

Are Aortic Aneurysms Caused by Atherosclerosis?

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Background. The emerging controversy concerning the causal role of atherosclerosis in the development of aortic aneurysms was examined using the accumulated clinical and autopsy data obtained during a 20-year follow-up of a cohort of more than 8,000 men of Japanese ancestry in Hawaii.

Methods and Results. Analyses of 174 clinical incident events indicated that there were two types of aneurysmal disease, 151 aortic aneurysms and 23 aortic dissections. The baseline risk factors that predicted the clinical aortic aneurysms were the same factors that predicted aortic atherosclerosis in the same cohort, namely, high blood pressure, high serum cholesterol, and cigarette smoking. These same risk factors were also significantly associated with the occurrence of 27 aortic aneurysms among 293 autopsied men. The less common aortic dissections had an age-specific incidence pattern indicative of an innate susceptibility precipitated by an exposure to another factor. This pattern was consistent with the findings that the incidence of aortic dissections was predicted mainly by baseline high blood pressure.

Conclusions. From the perspective of prevention, it appears that the risk factors for aortic atherosclerosis and probably atherosclerosis itself are necessary elements in the causal pathway for the great majority of aortic aneurysms in this cohort. (*Circulation* 1992;85:205-211)

T rue aortic aneurysms are dilatations of the aorta that contain all layers of the artery wall. They usually balloon out from a local area but may involve the entire circumference. Pathologically, they are characterized by deterioration of the aortic wall with loss of elastin and smooth muscle cells.^{1,2} Aortic dissections (dissecting aneurysms) involve a longitudinal splitting of the aorta wall that separates the intima from the adventitia. The initial event may be an intimal tear through which blood surges into the media or a hemorrhage into a diseased media with secondary rupture of the intima.³ Both of these types of aneurysmal disease tend to appear late in life and to occur more frequently among men than among women.²⁻⁴

Except for uncommon cases due to trauma, congenital disorders of connective tissue, and infection, aortic aneurysms have traditionally been thought to be caused by atherosclerosis because of the almost universal find-

ings of calcified atherosclerotic degeneration in the walls of the aneurysms.^{1,2} Recently, this atherosclerosis theory has been challenged on the basis of epidemiologic, genetic, and biochemical information indicating that other etiologic factors may be involved or that the role of atherosclerosis may be secondary.⁴⁻¹³

To examine this emerging controversy, we have analyzed the cumulative data concerning the predictors of incident aortic disease that has occurred during a 20-year follow-up of a cohort of 8,006 men

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of Japanese ancestry. We were also able to examine the pathological associations of aneurysms and atherosclerosis among the men in this cohort who died and had autopsy examinations.

The main focus of the present report is the evidence for and against the concept that atherosclerosis plays a major role in the occurrence of aortic disease. To our knowledge, there is only one other prospective study of aortic aneurysms,¹⁴ so we have provided detailed risk factor data. The term "cause" is used in the pragmatic sense of a factor that alters the risk of a disease.

Methods

Incidence Studies

The Honolulu Heart Program is a prospective study of a cohort of 8,006 men of Japanese ancestry

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who were born between 1900 and 1919 and were living on Oahu, Hi., in 1965. The initial examination was conducted between 1965 and 1968, and more than 90% of survivors were seen at follow-up examinations 2 and 6 years after the initial examinations. Continuous surveillance of all hospital discharge records and death certificates has been maintained from 1965 to the present.

All risk factor measurements were from the initial examination described earlier.¹⁵ Briefly, blood pressure was measured three times using a mercury sphygmomanometer, and the mean of all three measures was used. Body mass index was calculated as weight (kg) divided by height squared (m). Serum levels of cholesterol, triglyceride, uric acid, and glucose were determined from blood drawn 1 hour after a 50-g glucose load from nonfasting participants. Alcohol consumption was calculated from reported usual intake of beer, wine, and spirits in milliliters per day. Cigarette pack-years were calculated from the usual number of cigarettes smoked per day and the number of years smoked for both current and past smokers. A physical activity index was based on reported usual hours a day spent in different levels of activity. Dietary intakes were derived from 24-hour dietary reports.

The diagnoses, location, and type of the aortic aneurysms are determined by a single pathologist (G.S.) on the basis of all available medical, surgical, and autopsy records. A total of 190 aneurysms were found. Two were prevalent at the time of the initial examination, 13 did not meet the diagnostic standards or occurred among men who were not included because they had prevalent coronary heart disease at the initial examination, and one was of traumatic origin. There was no evidence that any of the aneurysms were due to syphilis or other infectious agents. Thus, there was a total of 174 aneurysms available for study. Of these, the diagnosis was made from reports of surgical or autopsy specimens for 154 (89%) and from combined clinical and radiologic records for 20 (11%).

Autopsy Studies

Details of the autopsy study protocol have been reported earlier.^{16,17} Following a standardized protocol, the coronary arteries and aorta were dissected free of fat and adventitial tissue, opened longitudinally, sewn to plastic sheets, and fixed in formalin. The degree of atherosclerosis was determined by one pathologist (T.H.) using the American Heart Association panel method.¹⁸ Each vessel was compared with a panel of photographs showing increasing levels of atherosclerosis and assigned an ordinal score of from 1 (completely free of raised lesions) to 7 (most of the surface affected by raised lesions or total stenosis of the vessel lumen). The readings were blinded to other autopsy and clinical findings. For some analyses, the category of "severe atherosclerosis" was used. This was defined as a panel score of 5 or greater, equal to 70% or more of the aorta surface being affected by raised lesions.¹⁷

Statistical Analyses

For illustration of the associations of aortic aneurysms with risk factors, age-adjusted rates by person-years of follow-up were calculated by quartiles or other groupings of the risk factors using actuarial methods. Univariate and multivariate associations were tested, and relative risks and 95% confidence intervals were calculated using Cox proportional hazard models.¹⁹ Measures of relative risk were based on comparisons of the difference in the mean values between the highest and lowest quartiles of the risk factor, called the "interquartile difference" in the present study.

Results

Among 7,682 men who were free of clinical aortic aneurysm and coronary heart disease at the initial examination in 1965–1968, 151 developed aortic aneurysms and 23 developed aortic dissections during the approximate 20-year follow-up period to 1988. Of the aneurysms, 138 were abdominal, and 13 were thoracic. Discriminant function analysis revealed no meaningful differences between the abdominal and thoracic aneurysms, so they were grouped together as "aortic aneurysms." The aortic dissections were analyzed separately.

In terms of fatality, 85 of the 151 men (56%) with aortic aneurysms had died by the end of 1988; of these, only 24 (28%) had aortic aneurysm noted as the immediate or contributing cause of death. Of the 23 men with aortic dissections, 16 (70%) had died, and all 16 had aortic aneurysm coded as the cause of death but not always as dissecting aneurysm.

Risk Factor Data

Figure 1 shows the incidence rates per 100,000 person-years for aortic aneurysms and dissections by age at diagnosis. There was a clear difference in the two patterns. Aortic aneurysms increased steadily with age after age 60, whereas the aortic dissections

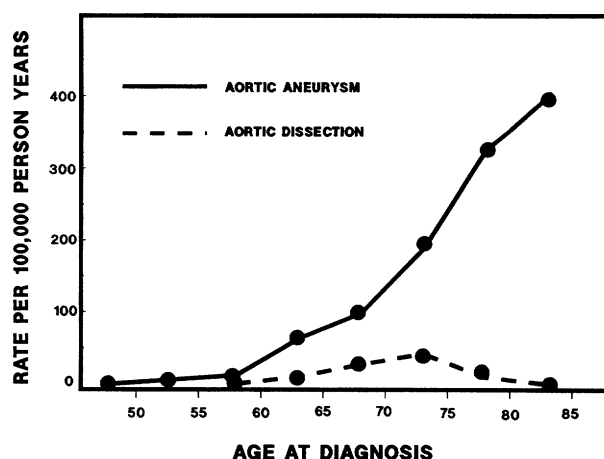


FIGURE 1. Plots of incidence rates of aortic aneurysm and dissection by age at diagnosis.

TABLE 1. Age-Adjusted Incidence Rates of Aortic Aneurysm and Aortic Dissection per 100,000 Person-Years by Quartiles of Selected Risk Factors

Variables	Incidence per 100,000 person-years		
	Person-years	Aortic aneurysm	Aortic dissection
Systolic blood pressure (mm Hg)			
80–118	29,152	52*	0*
119–131	41,136	83	13
132–146	37,152	103	11
147–262	35,366	164	38
Serum cholesterol (mg/dl)			
51–192	37,869	62*	14
193–215	38,757	93	19
216–240	37,662	93	13
241–537	37,657	158	16
Serum triglyceride (mg/dl)			
62–127	36,324	72	9*
128–185	38,881	97	6
185–278	38,405	123	26
279–1,793	36,369	108	25
Cigarette pack-years			
0	87,940	41*	12
1–29	21,426	104	16
30–43	22,208	175	31
40–104	20,592	206	14
Height (cm)			
124–157	42,926	69*	6
158–161	31,994	88	25
162–165	38,902	129	13
166–196	31,814	136	25

*Probability of association <0.05 from Cox proportional hazards models with age.

peaked between ages 70 and 75 and decreased after that.

Table 1 shows the age-adjusted incidence rates of aortic aneurysms and dissections by quartiles of selected risk factors. There were clear patterns of association of aneurysms with systolic blood pressure, cigarette pack-years, serum cholesterol, and height. In contrast, aortic dissections were associated only with systolic blood pressure and serum triglyceride. Both aneurysms and dissections were also associated

with diastolic blood pressure, but the patterns were not as strong as with systolic pressure. In separate analyses, there were no patterns of association of either aneurysms or dissections with obesity as measured by body mass index and skin folds, serum glucose, serum uric acid, physical activity, forced expiratory volume, alcohol intake, or nutrients measured in a 24-hour dietary recall (data not shown).

Table 2 shows the multivariate interquartile relative risks from Cox proportional hazard models re-

TABLE 2. Multivariate Interquartile Relative Risks* Relating Aortic Aneurysms and Dissections to Selected Risk Factors

Variable	Interquartile difference	Relative risk (95% confidence intervals)	
		Aortic aneurysm (n=151)	Aortic dissection (n=23)
Systolic blood pressure (mm Hg)	50	2.01 (1.41–4.84)	4.30 (1.97–9.43)
Serum cholesterol (mg/dl)	94	2.32 (1.62–7.04)	1.04 (0.38–1.84)
Serum triglyceride (mg/dl)	275	1.07 (0.85–1.35)	1.45 (1.12–1.89)
Cigarette pack-years	62	3.50 (2.57–4.66)	1.68 (0.67–4.18)
Height (cm)	16	2.33 (1.52–3.54)	1.08 (0.48–1.67)

*From Cox proportional hazards models including age and all listed variables. "Interquartile" refers to difference between mean values of first and fourth quartiles of risk variable.

TABLE 3. Age-Adjusted Percentages of Autopsied Men With Aortic Aneurysms by Degree of Aortic Atherosclerosis

Atherosclerosis score	n	Men with aneurysm (%)
1-3	103	1.0
4	75	1.4
5	59	9.3
6-7	56	31.0
Total	293	9.2*

* $p < 0.05$ from a logistic regression model with age. χ^2 for trend, 46.0. Relative risk (and 95% confidence intervals) of 4.13 (2.5-6.8) associated with 1-grade level increase in atherosclerosis score.

lating aortic aneurysms and dissections to selected risk factors. The patterns were similar to those found with the bivariate analyses. Aortic aneurysms were significantly associated with systolic blood pressure, serum cholesterol, cigarette pack-years, and height, whereas aortic dissections were associated with systolic blood pressure and serum triglyceride. Interaction terms of the significant variables were tested, and none was statistically significant. Discriminant function analyses indicated that the aortic aneurysms and dissection cases differed significantly in their overall associations with risk factors and specifically for serum cholesterol and triglyceride levels and height. Tests of differences of the β -coefficients from the Cox models were also statistically significant for these variables but not for cigarette pack-years.

Autopsy Studies

Of the total of 8,006 men examined, 2,415 had died between 1965 and 1988. Of these men, 605 were autopsied, including 332 with a study protocol autopsy that provided 293 aortas for examination. Among these 293 aortas, there were 27 with aortic aneurysms and five with aortic dissections. All except four of the 27 aneurysms were in the abdominal part of the aorta. The following analyses were limited to aortic aneurysms.

Table 3 shows the age-adjusted percentages of autopsied men with aneurysms by atherosclerosis scores. There was a clear, statistically significant association of aortic aneurysms with aortic atherosclerosis. All except two of the aneurysms occurred

among men with atherosclerosis scores of 5 or higher (approximately 70% or more of the surface affected by raised lesions). Logistic modeling with age indicated that a relative risk of 4.13 (95% confidence intervals, 2.5-6.8) was associated with a 1-grade level increase in aortic atherosclerosis.

Table 4 shows the multivariate relative risks relating aortic aneurysms and severe atherosclerosis to selected risk factors for the 293 men with graded aortas at autopsy. The associations for the two pathological end points were quite similar for systolic blood pressure, serum cholesterol, and cigarette pack-years. The association of severe atherosclerosis with height was not as strong as that for aortic aneurysms, but the trend was in the same direction, and there were no significant differences between the β -coefficients. Neither of these pathological end points was associated with several other variables, including obesity, serum glucose, serum triglyceride, physical activity, alcohol intake, and nutrients measured in the 24-hour dietary recall (data not shown).

Time Trends

Determining time trends of disease in a fixed cohort is difficult because of inconsistencies due to aging of the cohort. In this particular case, however, it was possible to calculate age-specific incidence rates of aortic aneurysms by person-years at risk for the age groups of 60-69 years and 70-79 years for much of the 20-year follow-up period. Figure 2 shows that for these two age groups, there was no indication of change with time. Earlier analyses of the trends of aortic atherosclerosis scores among autopsied cohort men with and without clinical cardiovascular disease showed a similar lack of change with time of autopsy between the years 1965 and 1983, although there was a clear declining trend for coronary artery atherosclerosis during the same time period.¹⁶

Discussion

The present study identifies two types of aneurysmal disease. What we call aortic aneurysms were the most common, and most of them (91%) occurred in the abdominal portion of the aorta. They increased exponentially with age as do other cardiovascular diseases and atherosclerosis in this cohort.^{16,20,21} The

TABLE 4. Multivariate Interquartile Odds Ratios* Relating Aortic Aneurysms and Severe Atherosclerosis at autopsy to Selected Risk Factors

Variable	Interquartile difference	Relative risks (95% confidence intervals)	
		Aortic aneurysms	Severe atherosclerosis†
Systolic blood pressure (mm Hg)	50	3.51 (1.16-10.50)	4.01 (2.10-6.69)
Serum cholesterol (mg/dl)	94	2.92 (1.21-7.07)	2.00 (1.15-3.48)
Cigarette pack-years	62	3.31 (1.32-8.36)	4.68 (2.40-9.10)
Height (cm)	16	2.55 (1.18-5.49)	1.50 (0.44-5.33)

*From logistic regression models with age and all listed variables in models. Interquartile refers to difference between mean values of first and fourth quartiles of risk variables.

†Severe atherosclerosis was defined as a panel score of 5 or greater indicative of 70% or more of surface affected by raised lesions.

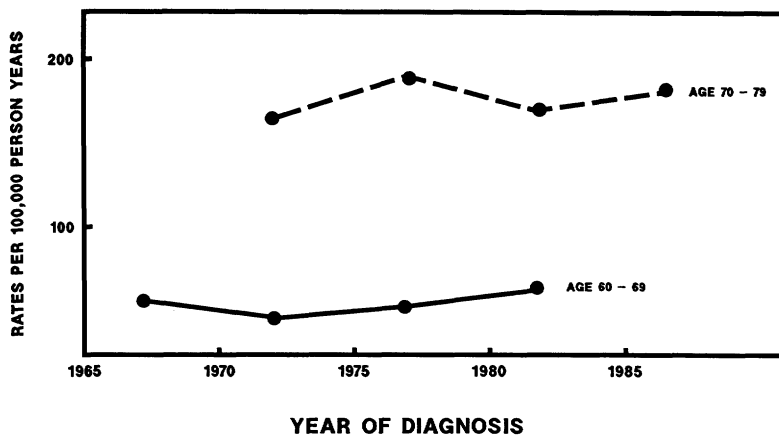


FIGURE 2. Plots of age-specific incidence rates of aortic aneurysms by time period of diagnosis.

risk factors that predicted these clinical aortic aneurysms in both the prospective analyses of clinical disease and in the autopsy studies were high blood pressure, high serum cholesterol, cigarette smoking, and height. Except for height, these risk factors were also the same ones that were independently associated with aortic atherosclerosis measured at autopsy in the present and past studies of this cohort.^{16,17} Furthermore, all except two of the 27 aortic aneurysms found at autopsy occurred in men with severe aortic atherosclerosis involving more than 70% of the surface of the aorta. It may be possible for an aneurysm to disturb blood flow over the surface of the dilated aorta, resulting in local atherosclerotic changes, but it appears less likely that such disturbances would affect more than 70% of the aorta surface.

It is not possible to determine from this type of study whether one or more of the risk factors that predicted both atherosclerosis and aortic aneurysm did so through a pathway of promoting atherosclerosis, which in turn increased the risk of aneurysm, or whether they had two separate effects. For example, high blood pressure could both have an atherogenic role and precipitate an aneurysm in a congenitally weak aorta wall. There is no clear understanding of the etiologic role of cigarette smoking in aortic atherosclerosis, although numerous mechanisms have been suggested, including direct endothelial cell damage, increased fibrinolytic activity, platelet aggregation, and obstruction of blood flow in small arteries such as the vasa vasorum in the aorta.²² This latter role is an example of how cigarette smoking could affect the nourishment of the aorta wall independent of atherosclerosis. It is difficult to explain the role of high serum cholesterol, except through atherogenesis.

Although the association of aortic aneurysms with height was unexpected, a similar association was reported in a study comparing a small number of patients with aneurysms with patients with atherosclerotic occlusive disease.²³ One possible explanation of this association is that large persons have large arteries, which in turn have greater circumferential wall stress (force per unit area) as described by

the physical law of Laplace (tension is equal to pressure multiplied by radius).²

In contrast to the findings for aortic aneurysms, aortic dissections occurred most frequently in the thoracic portion of the aorta and did not have the same patterns of risk factor associations. Perhaps the most striking difference was the age-specific incidence rates, which started to increase at about the same age as those for aortic aneurysms but peaked in the 70–74-year-old age group and declined in the older age groups (Figure 1). This is the pattern that one would expect for what Brody and Schneider²⁴ calls “age-related” diseases characterized by a combination of an innate susceptibility with exposure to a triggering agent. For example, a congenital weakness in the aortic wall combined with increasing blood pressure after age 50 could lead to increasing incidence rates of clinical disease followed by a drop in the rates when the pool of susceptible individuals had been exhausted. This pattern is also consistent with the strong association of aortic dissections with high blood pressure and lack of association with the other major risk factors for aortic atherosclerosis in this cohort. The association of aortic dissections with serum triglyceride, in the absence of such an association with serum cholesterol, is difficult to explain.

To our knowledge, there is only one other prospective study of aortic aneurysms.¹⁴ It was based on death certificates for more than 800,000 adults followed for 6 years after they had completed a medical interview. The 337 deaths due to nonsyphilitic aortic aneurysms among men aged 50–69 years at entry were reported to be associated with histories of hypertension, cigarette smoking, obesity, and physical inactivity, although few statistical details were provided.

Challenges to the Atherosclerosis Theory

The questions about atherosclerosis as an important cause of aortic aneurysms have come from a variety of scientific perspectives. The epidemiologic challenge is based on evidence that incidence and mortality rates for aortic aneurysms have not shown the same declines since the mid-1960s that have been reported for coronary heart disease and stroke.^{5,6}

The overall incidence of aortic aneurysms among the residents of Rochester, Minn., increased three-fold during the 30-year period of 1951–1980.⁵ This increase was entirely due to abdominal aneurysms, as the incidence of thoracic aneurysms appeared to decline. Much of the increase was thought to be due to improved case determination after the introduction of ultrasound in the mid-1960s, although other explanations are possible.

Mortality rates for aortic aneurysms in the United States increased from 1951 through 1968 and then declined slightly through 1981.⁶ The decline after 1968 appeared to be due mostly to aortic dissections and unspecified types, whereas rates for abdominal and thoracic aneurysms showed no change.

There are a number of problems with mortality data. In this cohort, only 24 of the 85 men (28%) with aortic aneurysms who had died had aortic aneurysm noted as the immediate or contributing cause of death. This suggests there is a great deal of underreporting, which may change with time. The introduction of new surgical techniques and diagnostic methods could also increase case finding during a period of decreased incidence. There have also been dramatic changes in the pathological types of aneurysms during the first 60 years of the 1900s.²⁵ In the early years, thoracic aneurysms were much more common than abdominal aneurysms, with ratios of approximately 8:1 clinically and 5:1 in autopsy series. The autopsy series ratios had changed to approximately 2:1 by 1950 and to less than 1:1 by 1964, probably due to a decrease in syphilitic aneurysms, which usually occur in the thoracic aorta.^{25,26}

A further difficulty with the time trend argument is that it assumes that atherosclerosis in the coronary arteries has the same natural history as atherosclerosis in the aorta, which is not necessarily true. Atherosclerosis starts 10–20 years earlier in the aorta, progresses at a more rapid rate, and is more severe than in the coronary arteries.²⁷ Geographically, aortic atherosclerosis has been found to be disproportionately severe in countries with low incidence rates of coronary artery disease.²⁸ Thus, it is quite possible that the factors that are associated with decreased mortality rates of coronary artery disease do not have the same effect on the aorta.

In considering other etiologic factors, Dobrin² described several anatomic and physiological characteristics that contribute to the risk of developing aortic aneurysms. First, important differences exist between the abdominal and thoracic segments. The abdominal segment tapers geometrically; has greater stiffness, resulting from less elastin and more collagen tissue; and has higher pressure waves reflecting off of the iliac and other arteries, resulting in a higher pulsatile stress in the abdominal than in the thoracic aorta. High pulsatile stress in the abdominal aorta could increase the development of atherosclerotic plaques in the artery wall as well as precipitate the development of an aneurysm in a weak wall. An interesting example of the hemodynamic effect was

noted in a study of leg amputations that resulted in an asymmetric flow pattern at the aortic bifurcation and an increased risk of aortic aneurysms.²⁹

The segments of the aorta also differ in vascular nourishment. Vasa vasorum is quite common in the outer portion of the thoracic aorta, whereas it is very rare in the abdominal aorta.¹² Oxygen and nourishment of the abdominal aorta must then come mainly by diffusion from within the lumen. Any thickening of the endothelial wall by fatty streaks or atherosclerotic lesions could reduce the flow of nutrients to the media and theoretically lead to deterioration of the elastic and collagen architecture of the aortic wall.

The concept that there may be a genetic connective tissue defect in the occurrence of aortic aneurysm is based on reports of familial clustering of cases, genetic linkage analysis, and a genetic mouse model.^{4,7–10} The reports of familial clustering indicate that as many as 20% of patients with aortic aneurysms know of one or more first-degree relatives with aortic aneurysms.^{4,7–9} One study with a control group estimated that this represented a 12-fold increase among first-degree relatives.⁹ It is difficult to determine if there are selection biases affecting the types of patients who get into these surgical case series or if family information bias (the flow of family history about disease that is stimulated by a new case in the family) affected these results.³⁰ The fact that male-to-female ratios as high as 8:1 have been reported in these studies^{2,4,7,8} compared with ratios of 4:1 from population-based incidence rates⁵ indicates that some selection had occurred.

Biochemical studies of possible genetic causes have focused on structural defects in the aortic matrix proteins, overactive proteolysis, and inadequate inhibition of proteolysis.^{2,4,11–13} Dobrin² demonstrated that failure of elastin is a critical step in the development of aneurysmal dilatation and that the rupture of aneurysms involves the failure of collagen. Although numerous studies have shown that elastin and collagen are lower and that elastase and collagenase activities are higher in patients with aneurysms compared with control subjects, it is not clear whether these changes are the cause or the result of aortic dilatation and rupture and the associated inflammatory process.^{2,4,11–13}

A recent study of a single family with a high risk of aortic aneurysms has revealed an abnormality in the production of type III procollagen in the affected members.³¹ The authors have developed a saliva test that identifies the defect, which can be used to test other patients with a family history. Such genetic markers can become extremely useful to screen relatives of aneurysm cases and to identify high-risk individuals who could be subjects for preventive efforts and ultrasound examinations. They can also be useful in the future to help determine if the proportion of aneurysms due to genetic defects is large or small.

In summary, the findings from the present study indicate that there are at least two different types of

aneurysmal disease. The most common type, aortic aneurysm, was predicted by the same risk factors that predicted atherosclerosis, and the aneurysms occurred almost exclusively in men who had severe levels of atherosclerosis in more than 70% of their aortas. This overall pattern indicates that the risk factors for atherosclerosis and probably atherosclerosis itself are necessary elements in the causal pathway of a large proportion of aortic aneurysms. This concept does not exclude the possibility of other causal factors, but from the perspective of prevention, it provides further stimulus for modification of the key atherosclerosis risk factors—high blood pressure, serum cholesterol, and cigarette smoking.

The smaller subset of aortic dissections had the age-specific incidence pattern of a disease involving innate (genetic) susceptibility and precipitation by hypertension. If genetic predisposition proves to be a necessary factor for this and other subsets of aortic disease, then screening for genetic markers could lead to even more effective preventive efforts among high-risk groups.

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