Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 33, No. 5, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00034-0

Atherosclerosis of the Ascending Aorta Is an Independent Predictor of Long-Term Neurologic Events and Mortality

Víctor G. Dávila-Román, MD, FACC, Suzan F. Murphy, RN, BSN, Nancy J. Nickerson, RN, BSN, Nicholas T. Kouchoukos, MD, FACC, Kenneth B. Schechtman, PHD, Benico Barzilai, MD, FACC
St. Louis, Missouri

OBJECTIVES This study was undertaken to determine whether atherosclerosis of the ascending aorta is a predictor of long-term neurologic events and mortality.

BACKGROUND Atherosclerosis of the thoracic aorta has been recently considered a significant predictor of neurologic events and peripheral embolism, but not of long-term mortality.

METHODS Long-term follow-up (a total of 5,859 person-years) was conducted of 1,957 consecutive patients ≥50 years old who underwent cardiac surgery. Atherosclerosis of the ascending aorta was assessed intraoperatively (epiaortic ultrasound) and patients were divided into four groups according to severity (normal, mild, moderate or severe). Carotid artery disease was evaluated (carotid ultrasound) in 1,467 (75%) patients. Cox proportional-hazards regression analysis was performed to assess the independent effect of predictors on neurologic events and mortality.

RESULTS A total of 491 events occurred in 472 patients (neurologic events 92, all-cause mortality 399). Independent predictors of long-term neurologic events were: hypertension ($p = 0.009$), ascending aorta atherosclerosis ($p = 0.011$) and diabetes mellitus ($p = 0.015$). The independent predictors of mortality were advanced age ($p < 0.0001$), left ventricular dysfunction ($p < 0.0001$), ascending aorta atherosclerosis ($p < 0.0001$), hypertension ($p = 0.0001$) and diabetes mellitus ($p = 0.0002$). There was >1.5-fold increase in the incidence of both neurologic events and mortality as the severity of atherosclerosis increased from normal-mild to moderate, and a greater than threefold increase in the incidence of both as the severity of atherosclerosis increased from normal-mild to severe.

CONCLUSIONS Atherosclerosis of the ascending aorta is an independent predictor of long-term neurologic events and mortality. These results provide additional evidence that in addition to being a direct cause of cerebral atheroembolism, an atherosclerotic ascending aorta may be a marker of generalized atherosclerosis and thus of increased morbidity and mortality. (J Am Coll Cardiol 1999;33:1308–16) © 1999 by the American College of Cardiology

Although embolism from the heart and/or carotid arteries is a common cause of neurologic events, the cause of stroke remains elusive in many patients (1–12). Analysis of data from The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Data Bank, a large prospective study of over 1,800 patients, showed that 40% of cases of cerebral infarction were of "undetermined cause" (13). An association between atherosclerotic disease of the thoracic aorta and cerebral and peripheral embolism (14–20) has been speculated for years, but the importance of the thoracic aorta as a source of cerebral and vascular emboli has been ascertained only recently (21–36).

Our group and others have shown that atherosclerosis of the ascending aorta is an independent predictor of perioperative stroke and postoperative renal dysfunction in patients undergoing cardiac surgery (21–27). Amarenco et al. showed in an autopsy study that ulcerated plaques in the ascending aorta and aortic arch were significantly more prevalent in those who had suffered cerebral embolic events compared with those without such plaques (28). Three recent studies, in which the majority of patients who had sustained a recent stroke were followed prospectively, have

From the Cardiovascular Division, Department of Internal Medicine, Department of Biostatistics, and the Cardiothoracic Surgery Division, Department of Surgery, Washington University School of Medicine, and Barnes-Jewish Hospital, BJC Health System, St. Louis, Missouri. Supported in part by a Minority Investigator Research Grant (MIRS) to Dr. Dávila-Román from the American Heart Association, Dallas, Texas.

Present address for Suzan F. Murphy, Nancy J. Nickerson, and Nicholas T. Kouchoukos is: Cardiac, Thoracic, and Vascular Surgery, Inc., Missouri Baptist Medical Center, BJC Health System, St. Louis, Missouri.

Presented in part at the 69th Scientific Sessions of the American Heart Association, New Orleans, November 1996.

Manuscript received August 14, 1998; revised manuscript received December 1, 1998, accepted January 11, 1999.

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
FAPS = French Aortic Plaques in Stroke study
LV = left ventricle
LVEF = left ventricular ejection fraction
TEE = transesophageal echocardiography
TIA = transient ischemic attack

shown an association between aortic arch atherosclerosis and cerebral and/or peripheral embolic events (33–35). However, an association between atherosclerosis of the thoracic aorta and long-term mortality has not been shown.

In this prospective study, we followed a cohort of 1,957 consecutive patients who underwent evaluation of their ascending aortas with epiaortic ultrasound at the time of cardiac surgery to determine the prognostic significance of atherosclerosis of this vessel as a predictor of long-term neurologic events and mortality. Our hypothesis was that increasing severity of atherosclerosis of the ascending aorta would be a significant and independent predictor of both events.

METHODS

Patient population. The study population consisted of 1,969 consecutive patients ≥50 years old (mean 68 ± 9 years, range 50 to 91) undergoing cardiac surgery and intraoperative evaluation of the ascending aorta with epiaortic ultrasound at Barnes-Jewish Hospital during the period from January 1990 to May 1994. Long-term follow-up was complete in 1,957 patients. The cardiac surgical procedures performed in these patients included: coronary artery bypass graft (CABG) surgery in 1,472 (75.2%), valve repair or replacement in 224 (11.5%) and CABG and valve surgery in 261 (13.3%). Carotid endarterectomy or graft replacement of the ascending aorta was performed in combination with one of the above procedures in 65 (3.3%) and 47 (2.4%) patients, respectively. The study protocol was approved by the Human Studies Committee at Washington University Medical Center.

Variables analyzed. At the time of cardiac surgery, the following characteristics were prospectively recorded: 1) age; 2) gender; 3) body mass index (kg/m^2); a history of any of the following (requiring treatment): 4) atrial fibrillation, 5) hypertension, and 6) diabetes mellitus; 7) history of smoking, 8) use of anticoagulants (warfarin and/or aspirin); 9) presence of mitral stenosis (mitral valve area <2 cm^2); 10) left ventricular (LV) function; 11) extent of coronary artery disease (CAD); 12) extent of carotid artery disease; and 13) serum cholesterol level. The LV function was assessed by angiography or by echocardiography according to the Coronary Artery Surgery Study, based on left ventricular ejection fraction (LVEF), as follows: LVEF >55% (score of 5) = normal; 40% to 54% (score 6–10) = mild dysfunction; 25% to 39% (score of 11–15) = moderate dysfunction, and <24% (score >16) = severe dysfunction (37).

Ultrasonic methods. Ultrasonic epiaortic imaging of the ascending aorta was performed during cardiac surgery in each patient by use of a 7-MHz linear ultrasound transducer (Acuson, Mountain View, California) inserted in a sterile sheath and placed directly over this vessel, as previously described (21,24–26,38). In brief, transverse and longitudinal images were obtained from the level of the aortic root to the level of the proximal aortic arch, just distal to the innominate artery. The ultrasonic images were evaluated for the presence of atherosclerosis by two observers blinded to the clinical data, as follows: 1) normal aorta (no intimal thickening), 2) mild atherosclerosis (<3 mm intimal thickening without intimal irregularities), 3) moderate aortic atherosclerosis (intimal thickening ≥3 mm, with diffuse irregularities and/or calcification) and 4) severe atherosclerosis (>5 mm intimal thickening and one or more of the following: large protruding or mobile atheromatous debris, ulcerated plaques and/or thrombi).

Carotid artery Doppler and duplex ultrasound was performed in all patients ≥65 years old and in younger patients with carotid bruits and/or symptoms or a history of neurologic events, including transient ischemic attack (TIA) and stroke. Carotid artery stenosis was graded based on results of the carotid artery ultrasound performed in the longitudinal and cross-sectional axes, as previously described (39,40): 1) insignificant or no disease (luminal narrowing ≤50%), 2) moderate disease (luminal narrowing >50% but <80%), 3) severe disease (luminal narrowing ≥80% but ≤99%) and 4) complete occlusion. For the purpose of analysis, severe disease and complete occlusion were combined.

Long-term follow-up. Each patient completed a questionnaire to identify those who had suffered a neurologic event such as stroke or TIA during the follow-up period. A stroke was defined as any neurologic impairment of motor, sensory or cognitive function that persisted >24 h, or was associated with death within 24 h, and that could not be explained by other neurologic (ie, dementia, head trauma), and/or medical (ie, metabolic abnormalities, drugs) etiologies; and a TIA as neurologic impairment that resolved within 24 h, and was unexplained by other neurologic and/or medical etiologies. All neurologic events were confirmed by the attending neurologist who cared for the patient at the time of the event, or were documented in the medical records, including results of computed tomography or magnetic resonance imaging of the brain. Death was investigated through a relative, the primary care physician or the hospital records. In all instances, death was documented by the death certificate. Three mailings of the questionnaire were sent within a six-month period; 1,676 (85%) of the patients responded, and for those who did not, a search of the National Death Index was performed, which yielded infor-

JACC Vol. 33, No. 5, 1999
April 1999:1308–16

Table 1. Baseline Patient Characteristics According to Severity of Ascending Aorta Atherosclerosis

Variable	All patients (n = 1,957)	Severity of Ascending Aorta Atherosclerosis				p value*
		Normal (n = 1,147)	Mild (n = 461)	Moderate (n = 250)	Severe (n = 99)	
Age, years	68.3 ± 8.5	67 ± 8	69 ± 9	71 ± 8	72 ± 8	< 0.0001
Male	64.1%	65.6%	61.2%	64.8%	58.6%	0.133
Body mass index, kg/m^2	26.8 ± 4.6	27.1 ± 4.6	26.6 ± 4.4	25.6 ± 4.4	26.4 ± 5.6	< 0.0001
Atrial fibrillation	12.6%	13.4%	10.7%	11.7%	14.1%	0.340
Hypertension	62.9%	62.8%	60.1%	65.4%	69.7%	0.563
Diabetes mellitus	27.2%	27.2%	27.9%	27.0%	23.5%	0.814
Smoking	45.4%	41.2%	46.1%	56.5%	62.6%	< 0.0001
Warfarin	9.3%	8.9%	9.2%	12.5%	8.3%	0.34
Aspirin	56.3%	57.8%	56.2%	53.0%	47.5%	0.051
Mitral stenosis	2.8%	3.7%	1.7%	2.0%	0%	0.006
Left ventricular function†	9.4 ± 4.0	9.3 ± 3.9	9.1 ± 3.9	9.5 ± 4.0	10.5 ± 4.3	0.0810
Extent of CAD, No. vessels	2.65 ± 6.1	2.64 ± .63	2.64 ± .60	2.69 ± .56	2.70 ± .57	0.11
Carotid artery stenosis:‡						
Normal-mild	76%	80%	78%	66%	63%	
Moderate	18%	14%	18%	26%	30%	
Severe	6%	6%	4%	8%	8%	< 0.0001
Serum cholesterol, mg/dL	210 ± 49	207 ± 46	213 ± 45	214 ± 51	223 ± 48	0.004

Data are mean ± SD
* p values refer to comparisons between all four groups. †Mean left ventricular score (CASS; ref. 37). ‡More severe of right or left carotid artery stenosis.
CAD = coronary artery disease.

mation on 281 (14%) of the patients. Long-term follow-up was unavailable on 12 patients (0.6% of the population); data from these patients were excluded from the analysis. The duration of follow-up was recorded as that from the day of cardiac surgery to the date of patient contact, the date of the neurologic event or the date of death. The mean follow-up time was 3.0 ± 1.9 years (range 0.1 to 7.6 years).

Statistical analysis. Data were analyzed with SAS version 6.11 (SAS Institute, Carey, North Carolina) and expressed as the mean ± SD. The association between the four categorical measurements of severity of atherosclerosis of the ascending aorta and the continuous variables was analyzed by analysis of variance (ANOVA). Wilcoxon's test was used to assess the relationship between ascending aortic atherosclerosis and all dichotomous variables. Kaplan-Meier survival analysis was used to describe the time to the first event (neurologic events and all-cause mortality). Comparisons of survival curves were performed by use of a log-rank test. In all event-specific survival analyses, data were censored at the time of death if the patient had not previously suffered a neurologic event. A Cox proportional-hazards multivariate regression analysis was used to assess the independent significance of six predefined potential predictors of the composite measure of neurologic events, all-cause mortality and all events. In these regression analyses, findings with respect to severity of atherosclerosis of the ascending aorta were grouped into three categories: normal-mild, moderate and severe. The normal and mild categories were grouped together for two reasons: it led to a better regression fit, and there were no differences between these two groups. A p value <0.05 was indicative of a statistically significant difference.

RESULTS

Of the 1,957 patients for whom follow-up data regarding neurologic events and death were available, 1,147 (58.6%) had a normal ascending aorta, 461 (23.5%) had mild atherosclerosis, 250 (12.8%) had moderate atherosclerosis and 99 (5.1%) had severe atherosclerosis of the ascending aorta. The baseline characteristics of the study patients according to the severity of atherosclerosis of the ascending aorta are listed in Table 1. Increasing severity of ascending aorta atherosclerosis was associated with increasing age of the patient, lower body mass index, history of smoking, increased severity of carotid artery disease and higher serum cholesterol levels. Patients with significant atherosclerosis of the ascending aorta also tended to use less aspirin.

During the follow-up period, 92 neurologic events and 399 deaths occurred. Univariate predictors of long-term neurologic events, all-cause mortality and all events (neurologic events and all-cause mortality) are listed in Table 2. Univariate predictors for neurologic events were male gender; history of atrial fibrillation, hypertension and diabetes mellitus; use of warfarin; severe carotid artery disease; and severe atherosclerosis of the ascending aorta. Univariate predictors of all-cause mortality were advanced age; male gender; lower body mass index; history of atrial fibrillation, hypertension and diabetes mellitus; LV dysfunction; severe

Table 2. Univariate Predictors of Long-Term Neurologic Events, All-cause Mortality, and All Events

Variable	Neurologic Event		All-cause Mortality		All Events	
	No (n = 1,865)	Yes (n = 92)	No (n = 1,558)	Yes (n = 399)	No (n = 1485)	Yes (n = 472)
Age, years	68.2 ± 8.6	69.5 ± 7.9	67.4 ± 8.6	71.6 ± 7.7*	67.4 ± 8.6	71.0 ± 7.8*
Male	64.6%	54.4%§	65%	60.4%§	64.9%	61.4%§
Body mass index	26.8 ± 4.6	26.1 ± 4.0	27.0 ± 4.4	26.0 ± 5.1†	27.0 ± 4.5	26.2 ± 5.0
Atrial fibrillation	12.3%	17.4%§	10.6%	20.4%*	10.6%	18.7%*
Hypertension	62.2%	76.1%‡	60.2%	73.2%*	59.6%	73.3%*
Diabetes mellitus	26.7%	35.9%†	24.5%	37.6%*	24.3%	36.2%*
Smoking	45.5%	42.4%	44.0%	50.9%	43.8%	50.2%
Warfarin	7.8%	41.4%*	8.7%	13.0%	6.5%	21.4%*
Aspirin	56.5%	51.1%	58.7%	46.7%*	58.9%	48.0%*
Mitral stenosis	2.7%	4.3%	2.9%	2.5%	3.0%	2.3%
Left ventricular function	9.3 ± 3.9	9.6 ± 4.3	9.1 ± 3.8	10.5 ± 4.3*	9.1 ± 3.8	10.3 ± 4.3*
Extent of CAD:						
1 vessel	7.2%	9.9%	7.2%	7.6%	7.2%	7.6%
2 vessels	20.4%	14.8%	19.5%	22.7%	20.1%	20.4%
3 vessels	72.4%	75.3%	73.3%	69.7%	72.7%	72.0%
Carotid artery disease:						
Normal-mild	76.2%	67.1%	78.2%	70.6%	78.7%	70.3%
Moderate	17.4%	21.0%	16.3%	21.8%	16.2%	21.2%
Severe	5.7%	11.8%‡	5.5%	7.6%§	5.1%	8.5%
Cholesterol, mg/dL	210 ± 47	215 ± 46	211 ± 45	206 ± 54§	211 ± 45	206 ± 52§
Atherosclerosis Ascending Aorta:						
Normal-mild	82.6%	73.9%	85.3%	69.3%	86.6%	71.4%
Moderate	12.6%	15.2%	11.1%	19.3%	10.8%	18.9%
Severe	4.8%	10.9%§	3.6%	10.8%†	3.6%	9.7%*

*$p < 0.0001$, yes vs. no. †$p < 0.001$, yes vs. no. ‡$p < 0.01$, yes vs. no. §$p < 0.05$, yes vs. no. Data are mean ± SD.
CAD = coronary artery disease.

carotid artery disease; lower serum cholesterol level; and severe atherosclerosis of the ascending aorta. Use of aspirin was associated with a lower incidence of all-cause mortality. The event rates according to the severity of ascending aorta atherosclerosis are listed in Table 3. The total number of neurologic events during follow-up was significantly higher in the group with severe ascending aortic atherosclerosis ($p = 0.05$). The neurologic events, mortality and the all-event rates significantly and incrementally increased with increases in severity of ascending aortic atherosclerosis.

When stratified by extent of atherosclerosis, the Kaplan-Meier survival curves for neurologic events and all-cause mortality varied significantly with severity of disease (Fig. 1). Univariate analyses indicated that for both outcomes (ie, neurologic events and all-cause mortality), there were consistent and statistically significant associations between adverse outcome and increasing severity of ascending aortic

Table 3. Event Rates in the Study Patients According to Severity of Ascending Aorta Atherosclerosis

Event	Severity of Ascending Aorta Atherosclerosis				p value
	Normal (n = 1,147)	Mild (n = 461)	Moderate (n = 250)	Severe (n = 99)	
Neurologic:					
Stroke	37 (3.2%)	17 (3.7%)	11 (4.4%)	9 (9.0%)	
TIA	14 (1.2%)	2 (0.4%)	3 (1.2%)	1 (1.0%)	
Total	49 (4.3%)	19 (4.1%)	14 (5.6%)	10 (10.1%)	0.05
Death:					
Total	177 (15.4%)	102 (22.1%)	77 (30.8%)	43 (43.4%)	< 0.0001
All events*	220 (19.2%)	117 (25.4%)	89 (35.6%)	46 (46.5%)	< 0.0001

*Includes neurologic events and all-cause death.
TIA = transient ischemic attack.

JACC Vol. 33, No. 5, 1999
April 1999:1308–16

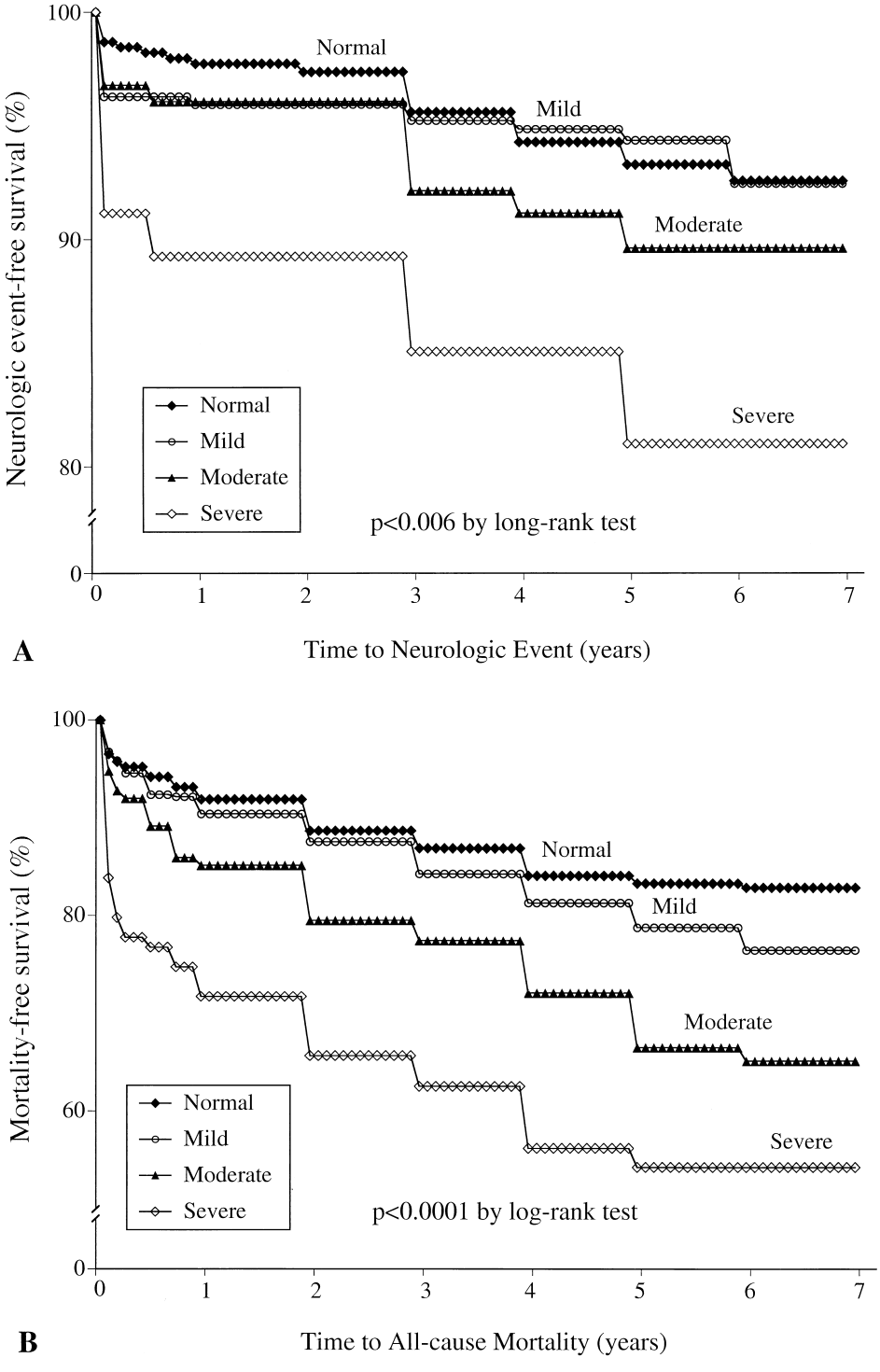

Figure 1. Kaplan-Meier analysis of survival without neurologic events **(A)** and without all cause-mortality **(B)**, according to severity of atherosclerosis of the ascending aorta (normal, mild, moderate, severe).

atherosclerosis, and although the significant association was apparent early, it continued to increase throughout the follow-up period.

Multivariate Cox regression analysis was performed to define predictive variables that had an independent association with each of the three outcomes (Table 4). Advanced age, LV dysfunction, atherosclerosis of the ascending aorta, hypertension and diabetes mellitus showed a highly significant independent association with all events (Table 4). For example, the risk ratio for aortic atherosclerosis indicated

Table 4. Independent Predictors of Long-Term Neurologic Events, All-cause Mortality, and All Events

Variable	Chi square	RR	95% CI	p value
All events (number of events = 472)				
Age*	37.1	1.43	1.27–1.60	< 0.0001
Left ventricular function†	32.8	1.39	1.24–1.56	< 0.0001
Ascending aorta atherosclerosis	30.0	1.3	1.19–1.44	< 0.0001
Hypertension	20.7	1.64	1.32–2.02	< 0.0001
Diabetes mellitus	11.9	1.41	1.16–1.72	0.0006
All-cause mortality (number of deaths = 399)				
Age*	47.2	1.56	1.37–1.77	< 0.0001
Ascending aorta atherosclerosis	40.0	1.38	1.25–1.53	< 0.0001
Left ventricular function†	35.5	1.45	1.28–1.64	< 0.0001
Hypertension	14.5	1.57	1.24–1.98	0.0001
Diabetes mellitus	14.3	1.51	1.22–1.87	0.0002
Neurologic events (number of neurologic events = 92)				
Hypertension	6.84	1.91	1.18–3.11	0.009
Ascending aorta atherosclerosis	6.52	1.31	1.06–1.62	0.011
Diabetes mellitus	5.97	1.72	1.11–1.64	0.015

*The risk ratio associated with age is the increased risk that is associated with a 10-year increase. †Left ventricular function based on the CASS score (37).
RR = risk ratio; CI = confidence interval.

that moderate atherosclerosis was associated with an increase of 1.30 in the risk of an event compared with normal-mild disease. However, the risk ratio was 1.7 times higher (1.30 × 1.30) for those with severe atherosclerosis than for those with normal-mild atherosclerosis. Advanced age, ascending aorta atherosclerosis, LV dysfunction, hypertension and diabetes mellitus also were significantly and independently associated with all-cause mortality (Table 4). Hypertension, atherosclerosis of the ascending aorta and diabetes mellitus were the only significant independent predictors of neurologic events (Table 4).

The incidence of long-term events per 100 person-years of follow-up according to severity of ascending aorta atherosclerosis is listed in Table 5. There was a greater than 1.5-fold increase in the incidence of both neurologic events and mortality as the severity of atherosclerosis increased from normal-mild to moderate, and a greater than threefold increase in the incidence of both as the severity of atherosclerosis increased from normal-mild to severe.

DISCUSSION

In this prospective study, long-term follow-up was performed in 1,957 patients (mean duration 3.0 ± 1.9 years) for the development of neurologic events and all-cause mortality. A statistically significant association was found between hypertension, atherosclerosis of the ascending aorta, diabetes mellitus and the subsequent occurrence of neurologic events; and between advanced age, LV dysfunction, atherosclerosis of the ascending aorta, hypertension, diabetes mellitus and the occurrence of all-cause mortality. Patients with severe atherosclerosis of the ascending aorta were found to have the highest incidence of neurologic events and of all-cause mortality, and these incidence rates were three-times higher than in patients with normal aortas, even after correcting for variables known to be associated with an increased incidence of these events, such as age, carotid artery disease and atrial fibrillation. These findings are in agreement with recent prospective studies that

Table 5. Incidence of Long-Term Events According to Severity of Ascending Aorta Atherosclerosis

Severity of ascending aorta atherosclerosis	Neurologic Events		All-cause Mortality	
	No. of events	Incidence per 100 person-years of follow-up	No. of events	Incidence per 100 person-years of follow-up
Normal-mild	68	1.8	279	4.3
Moderate	14	2.9*	77	8.3‡
Severe	10	5.8†	43	14.3§

Increased incidence: *for normal-mild to moderate is 1.6; †for normal-mild to severe is 3.1; ‡for normal-mild to moderate is 1.9; §for normal-mild to severe is 3.4.

JACC Vol. 33, No. 5, 1999
April 1999:1308–16

show a high recurrence rate of brain infarction in patients with large plaques in the aortic arch (33–35), but this is the first prospective study to show that ascending aorta atherosclerosis is an independent predictor of long-term mortality.

Importance of hypertension, diabetes mellitus and atherosclerosis of the ascending aorta as predictors of stroke. The role of hypertension as the most powerful risk factor for stroke, and the reduction of this risk with adequate therapy, has been documented in numerous studies (41–45). Similarly, but to a lesser extent, diabetes mellitus has been associated with increased risk of stroke and a poorer prognosis after stroke (46–48). Thus, it is not surprising that these two risk factors, in addition to atherosclerosis of the ascending aorta, were the most significant predictors of neurologic events in the present study. Numerous case reports have identified an atherosclerotic thoracic aorta as a likely source of arterial embolism to the brain and peripheral vessels (14–19,31,49–50), and have been documented to occur spontaneously (20), after initiation of anticoagulation (51,52), in association with cardiac surgery (21–25,53), and after invasive procedures (54). Atherosclerosis of the ascending aorta is a risk factor that has an independent association with previous cerebrovascular events (26). A recent autopsy study showed that the presence of ulcerated plaques in the ascending aorta and/or the aortic arch was associated with a significantly greater prevalence of cerebral embolic events than that in the absence of such plaques (28). In addition, three recent prospective studies have shown an association between an atherosclerotic thoracic aorta (detected by transesophageal echocardiography [TEE]), and cerebral and/or peripheral vascular ischemic events (33–35).

Our findings support the results of these three studies, but differ in several respects. First, our patient population was almost six times that in the French Aortic Plaques in Stroke (FAPS) study, and more than 10 times larger than those in the studies by Tunick and by Mitusch. Second, the mean follow-up period in the present study was 3.2 years, compared with 2.4, 1.4, and 1.2 years in the FAPS, the Mitusch, and in the Tunick studies, respectively. Third, the techniques used for detection of atherosclerotic disease and the locations at which disease was sought differed. The three previous studies evaluated, by use of TEE, atherosclerotic disease of the aortic arch only. In the present study, only the ascending aorta was evaluated, and we used epiaortic ultrasound. Although the utility of TEE for the detection of atherosclerosis of the aortic arch and the descending thoracic aorta has been demonstrated (29–36), our group and Konstadt et al. have shown that intraoperative visualization of the ascending aorta is suboptimal with TEE as compared with epiaortic ultrasound (38,55). Fourth, the patient populations differ: we followed 1,957 consecutive patients undergoing cardiac surgery, and of these, only 87 (4.4%) had a history of a previous neurologic event. In the FAPS study, all 331 patients were hospitalized for recent brain infarctions, in the study of Tunick et al, over half of the 42 patients had suffered a previous vascular embolic event, and in the study of Mitusch et al., over one third of the patients had a history of thromboembolic disease. Since a history of previous cerebrovascular event is known to be a predictor of future events, it could be argued that there was selection bias in these three studies. Fifth, the incidence of recurrent neurologic events according to severity of aortic arch atherosclerosis in the FAPS study was higher than in our study (Table 5). This is likely due to differences in study populations and in duration of follow-up. Thus, our study confirms the findings of the FAPS study, that the incidence of neurologic events increases as the severity of aortic atherosclerosis increases. However, our study is unique because it documents, for the first time, that increasing severity of atherosclerotic disease of the ascending aorta is a significant predictor of long-term mortality.

Atrial fibrillation and carotid artery disease. Atrial fibrillation and carotid artery disease have been associated with an increased risk of neurologic events (6,7,11–12). In the present study, 75% of patients underwent carotid artery ultrasound, only 88 (6%) had >80% occlusion of one or both carotid arteries, and most of these underwent carotid artery endarterectomy in association with their cardiac surgery. Even though severe carotid artery stenosis was a univariate predictor of neurologic events and of all-cause mortality, this variable was not a predictor in the multivariate analysis. The small number of patients with uncorrected severe carotid artery disease may explain why this was not a predictor of subsequent neurologic events in our study. Our findings do not contradict those of previous studies in which severe carotid artery disease was found to be an independent predictor of neurologic events.

Atrial fibrillation also has been shown to be an independent predictor of neurologic events. In the present study, a history of atrial fibrillation was a univariate predictor of long-term neurologic events, but it was not a predictor in the multivariate analysis. Since only 92 patients suffered neurologic events, it is likely that statistical power is lacking to definitively determine the independent predictive value of atrial fibrillation for the development of neurologic events. Pooled data from studies comparing treatment with warfarin and placebo in patients with atrial fibrillation have shown an event rate of approximately 4.5% per year in the placebo group versus 1.4% in the warfarin group (56). Since 246 of the patients in the present study had a history of atrial fibrillation on enrollment, approximately 30 neurologic events attributable to atrial fibrillation would be expected over a three-year follow-up, but only if atrial fibrillation were left untreated. In the present study, most patients with atrial fibrillation were treated with aspirin and/or warfarin, which would mitigate against an effect of atrial fibrillation on neurologic events.

Limitations of the study. Our study population was limited to cardiac patients who underwent cardiac surgery, but

because of the known association between CAD, hypertension and neurologic events, the results of this study may be generalizable to a large number of patients with these three conditions, who are at high risk for suffering neurologic events. In addition, a large number of deaths in patients with neurologic events occur in this high-risk population (57,58).

The strength of the relationship found in this study between aortic atherosclerosis and neurologic events may have been limited by a number of factors. First, we collected data on atherosclerosis of the ascending aorta only, not on the aortic arch or the descending thoracic aorta. Studies have documented that atherosclerotic disease in the aortic arch or the descending aorta is associated with an increased risk of stroke and/or peripheral vascular ischemic events (33–36). If the association between cerebrovascular events and atherosclerosis of the aortic arch is at least as strong as the association observed between the former and ascending aortic atherosclerosis, additional neurologic events could be explained by atherosclerosis of the aortic arch in the absence of disease in the ascending aorta. Thus, it is possible that the true incidence of neurologic events associated with atherosclerosis of the aorta was underestimated. Second, even though we obtained confirmation of the occurrence of neurologic events (eg, we required neurologic confirmation and/or hospital records clearly documenting the occurrence of stroke or TIA) and mortality (eg, the death certificate) in all cases, we were unable to determine the exact anatomic location of some of the neurologic events. If we had been able to confine our analysis to neurologic events that could not have been explained by significant contralateral carotid artery disease (in those who underwent carotid artery ultrasound), it may have been possible to ascertain the relative contribution of aortic atherosclerosis more definitively. Third, some patients underwent alterations in the surgical technique as a result of the epiaortic ultrasound findings, which may have reduced the observed long-term risk related to atherosclerosis of this vessel (24,25).

The therapeutic implications of the findings in this study are unknown. Further investigation will be needed to define better diagnostic strategies and to determine whether treatment with anticoagulants and/or neuroprotective agents will be effective in the prevention of atheroembolic neurologic events in these high-risk patients (59,60).

Conclusions. In this prospective, long-term follow-up study of 1,957 patients, we have shown that atherosclerosis of the ascending aorta is an independent predictor of neurologic events and of all-cause mortality. In addition to being a direct cause of atheroembolism, the atherosclerotic aorta may be a marker of generalized atherosclerosis and thus of increased morbidity and mortality.

Reprint requests and correspondence: Dr. Víctor G. Dávila-Román, Cardiovascular Division, Box 8086, Washington University, 660 S. Euclid Ave., St. Louis, Missouri 63110. E-mail: vdavila@imgate.wustl.edu.

REFERENCES

1. Sirna S, Biller J, Skorton DJ, Seabold JE. Cardiac evaluation of the patient with stroke. Stroke 1990;21:14–23.
2. Keating EC, Gross SA, Schlamowitz RA, et al. Mural thrombi in myocardial infarctions: Prospective evaluation by two-dimensional echocardiography. Am J Med 1983;74:989–95.
3. Greenland P, Knopman DS, Mikell FL, et al. Echocardiography in diagnostic assessment of stroke. Ann Intern Med 1981;95:51–3.
4. Adams PC, Cohen M, Chesebro JH, Fuster V. Thrombosis and embolism from cardiac chambers and infected valves. J Am Coll Cardiol 1986;8:(Suppl B)76B–87B.
5. Pop G, Sutherland GR, Koudstaal PJ, et al. Transesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. Stroke 1990;21:560–5.
6. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. Neurology 1978;28:973–7.
7. Wolf PA, Kannel WB, McGee DL, et al. Duration of atrial fibrillation and imminence of stroke: The Framingham study. Stroke 1983;14:664–7.
8. Benjamin EJ, Plehn JF, D'Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374–9.
9. Barnett HJM, Jones MW, Boughner DR, Kostuk WJ. Cerebral ischemic events associated with prolapsing mitral valve. Arch Neurol 1976;33:777–82.
10. Daniel WG, Nellessen U, Schroder E, et al. Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. J Am Coll Cardiol 1988;11:1204–11.
11. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445–53.
12. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421–8.
13. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: The NINCDS Stroke Data Bank. Ann Neurol 1989;25:382–90.
14. Winter WJ. Atheromatous emboli; a cause of cerebral infarction. Arch Pathol 1957;64:137–42.
15. Sturgill BC, Netsky MG. Cerebral infarction by atheromatous emboli. Arch Neurol 1963;76:185–96.
16. Soloway HB, Aronson SM. Atheromatous emboli to central nervous system. Arch Pathol 1964;11:657–67.
17. Beal MF, Williams RS, Richardson EP Jr, Fisher CM. Cholesterol embolism as a cause of transient ischemic attacks and cerebral infarction. Neurology 1981;31:860–5.
18. Flory CM. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. Am J Pathol 1945;21:549–58.
19. Hoye SJ, Teitelbaum S, Gore I, Warren R. Atheromatous embolization: a factor in peripheral gangrene. N Engl J Med 1959;261:128–31.
20. Gore I, Collins DP. Spontaneous atheromatous embolization: review of the literature and report of 16 additional cases. Am J Clin Pathol 1960;33:416–26.
21. Dávila-Román VG, Barzilai B, Wareing TH, et al. Intraoperative ultrasonographic evaluation of the ascending aorta in 100 consecutive patients undergoing cardiac surgery. Circulation 1991;84(Suppl III):47–53.
22. Hosoda Y, Watanabe M, Hirooka Y, et al. Significance of

atherosclerotic changes of the ascending aorta during coronary bypass surgery with intraoperative detection by echography. J Cardiovasc Surg 1991;32:301–6.
23. Ohteki H, Itoh T, Natsuaki M, et al. Intraoperative ultrasonic imaging of the ascending aorta in ischemic heart disease. Ann Thorac Surg 1990;50:539–42.
24. Wareing TH, Dávila-Román VG, Barzilai B, et al. Management of the severely atherosclerotic ascending aorta during cardiac operations. J Thorac Cardiovasc Surg 1992;103:453–62.
25. Wareing TH, Dávila-Román VG, Daily BB, et al. Strategy for the prevention of stroke in cardiac surgical patients. Ann Thorac Surg 1993;55:1400–7.
26. Dávila-Román VG, Barzilai B, Wareing TH, et al. Atherosclerosis of the ascending aorta: Prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. Stroke 1994;25:2010–6.
27. Dávila-Román VG, Schechtman KB, Kouchoukos NT, Barzilai B. Atherosclerosis of the ascending aorta is a predictor of renal dysfunction after cardiac operations. J Thorac Cardiovasc Surg 1999;117:111–6.
28. Amarenco P, Duyckaerts C, Tzourio C, et al. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. N Engl J Med 1992;362:221–5.
29. Tunick PA, Perez JL, Kronzon I. Protruding atheromas in the thoracic aorta and systemic embolization. Ann Intern Med 1991;115:423–7.
30. Karalis DG, Krishnaswamy C, Victor MF, et al. Recognition and embolic potential of intraaortic atherosclerotic debris. J Am Coll Cardiol 1991;17:73–8.
31. Rubin DC, Plotnick GD, Hawke MW. Intraaortic debris as a potential source of embolic stroke. Am J Cardiol 1992;15: 819–20.
32. Dávila-Román VG, Westerhausen D, Hopkins WE, et al. Transesophageal echocardiography in the detection of cardiovascular sources of peripheral vascular embolism. Ann Vasc Surg 1995;9:252–60.
33. Tunick PA, Rosenzweig BP, Katz ES, et al. High risk for vascular events in patients with protruding aortic atheromas: a prospective study. J Am Coll Cardiol 1994;23:1085–90.
34. The French Study of aortic plaques in stroke group. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. N Engl J Med 1996;334:1216–21.
35. Mitusch R, Doherty C, Wucherpfenning H, et al. Vascular events during follow-up in patients with arch atherosclerosis. Stroke 1997;28:36–9.
36. Hartman GS, Yao F-S F, Bruefach M, et al. Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. Anesth Analg 1996;83:701–8.
37. Kennedy JW, Kaiser GC, Fisher LD, et al. Clinical and angiographic predictors of operative mortality from the collaborative Study in Coronary Artery Surgery (CASS). Circulation 1981;63:793–802.
38. Dávila-Román VG, Phillips KJ, Daily BB, et al. Intraoperative transesophageal echocardiography and epiaortic ultrasound for assessment of atherosclerosis of the thoracic aorta. J Am Coll Cardiol 1996;28:942–7.
39. Berens ES, Kouchoukos NT, Murphy SF, Wareing TH. Preoperative carotid artery screening in elderly patients undergoing cardiac surgery. J Vasc Surg 1992;15:313–27.
40. Steinke W, Kloetzsch C, Hennerici M. Carotid artery disease assessed by color Doppler flow imaging: Correlation with standard Doppler sonography and angiography. Am J Radiol 1990;154:1061–8.
41. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham Study. JAMA 1970;214:301–10.
42. Whisnant JP. Epidemiology of stroke: emphasis on transient cerebral ischemic attacks and hypertension. Stroke 1974;5:68–70.
43. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. J Hypertens 1994(Suppl);12:5–14.
44. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, part 2: Short-term reductions in blood pressure. Overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827–38.
45. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255–64.
46. Weinberger J, Biscarra V, Weisberg MK, Jacobson JH. Factors contributing to stroke in patients with atherosclerotic disease of the great vessels: the role of diabetes. Stroke 1983;14:709–12.
47. Kjell A, Erik H, Claes H, et al. The natural history of stroke in diabetic patients. Acta Med Scand 1980;207:417–24.
48. Helgason CM. Blood glucose and stroke. Stroke. 1988;18: 1049–53.
49. Moldveen-Geronimus M, Merriam JC Jr. Cholesterol embolization: from pathological curiosity to clinical entity. Circulation 1967;35:946–53.
50. Smith MC, Ghose MK, Henry AR. The clinical spectrum of renal cholesterol embolization. Am J Med 1981;71:174–80.
51. Feder W, Auerbach R. "Purple toes": an uncommon sequela of oral coumarin drug therapy. Ann Intern Med 1961;55: 913–7.
52. Bruns FJ, Segel DP, Adler S. Control of cholesterol embolization by discontinuation of anticoagulant therapy. Am J Med Sci 1978;275:105–8.
53. Blauth CI, Cosgrove DM, Webb BW, et al. Atheroembolism from the ascending aorta: an emerging problem in cardiac surgery. J Thorac Cardiovasc Surg 1992;103:1104–12.
54. Harrington JT, Sommers SC, Kassirer JP. Atheromatous emboli with progressive renal failure: renal arteriography as the probable inciting factor. Ann Intern Med 1968;68:152–60.
55. Konstadt SN, Reich DL, Quintana C, Levy M. The Ascending Aorta: How Much Does Transesophageal Echocardiography See? Anesth Analg 1994;78:240–4.
56. Laupacis A, Albers G, Dalen J, et al. Antithrombotic therapy in atrial fibrillation. Chest 1995;(Suppl)108:352–9.
57. Rokey R, Rolak LA, Harati Y, et al. Coronary artery disease in patients with cerebrovascular disease: a prospective study. Ann Neurol 1984;16:50–3.
58. Kannel WB, Wolf PA, Verter J. Manifestations of coronary disease predisposing to stroke. The Framingham study. JAMA 1983;250:2942–6.
59. Dressler FA, Craig WR, Castello R, Labovitz AJ. Mobile aortic atheroma and systemic emboli: efficacy of anticoagulation and influence of plaque morphology on recurrent stroke. J Am Coll Cardiol 1998;31:134–8.
60. Fisher M, Jones S, Sacco RL. Prophylactic neuroprotection for cerebral ischemia. Stroke 1994;25:1075–80.