, apart from detecting degree of carotid stenosis, it provides unique information regarding the structure of the arterial wall and the characteristics of atherosclerotic plaque. This information has great predictive value, because echolucent plaque or plaque with gray scale median less than 32 or 40 is associated with higher incidence of cerebrovascular events.[16,34-38] We recently showed that echolucent plaques are associated with higher incidence of future cardiovascular events in a population of patients undergoing carotid endarterectomy.[17] On the basis of these findings, we suggested that there might be a correlation between plaque echolucency in the carotid arteries and plaque instability and rupture in the coronary arteries. The results of the present study lend further support to this theory, in that patients with AAA and echolucent carotid plaque had an almost fourfold increase in cardiovascular mortality compared with patients with AAA and echogenic plaque.

Findings of carotid duplex scanning are of particular interest in the context of the current guidelines for cholesterol-lowering therapy. According to the Adult Treatment Panel III of the National Cholesterol Education Program,[39] carotid stenosis greater than 50% is defined as a coronary heart disease equivalent, and automatically designates a patient to a higher risk category. This practically means a lower low-density lipoprotein cholesterol cutoff point for initiation of therapeutic lifestyle changes (>100 mg/dL) and drug therapy (>130 mg/dL) and more aggressive treatment goals (<100 mg/dL). Best medical treatment of these patients should also include aspirin or other oral antiplatelet drug, because the beneficial effects of these agents are well recognized in most patients with atherosclerotic disease, including those with carotid stenosis.[40]

Better risk assessment also means better stratification of the need for follow-up. We currently advocate annual follow-up for patients with AAA with carotid stenosis 50% or greater or echolucent plaque, and biennial testing for patients with carotid stenosis less than 50% and echogenic plaque. Although our study was not designed to test the cost-effectiveness of this strategy, we believe the long-term benefits of an accurate, noninvasive, and relatively inexpensive method of risk assessment outweighs its initial cost.

In conclusion, a single preoperative carotid duplex US scan may be valuable in patients undergoing AAA repair, to differentiate between patients with AAA as a local manifestation and those with AAA as part of generalized atherosclerosis, because the long-term course differs in these two groups. Patients with AAA with carotid stenosis 50% or greater, indicative of widespread atherosclerosis, and those with echolucent plaque, indicative of plaque instability, are at significantly increased risk for cardiovascular mortality and consequently are in greater need of further evaluation, rigorous follow-up, and risk factor modification.

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