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Predicting rupture, death and dissection : the natural history of thoracic aortic disease

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Thoracic Aortic Disease

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ABSTRACT

Predicting Rupture, Death, and Dissection: The Natural History of Thoracic Aortic Disease

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Background - Thoracic aortic aneurysms and dissections are serious, potentially fatal diseases. Ability to estimate simply the *yearly* rate of rupture/dissection would greatly enhance clinical decision making for specific patients.

Methods – Data on 668 patients (414m, 254f) (median age 65.8 yrs) with thoracic aortic disease was entered into a computerized database over nine years. 3115 imaging studies were available. 304 patients were dissection-free at presentation; their natural (unoperated) history was followed for rupture, dissection, and death. In order to assess the impact of familial clustering of aortic or aneurysmal disease, family pedigrees were obtained through telephone inquiry of 218 (142m, 76f) patients without Marfan syndrome (MFS).

Results – 5-year survival in unoperated patients was 54% at 5 years. Aortic size was a very strong predictor of rupture, dissection, and mortality. For aneurysms ≥ 6.0 cm in diameter: rupture occurred at 3.6% per year, rupture or dissection at 6.4% per year, death at 10.8%, and death, rupture or dissection at 14.1% per year. At size ≥ 6.0 cm, the odds ratio for rupture was increased 15-fold ($p = 0.0041$). Elective, pre-emptive surgical repair restored life-expectancy to normal. Of 218 patients contacted, 44 (18.9%) had one or more first-order relatives with aneurysmal disease. Patients with non-MFS familial aggregation were similar to those with sporadic disease, but had a trend toward higher growth rates and mortality (odds ratio 1.594, $p = 0.5124$).

Conclusions – This study indicates that (1) Thoracic aneurysm is a lethal disease. (2) familial aggregation occurs in 19% of cases and may carry a worse prognosis (3) Aneurysm size has a profound impact on rupture, dissection and death. (4) For counseling purposes, the patient with an aneurysm exceeding 6 cm can expect a *yearly* rate of rupture or dissection of at least 6.4% and a death rate of 10.8%. (5) Elective surgical repair restores survival to near normal. This analysis strongly supports careful radiologic follow-up and elective, pre-emptive surgical intervention for the otherwise lethal condition of large thoracic aortic aneurysm.

ACKNOWLEDGEMENTS

I have worked on this project throughout my time in medical school, and it could not have been completed without the help and guidance of a substantial number of people. Obviously, I would like to thank my mentor, John Elefteriades, MD, Chief of the Section of Cardiothoracic Surgery. Invaluable guidance and assistance in all parts of this work was provided by Michael Coady, MD, MPH, who was a general surgery resident at Yale and has moved on to Stanford, CA to complete his training in thoracic surgery. In addition to first introducing me to the project, he provided day-to-day guidance in data collection, statistical analysis, and the writing of scientific articles.

Other people who I should thank for their help include: Lee J. Goldstein, MD, and John A. Rizzo, PhD. I would also like to thank Graeme L. Hammond, M.D. for his close reading of the manuscript and his assistance in preparing the final version. Rhaea Miller has provided vital assistance throughout my time working with the Section of Cardiothoracic Surgery. The personnel in the laboratory of Richard P. Lifton, M.D., Ph.D., especially Dr. Lifton and Carol Nelson-Williams, have provided guidance on the genetic aspects of the project and assistance in collecting DNA from patients. Personnel in the lab also performed the genetic analysis described below.

Finally, I would like to thank my parents and family for their support throughout my education at Yale.

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* Unless otherwise noted, images (CT, MRI, microscopic) are from the Section of Cardiothoracic Surgery and all diagrams are my own.

EQUATIONS

ABBREVIATIONS

The first appearance of an abbreviation occurs in parentheses following the full term. The following table is provided for reference purposes:

AAA	abdominal aortic aneurysm
CAD	coronary artery disease
CHF	congestive heart failure
CI	confidence interval
CMN	cystic medial necrosis
CT	computed tomography
CVA	cerebrovascular accident
EDS-IV	Ehlers-Danlos Syndrome Type IV
F-AAA	familial abdominal aortic aneurysm
IEL	internal elastic lamina
IMH	intramural hematoma
MFS	Marfan syndrome
MRI	magnetic resonance imaging
nMFS familial	non-Marfan syndrome-related familial
PAU	penetrating atherosclerotic ulcer
SMC	smooth muscle cell
TAA	thoracic aortic aneurysm
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram

INTRODUCTION

Anatomy and Physiology of the Thoracic Aorta

Structural Proteins of Arterial Walls

Collagen (especially types I and III) and elastin are the most important structural proteins in the aorta.[6,7] Collagens consist of three polypeptide chains which coil around each other to form three-stranded ropes or *collagen fibris*,[8,9] (Figure 1) which aggregate into "cable-like" *collagen fibers*.[5]

Secreted elastin molecules, on the other hand, form extensive cross-links to generate a network of fibers and sheets. The exact mechanism for their subsequent elasticity is not completely understood, but Figure 2 illustrates one hypothesis. The elastin core of the elastic fiber is covered in a sheath of microfibrils. The microfibrillar proteins appear to act as scaffolding for the subsequent deposition of elastin, and may also play a role in tissue homeostasis.[5,10,11]. They include fibrillin-1, whose encoding gene, *FBN1*, has been identified as the defective gene in Marfan syndrome (MFS).[12]

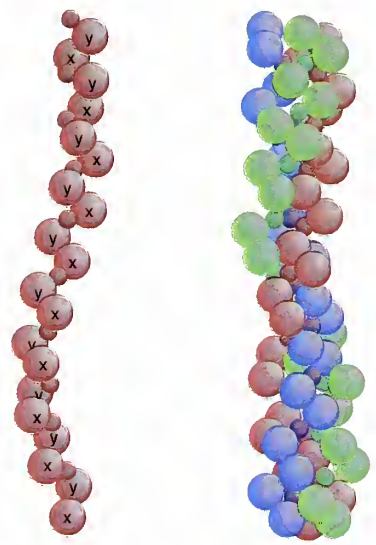


Figure 1. Diagrammatic representations of the molecular structure of collagen. (A) An individual α-chain composed of triplet repeats (Gly-X-Y), X and Y are usually (but not necessarily) proline and hydoxyproline. (B) A completed *collagen fibril*, a left-handed triple helix formed of three α-chains (in different colors). Only the glycine molecule is small enough to fit into the tight interior of the helix. Adapted from Alberts et al.[5]

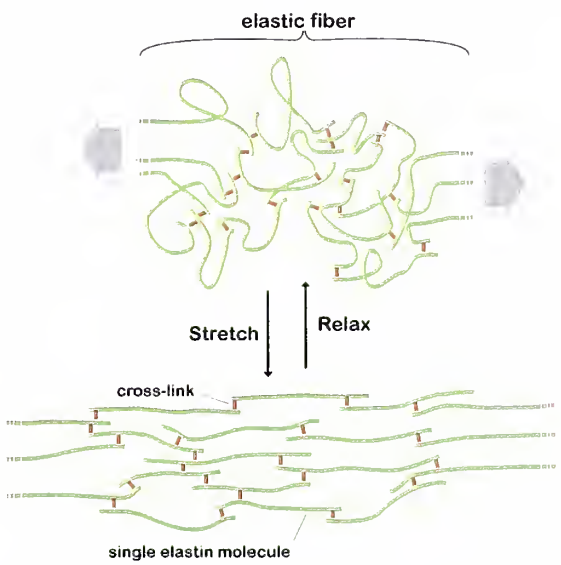


Figure 2. Hypothetical mechanism for the stretching of elastin molecules. The elastin molecules are shown in green joined together by the covalent cross-links (red) to form a network. When relaxed, they form a loose conglomeration of fibers (upper image), but when stretched, adopt a linear structure. Adapted from Alberts et al.[5]

The Structure of the Aorta

The aorta is an elastic artery with three defined layers: the intima, media and adventitia. (Figure 3) The intima consists of a single layer of endothelial cells supported by a layer of collagenous

tissue rich in elastin. This subendothelial tissue also contains fibroblasts and cells similar to smooth muscle cells (SMC) known as myointimal cells; these two cells types are both thought to contribute to the elaboration of extra-cellular components.

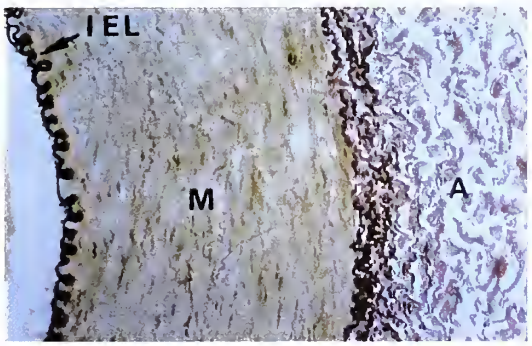


Figure 3. Elastic van Gieson stained section of the aorta (original magnification X 20) demonstrating the internal elastic lamina (IEL) delineating the intima from the media (M). The IEL (composed of elastin), has fenestrae that allow substances to diffuse to nourish cells deep within the aortic wall. The media comprises a mixture of smooth muscle cells and reticular and elastic fibers. The adventitia (A) and the outer part of the media have small blood vessels (vasa vasorum) and elastic and collagenous fibers.

The media is a broad, highly elastic layer composed of SMC within a matrix of elastin, collagen, and ground substance. The elastic fibers are arranged as circumferential lamallae. In the thoracic aorta there are approximately 45 to 56 lamallae, whereas the abdominal aorta contains only 28.[13-15] This may contribute to the higher prevalence of abdominal aortic aneurysm (AAA) compared to thoracic aortic aneurysm (TAA).[16]

The elastic lamellae play a central role in circulatory physiology: during systole, the diameter of the lamellae increase, then, during diastole, the elastic fibers recoil: maintaining forward blood flow during diastole.[17] Thus the elastic fibers function as shock absorbers for the kinetic energy of the fluid shockwave which strikes the aortic wall with each cardiac contraction.[18-20] The medial SMC control vascular resistance, perform a macrophage-like function, and secrete collagen into the extracellular matrix.[21] Deposition of collagen continues throughout life, but humans are unable to synthesize elastic fibers in adulthood—little elastin synthesis can be detected after infancy.[22]

The adventitial layer surrounds the media and maintains the maximal aortic diameter.[23] It is composed of loose connective tissue consisting of fibroblasts, elastic fibers and collagen. Unlike the media, the adventitial elastic fibers are not organized into lamellae. Collagen in the adventitia limits the maximal expansion of the vessel and thereby determines its bursting strength.[24,25] White et al. postulated that aneurysm formation may depend on a loss of elastin's ability to return the aorta to a normal diameter, whereas aneurysm growth may depend on the balance between degradation and deposition of collagen.[26]

Classification of Thoracic Aortic Disease

Thoracic aortic disease consists of a number of different disease processes, all of which may lead to rupture and catastrophic hemorrhage. These processes include aneurysms, dissections, penetrating atherosclerotic ulcers (PAU) and intramural hematomas (IMH). Although classified separately, these are all

inter-related pathologies, and distinctions between them have been made to facilitate descriptions of clinical presentation.

Aneurysms

TAA is simply a localized dilatation of the thoracic aorta (Figure 4). The natural history and optimal therapy of TAA varies based on the location and extent of the aneurysm. Therefore, they are classified largely on the basis of location (Table 1). Ascending aortic aneurysms comprise approximately 50% of TAA, aortic arch aneurysms 10%, and descending and thoracoabdominal the remaining 40%.[29]

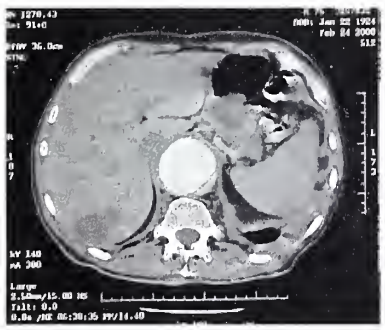


Figure 4. Computed tomography (CT) of patient with a large aortic aneurysm. (A concomitant dissection is visible in the left posterior portion of the aorta).

Table 1. Classification of thoracic aortic aneurysm*

Ascending aortic: annulus of aortic valve to origin of the innominate artery
Transverse aortic arch: origin of innominate artery to left subclavian artery
Descending aortic: lowest margin of left subclavian artery to aortic diaphragmatic hiatus
Thoracoabdominal (Crawford's classification)[27]
Type I: proximal descending aorta to upper abdominal aorta
Type II: proximal descending aorta to below the origin of the renal arteries
Type III: Distal half of descending aorta extending into the abdomen
Type IV: Most of/the entire abdominal aorta

* Adapted from a table by Pitt and Bonser.[28]

Dissection

Aortic dissection occurs when a tear in the aortic intima and inner layer of the media allows blood to course freely along a false lumen in the outer third of the media. The result is a dissection flap that traverses the aortic lumen, dividing the aorta into true and false lumina (Figure 5 and Figure 6). The misnomer *dissecting aortic aneurysm* has been used to describe this process. But in the acute setting, dilatation of the aorta does not occur. Rather, if the patient survives the acute event, gradual dilatation of the false lumen will result.[30] Therefore, we prefer the term *aortic dissection* to indicate the splitting of the media by

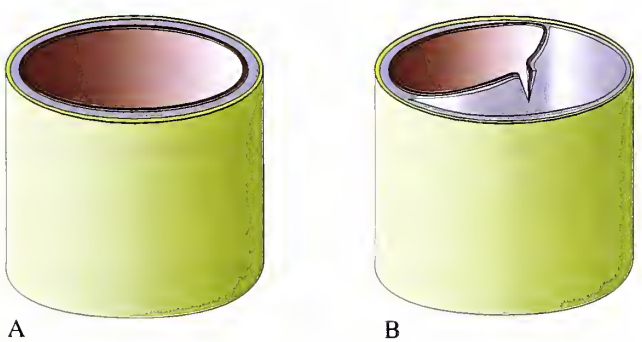


Figure 5. A. The three layered aortic wall, the intima (red) lines the lumen, the adventitia (yellow) forms the external layer, and the media (pink) sits between. B. A tear through the intima allows a column of blood to split the layers of the media. This leads to the intimal flap crossing the lumen, and dividing it into the true lumen (upper left) and false lumen (lower right)

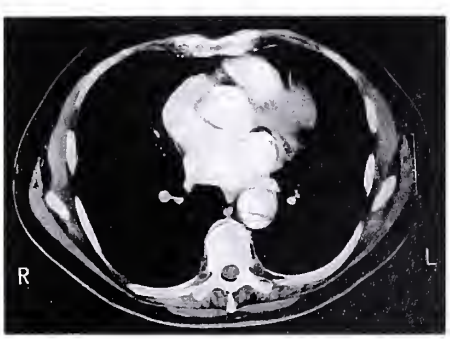


Figure 6. Computerized tomography (CT) of a patient with a classic type B aortic dissection. Note the intimal flap and presence of both true and false lumina.

circulating blood, and the term *aortic aneurysm* to indicate a dilatation of the aorta.

Clinically, dissections identified within 2 weeks of the onset of symptoms are classified as *acute*; subsequently they are termed *chronic*. There are two classification systems which indicate the extent of the dissection in the aorta. The simplified DeBakey classification consists of three types, while the simpler —and more commonly used—Stanford classification recognizes two. (Figure 7)

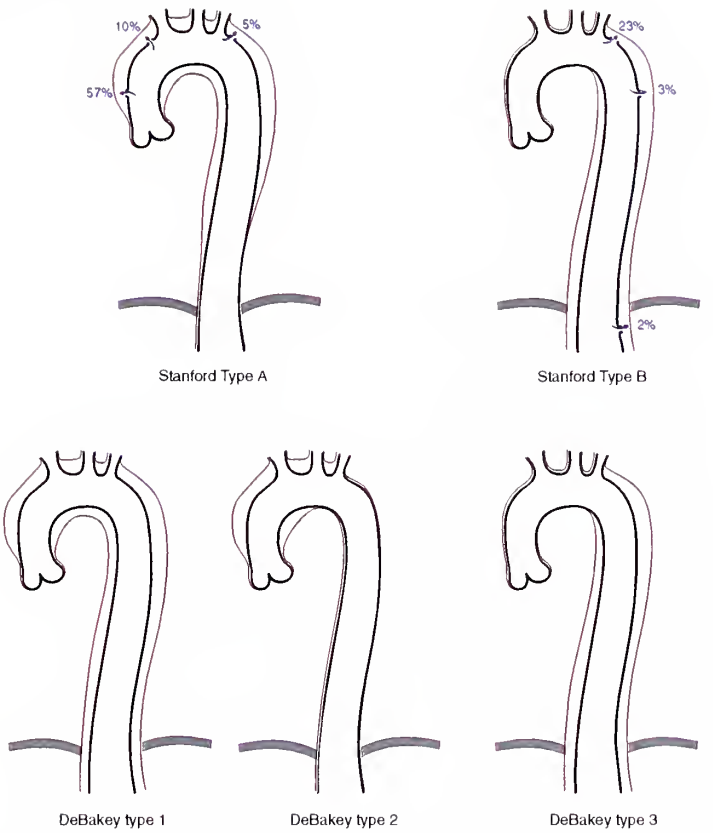


Figure 7. The classification of aortic dissection. The top row shows the Stanford classification, the bottom the simplified DeBakey classification. Stanford type A includes any dissection with involvement of the aorta proximal to the left subclavian artery, (this includes both DeBakey type I, which extend the length of the aorta, and DeBakey type II, which are confined to the proximal aorta). Stanford type B and DeBakey type III are equivalent categories comprising dissections limited to the aorta distal to the left subclavian artery. Included with the Stanford classification is the incidence of intimal tears in each region of the aorta based on autopsy studies. Adapted from a diagram by Ergin and Griepp.[30]

Penetrating Ulcer

In PAU, atheromatous plaques ulcerate and disrupt the internal elastic lamina. The ulcer then penetrates through the intima into the aortic media.[31-33](Figure 8). Although this may precipitate a localized intramedial dissection, in contrast to classical aortic dissection, this localized process is limited by areas of severe calcification associated with the locally advanced atherosclerotic disease.[34,35] The natural history and optimal

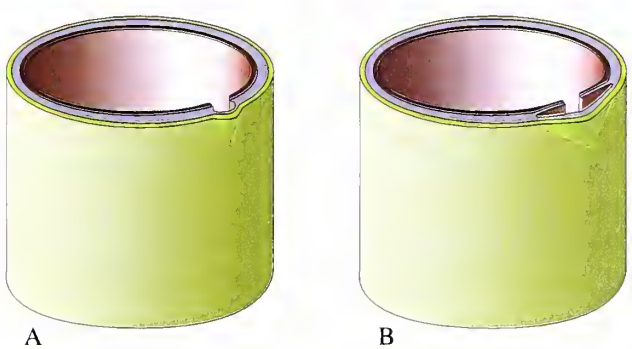


Figure 8. Diagram of PAU. A. An atherosclerotic plaque penetrates through the intima into the media. B. With time, an intramural hematoma may form, but it will be limited in extent by fibrotic and calcified tissue.

treatmcnt of PAU is only now beginning to be explored[36] as better imaging techniques (including MRI, Figurc 9) allow for non-operativc diagnosis.

Intramural Hematoma

Whereas classical aortic disscetions are thought to begin with a tear whieh allows blood to dissect rapidly along a plane in the outer third of an intrinsieally diseased media, IMH is thought to occur following rupturc of the vasa vasorum in the aortic wall.[34] This was first described in 1920 by Krukenberg as a "dissection without intimal tear." A diagrammatic representation of IMH can be seen in Figurc 10, and Figure 11 shows the appearance of IMH on transthoracic echocardiogram. Thc relationship between IMH, PAU, and classical disscetion has not been established. They may in faet lie on a continuum with dissection, and much work remains to clarify their pathophysiology, natu-

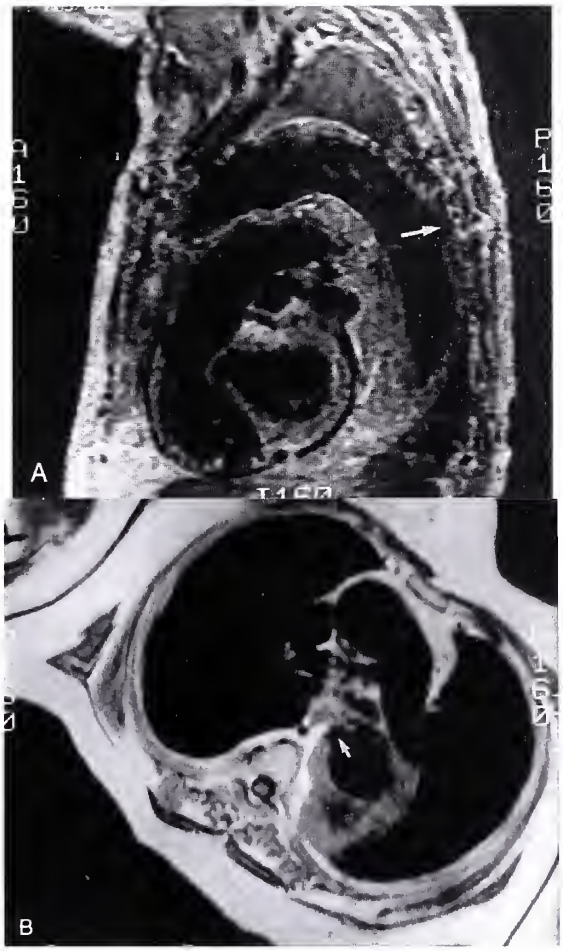


Figure 9. A. MR image (sagittal view) of a patient with a penetrating atherosclerotic ulcer. The penetrating atherosclerotic ulcer is diagnosed by visualization of a distinct ulcer crater in the absence of an intimal flap or false lumen. B. MR image (axial view) of a patient with a penetrating atherosclerotic ulcer

Figure 10. Diagram of IMH. Blood in the media (possibly secondary to a rupture of the vasa vasorum leads to a concentric hematoma without intimal tear.

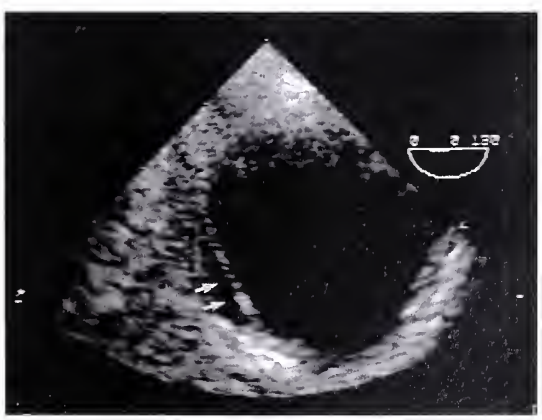


Figure 11. Transthoracic echocardiogram (TEE) of a patient with an intramural hematoma. Note the absence of intimal disruption or penetrating atherosclerotic ulcer.

ral history, and relationship to classical dissection.[34]

Familial Aggregation

Because this paper examines familial aggregation as a risk factor for complications in thoracic aortic disease, and no standardized terminology exists for the various types of aggregation described in the literature, it is important to define the use of some terms. Patients with the diagnosis of MFS, MFS-related syndromes, or other inherited systemic diseases of the connective tissue are referred to as *syndromic* patients. Those patients without such a history, but whose families do illustrate familial *aggregation* or *clustering*[*] of disease are termed *non*-syndromic familial aggregation or non-MFS-related familial aggregation (abbreviated throughout this paper as nMFS familial), because in thoracic aortic disease MFS is the predominant inherited syndrome involving a connective tissue defect. Those patients without any evidence of familial aggregation are termed *sporadic*.

Thoracic Aortic Aneurysms

History

Arterial aneurysms have been recognized since at least the 2nd century AD, when Galen (Figure 12) is credited with the first description. At the time, he recognized the catastrophic implications of aneurysm rupture, noting, "if an aneurism be wounded, the blood is spouted out with so much violence that it can scarcely be arrested."[37] The great anatomist Vesalius is credited with the first correct clinical diagnosis, in 1557.[37] Since then, speculation as to the cause or causes of aneurysm have continued unabated; unfortunately, almost 450 years later, they remain—to a large extent—unclear.

Figure 12. Early depiction of Galen. Courtesy Cushing/Whitney Medical Library at Yale University, Historical Library.

[*] Different studies will define familial aggregation differently, for example, they may include families with a history of sudden death, but without confirmed aortic disease, or they may include any family member or restrict it to first-degree family members. Our definition will be explained below in the Methods section. The definition used in other studies will be noted where appropriate.

Much of what we do know about thoracic aortic aneurysms (TAA) has been extrapolated from studies of abdominal aortic aneurysms (AAA); less scientific evidence is available on TAA. While the known risk factors described in the abdominal aorta are probably important in the thorax, differences between AAA and TAA necessitate a complete understanding of TAA independent of abdominal disease.

Etiology

Normal vessel wall biology involves a balance between the distending forces placed on the aorta by the flow of blood under pressure and the ability of the aorta (through the structural integrity of the aortic wall) to resist dilatation and elastically rebound when the pressure pulse of each cardiac systole has passed. Therefore, factors which either (1) decrease the ability of the aorta to resist distention or, (2) increase the distending forces would be expected to result in aneurysmal dilatation. In aortas weakened by processes such as genetic defects, atherosclerosis or inflammation,[38-40] normal aging,[41,42] prolonged hypertension,[35] or cigarette smoking,[43-47] factors increasing the load on the aorta may increase the risk of aneurysmal dilatation. These factors include hypertension,[48-52] the process of dilatation itself, and the location of the weakening along the course of the aorta. Thus, the etiology of aortic disease involves a complex interplay between a variety of factors contributing to weakness of the arterial wall and increased aortic wall pressure.[53]

Natural History

Epidemiology: Incidence and Prevalence

Because aortic aneurysms are a frequently silent disease, precise estimates of incidence and prevalence have been difficult to obtain. Changes in the incidence and prevalence due to changing disease patterns have further complicated the matter.[50,54,55] The most recent evidence suggests that the incidence of TAA is approximately 5.9 per 100,000 patient-years.[29] This is consistent with published autopsy rates of 437 per 100,000 in women and 489 per 100,000 in men.[56]

Traditionally the incidence has been thought to be higher in men than women;[57-59] however, this likely reflects the greater number of men seen in a referral population and possibly a higher rate of recognized syphilitic aneurysms in men, rather than a true difference in the occurrence of aneurysms in the two sexes.[29]

Growth Rates of Thoracic Aortic Aneurysms

One might expect that the calculation of aortic growth rates is a simple process. Simply take the last size measurement (S_l), subtract the first size measurement (S_f) and then divide by the time interval (T) between them:

Equation 1. Traditional growth rate formula

$$Gr = \frac{S_l - S_f}{T}$$

However, that method is highly subject to measurement error, especially when the time between studies is short. In order to account for measurement error, some groups truncate negative growth rates to zero; others exclude them from analysis. These divergent methods may explain some of the variation in their results. In studies of descending and thoraco-abdominal aortic aneurysms, growth rates have varied from 0.2 cm/yr[60] to 0.32 cm/yr[61]. The variation among growth rates when all sites are measured together is even higher: 0.10 cm/yr[62] to 0.42 cm/yr[63].

Despite the disparities in the exact rates, some consensus exists as to which factors are associated with higher relative rates. Chronic obstructive pulmonary disease (COPD) has been associated with faster growth rates in multiple studies.[51,60] The reason for this association is not clear. Although one might postulate that it reflects differences in smoking behavior,[61] or genetic differences in susceptibility to connective tissue disease leading to both increased risk of COPD and increased aneurysm expansion rates.[60] Alternatively, thoracic physiology and mechanics, which undergo significant changes in patients with COPD, may influence the expansion rate in these patients.

Initial aortic size greater than 5 cm has been associated with higher relative growth rates,[61,64] as has the presence of renal failure[64]. Interestingly, as noted above, a history of hypertension has not been found to be associated with either faster growth rates or an increased susceptibility to rupture.[61,65] The only exception to this, the study by Masuda et al.,[64] measured diastolic blood pressure rather than examining a *history* of hypertension. This supports the idea that adequate treatment of hypertension mitigates the potentially increased risk associated with a history of such disease; follow-up with serial blood pressure measurements is the only way to clarify the relationship. Finally, the presence of chronic dissection has

been identified as a predictor of higher growth rates in our previous work;[66] however, this has not been shown universally.[61]

Complications: Rupture and Dissection

The main complications associated with aneurysms are rupture and dissection, either of which may result in subsequent death. As noted above the silent nature of TAA has made epidemiological characterization of the disease difficult. In addition, the high mortality rates and the selection of patients for surgery lead to several sources of bias in studies of predictors of complications. Few groups have attempted systematic statistical analysis of risk factors for complications in TAA to enable the optimal selection of patients for surgical extirpation of their aneurysm.

Learning from Abdominal Aortic Aneurysms

Research into the complications of AAA has provided some insights into the behavior of aortic aneurysms. However, given the differences between the diseases, extrapolation of those results to TAA should be done cautiously, especially since surgery for the thoracic aorta carries significantly different risks than surgery of the abdominal aorta.

Traditionally, size has been the best predictor of AAA rupture.[67,68] Szilagyi showed that the natural (unoperated) history of AAAs > 6 cm had 5 year survival of only 6%, compared with survival of 48% in those with smaller aneurysms.[69] Hypertension and COPD are independently predictive of higher rupture rates.[68,70,71] Because the incidence of COPD is so intertwined with the prevalence of tobacco use, it has been difficult to separate the influence of the two factors.[72] But, in studies which have examined both tobacco use and COPD, COPD has consistently been the stronger predictor.[68,71]

The impact of higher expansion rates on rupture risk has similarly been difficult to separate from the related increase in absolute aortic diameter. Some studies have found both to be predictive, while others have not.[68] Dr. Cronenwett succinctly summarizes the difficulty in obtaining a full understanding of the natural history of aortic disease: "It would require ... a large series of patients with comparably sized AAAs but different expansion rates, *followed without intervention,* to determine whether expansion rate per se, or only final AAA size is an independent predictor of rupture. Unfortunately, these results are not available."[68]

Thoracic Aortic Aneurysms

Until reeently, most of our knowledge of the natural behavior of TAA (outside of what we have learned from analysis of AAA) was derived from a small number of observational studies, and some population studies. The first systematic investigation of TAA was done by Boyd in 1924.[73] While this study deseribed the consequences of rupture, it made no effort to examine risk factors for rupture. Population studies have revealed an incidence of ruptured TAA of approximately 5 per 100,000 population.[74] Cumulative risks for patients with TAA are substantial: Bickerstaff, et al.[29] reported a cumulative rupture rate of 51% for aneurysms without disseetion. Mortality following rupture was a devastating 94%. Subsequent work by Kampmeier suggested that arch aneurysms have a worse prognosis,[75] but no other attempt to delineate groups at increased risk was attempted. While many of these studies followed large populations, they did not attempt to use detailed statistical analyses to understand predictive factors for rupture and thereby establish criteria for surgical intervention.

More recently, Pressler and McNamara followed a group of 260 patients and looked at the timing of rupture.[57] Late rupture (more than three days following diagnosis or onset of symptoms) accounts for 91% of TAA rupture, and 68% of TAA ruptures occurred more than one month after diagnosis.[57] Rupture accounted for 44% of deaths in their series.[57] However, none of these studies addressed the important question of which patients were at highest risk for early rupture.

Previous work in our group showed that high initial aortic size was highly predictive of rupture and dissection.[66] In the ascending aorta, the odds of incurring rupture or dissection with aneurysms of 6.0 to 6.9 cm was 4.27 times that for aneurysms of 4.0 to 4.9 cm. In descending aortas, a similar phenomenon occurred for the 7.0 to 7.9 cm range (indicating their lower propensity for rupture). We identified dramatic hinge points in the

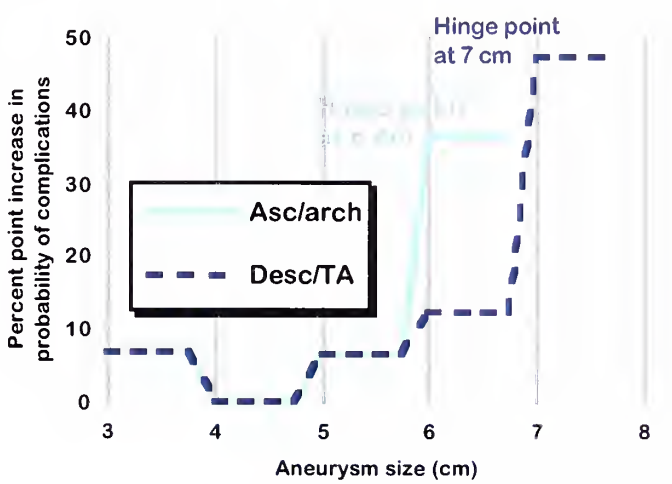


Figure 13. Estimated effect of aneurysm size on risk of complication (rupture or dissection) for ascending/arch and descending/thoraco-abdominal aneurysm location. Adapted from Coady et al.[66]

incidence of complications at these size ranges (Figure 13). However, separate analyses were not performed to identify other risk factors for either rupture or dissection. Furthermore, this data provided a static "snap-shot" of risk and failed to examine the risk of complications over time, so that a patient followed for one month who ruptured had the same impact on the analysis as a patient who ruptured following a five-year follow-up.

The group at Mount Sinai led by Dr. Griepp has published detailed analyses of the incidence of rupture in patients with descending or thoraco-abdominal aneurysms.[65] Using a logistic regression analysis they were able to provide a multivariable equation to enable the prediction of rupture within one-year based on specific patients characteristics (Equation 2) . However, their analysis was limited to aneurysms of the descending aorta, and their work did not analyze the incidence over time but instead looked at incidence within a set time period.

Equation 2. Griepp's formula for prediction of rupture within one year of size measurement

$$\text{Probability of rupture within 1 year} = 1 - e^{-\lambda(365)}$$

$$\text{where } \ln\lambda = -21.055 + 0.093(age) + 0.841(pain) + 18.22(COPD) + 0.643(\text{descending diameter, cm}) + 0.405(\text{ascending diameter, cm})$$

Intuitively, one would expect that hypertension would increase the risk of rupture and dissection, but that has not been demonstrated in any studies.[65,66] This may be due to the fact that patients with identified aneurysms tend to be treated medically with β-blockade, thereby minimizing the effect of a history of hypertension.[65] This possibility is supported by the fact that although hypertension predicts higher initial aortic sizes,[61] it does not predict higher growth rates in most series.[61,66] (A study by Masuda, et al[76] is one exception). Juvonen and associates identified chronic obstructive pulmonary disease (COPD) as the risk factor most predictive of rupture.[65] This is consistent with studies of AAA as described above.

Growth rates measurements have been highly variable (see *Growth Rates* on page 8). So it is not surprising that examination of growth rates as a risk factor for rupture has been inconsistent. Some studies have correlated higher growth rates with rupture,[61] but others have not been able to demonstrate a similar association.[60]

It is important to note that complications other than rupture or dissection may occur in these patients. These less catastrophic complications include aortic regurgitation which may occur in ascending

aneurysms,[77] hoarseness due to compression of the recurrent laryngeal nerve by aortic arch aneurysms, and dysphagia or dyspnea due to pressure on the esophagus or trachea.[73,75]

Mortality

Despite their rarity, aortic aneurysms (both AAA and TAA) are the 13th most common cause of death in the United States, and their prevalence appears to be increasing .[78,79] Overall 5-year survival in patients with TAA is only 56%.[80] In 1964, Joyce, et al. demonstrated that patients with aneurysms less than 6.0 cm in diameter had a 5-year survival rate of 61%, while those with aneurysms larger than 6.0 cm had a 5-year survival rate of only 38%.[59] Since then, little work has further delineated risk factors predictive of mortality in this population, and no further examination of the predictive power of aortic size on mortality has been done (probably because of the large sample sizes and detailed follow-up required). Mortality in these patients may be attributed to both dissection and rupture.[81-83]

Our previous work has shown that survival is significantly worse in patients with descending or thoraco-abdominal aortic aneurysms (39% at 5 years) than in aneurysms of the ascending aorta or aortic arch (77%, p =0.031).[66] In addition patients with a concomitant dissection have poor long-term prognosis independent of aneurysm location (46% at 5 years).[84] Symptomatic aneurysms also have poor prognosis when compared to asymptomatic disease (5 year survival 26.9% versus 58.3%).[84]

Treatment

Advances in the surgical treatment of thoracic aortic disease have led to significantly improved early and late results in recent years. However, surgical repair of the thoracic aorta still carries significant risk. Because aortic aneurysms are often asymptomatic until rupture or dissection, identifying those patients who are at risk for complications is central to optimal surgical therapy. Operate early on patients at low risk and the risk of complications may not justify the risk of surgery, but operate too late and rupture or dissection may occur, necessitating an emergent intervention with higher morbidity and mortality.

Some patients clearly require surgical intervention, including those with Type A dissections, those who are symptomatic, and those with rapidly enlarging aortas. However, a substantial portion of patients lack these indications for surgery but remain at risk for serious complications. Identifying those patients at highest risk remains a significant challenge.

Rupture occurs in 32% to 68% of patients not treated surgically, and 1-, 3- , and 5-year survival estimates for patients not undergoing surgical repair are approximately 65%, 36%, and 20% respectively.[29,57,85] In contrast, mortality from elective repair at experienced centers may be as low as 2%, although estimates range as high as 9%.[66,86] The high mortality rate (up to 21%)[66] from emergent procedures reinforces the need to identify patients at risk for rupture and operate sooner and electively.

For patients not considered good operative candidates, the options for medical therapy are limited. Currently, β-blockade is the mainstay of medical treatment. It is thought to exert beneficial effect through a reduction in pulse-pressure, mean pressure, and heart rate.[87] Although it has been shown to reduce the rate of aortic root dilatation and the development of aortic complications in patients with Marfan syndrome,[88] its use in non-MFS patients has recently come under significant scrutiny because of its effects on vascular wall compliance.

The Inheritance of Thoracic Aortic Disease

Marfan Syndrome and Inherited Connective Tissue Disease

Systemic disorders of connective tissue proteins, such as Marfan syndrome (MFS) and Ehlers-Danlos syndrome type IV (EDS-IV, resulting from defective synthesis of type III collagen), are known causes of dominantly inherited aortic disease. In the case of MFS, 99 different mutations in the fibrillin-1 gene (*FBN1*) have been identified in patients with MFS and Marfan-related syndromes.[89] Patients with MFS and related syndromes present with a variety of connective tissue symptoms, including skeletal manifestations,[90,91] ocular manifestations,[90] and cardiovascular manifestations (especially aortic root enlargement and Type A dissections).[90,92,93] To date, no genotype-phenotype correlation between the physical location of the genetic defect and the systemic manifestations of disease has been identified.[93]

In MFS, mutations in *FBN1* cause abnormalities in the synthesis and extracellular deposition of fibrillin. Patients with decreased amounts of deposited fibrillin-1 have more severe cardiac complications and undergo aortic surgery at an earlier age.[94] The pathogenesis of the mutant *FBN1* gene to be of the *dominant negative* type, where the phenotypic expression depends on the presence of the mutant fibrillin-1 rather than decreased concentration of wild-type protein.[95-97] Additionally, the mutant-type protein may

disturb aortic wall homeostasis in the adventitial layer.[10] Further work must be done to define the precise relationship between defective fibrillin synthesis and aortic dilatation.

Familial Inheritance in Patients without Systemic Connective Tissue Disease

Familial aggregation of AAA in patients without known hereditary connective tissue disorders, was noticed as early as 1977.[98] Subsequently, Tilson and colleagues described 50 families in which more than one individual had been diagnosed with AAA.[99-101] Further work demonstrated that 19% to 33% of patients with AAA had a family member who also had clinically diagnosed disease.[102,103]

Familial aggregation of aneurysms and dissections in patients with thoracic aortic disease was noted as early as 1967,[105] but further case studies were not added until after the increased interest in familial AAA (Figure 14).[104,106] Biddinger et al. went further and in a case-control study, examined the prevalence of thoracic aortic disease (TAA, aortic dissection, and sudden death) in probands with disease compared to the families of their healthy spouses.[107] The relative risk for thoracic aortic disease in the families of probands ranged from 1.8 to 10 for sisters and brothers respectively.

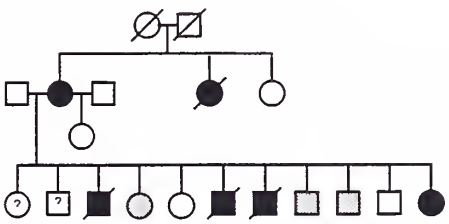


Figure 14. Pedigree of a family demonstrating aggregation of thoracic aortic disease identified by Nicod, et al.[104] *Circles* represent women and *squares* men. Affected members are represented by *black circles* or *squares*. Possibly affected members are represented by *grey circles* or *squares*. *Diagonal bars* indicate deceased members.

More recently, research groups have begun to examine these patients for molecular and genetic defects. Two separate groups have identified patients in whom disease can be attributed to mutations in *FBN1*, the same gene implicated in MFS.[108,109] Thus mutations in *FBN1* can cause a range of phenotypic disease from isolated aortic disease to systemic MFS: again no genotype-phenotype correlation has been postulated. Less clear was whether or not other genes might be responsible for non-MFS-related familial aggregation; especially since these two reports examined a total of only three probands.

Impact of Familial Aggregation on Natural History

The natural history of aneurysms due to MFS and MFS-related disorders reveals poor long-term prognosis in these patients. In 1972, mean age at death was 32 years, but by 1993 it was 41 years, and median expected survival in the living population had increased from 48 to 72 years.[110,111] However, patients with MFS are more likely to have aortic regurgitation in association with ascending aneurysms than pa-

tients without hypertension.[112] Also, despite improved survival, patients with MFS continue to require repeat aortic surgery at higher rates (25% versus 0% for non-MFS-related aneurysms).[112]

Because of small sample sizes, the natural history of aortic disease in patients with nMFS familial disease as compared to sporadic cases has not been adequately assessed. Biddinger et al. have performed the only analysis for thoracic aortic disease. They noted that there was no statistically significant difference in the incidence of hypertension in the probands versus their spouses/controls; however, the controls were unaffected individuals, not individuals with sporadic aortic disease.[107] More substantial work has been done examining the impact of family history on the course of disease in AAA.[101,113,114] Darling et al., found that patients with familial AAA and a female family member with an aneurysm had an increased risk of rupture (63% versus 37%, $p < 0.05$).[113] They used the term *black widow syndrome* to describe this increased risk. On the other hand, there was no difference between the patients with sporadic and familial AAA in terms of anatomic extent of disease, multiplicity of aneurysms, or associated occlusive disease.

STATEMENT OF PURPOSE

Thoracic aortic disease consists of four entities: aneurysm, dissection, PAU and IMH, all of which have high mortality and morbidity rates. On the other hand, surgical repair of the aorta, particularly regions with branch vessels to the brain or spinal cord is difficult, and it carries substantial risk of paraplegia, stroke and death. Therefore, in order to provide realistic prognostic information, guide the timing of surgery, and ultimately improve the outcome in these patients, detailed knowledge of the risk factors associated with poor outcomes—both with and without surgery—is required.

Heretofore, anecdotal evidence has been the mainstay of literature on diseases of the thoracic aorta. Thus, despite detailed knowledge of the histopathology associated with aneurysm and dissection, the etiologic events leading to aneurysmal dilatation in some people and dissection in others despite pathologic findings similar to healthy controls remain unknown. Instead, successive authors have postulated different theories which have been difficult to substantiate experimentally and unhelpful in establishing high-risk groups for complications (outside of the comparative risk associated with type A versus type B dissections).

Despite an extensive literature examining autopsy findings, describing techniques for surgical repair and reporting post-operative outcomes, little literature has focused on the question of which patients merit surgery and when. Small sample sizes and early selection for surgery have mitigated the statistical power of most series. Our group has published a frequently cited report[66] examining size as a risk factor for complications, but even this paper examining 230 patients lacked the statistical power to look at complication risk over time. Some risk factors, including the impact of a family history, were also ignored. The group led by Dr. Griepp at Mount Sinai have published the only prospective examination of rupture,[65] but it was limited to patients with descending and thoraco-abdominal aneurysm, and did not address those patients with ascending or arch aneurysms.

Given the apparent differences between the behavior of aortic disease in patients with MFS and in those without syndromic family history,[66] non-syndromic patients with a family history may also be at higher risk for rupture. Although family history of AAA has been extensively examined, little is known about non-syndromic family history in TAA, and its impact on outcome has not been assessed.

Therefore, much remains unclear about the etiology and optimal treatment of patients with thoracic aortic disease. Much must be learned if we are to provide effective timing of surgical therapy in these patients. In this paper, we examine nearly 700 patients with thoracic aortic disease seen at the Yale Center for Thoracic Aortic Disease between October 1985 and December 2000. This analysis aims to define specific *yearly* predicted rates of complications and death in this population and sub-populations composed of patients with a variety of risk factors in order to develop simple, scientifically-based prognostic indicators and surgical intervention criteria for patients with TAA and dissection.

METHODS

Patients and Data Collection

The patient population we analyzed consisted of all patients seen at the Yale Center for Thoracic Aortic Disease during the period October 1985 to December 2000. This population was initially collected in 1996 through retrospective analysis of hospital records as described in our previous publication.[66] Later, patients were added by the author to the retrospectively-collected population through the prospective addition of patients to a computerized database.

Initial Recruitment of Study Population

Patients were initially enrolled in the study by Dr. Michael Coady, Dr. John Rizzo and Dr. John Elefteriades after a computerized search had been conducted by Dr. Coady of all patients undergoing magnetic resonance imaging, computed tomographic scanning, or echocardiography of the thoracic aorta at Yale-New Haven Hospital from October 1985 to March 1996. The search was formatted to exclude patients who had normal aortic diameters (defined as patients with ascending or descending thoracic aortas of less than 3.5 cm in diameter) and no evidence of dissection, PAU or IMH. A search was also conducted to identify patients undergoing aortic operations, and autopsy records were examined for all patients who died of aortic disease during this time period. This initial recruitment phase identified 230 patients with thoracic aortic aneurysm.

Prospective Recruitment of Study Population

Subsequent to the collection of the initial population described above and the publication of some initial reports with this smaller sample size, the decision was made to begin the prospective addition of patients seen at the Yale Center for Thoracic Aortic Disease to the database. All patients diagnosed with aortic disease seen at the Yale Center between April 1996 and December 2000 were included. At the time of initial surgical consultation, datasheets were filled out by the consulting physician. Data collected at that time included a history of symptomatic or asymptomatic aortic disease, past medical history including detailed information about specific risk factors for vascular disease, past surgical history, and previous

imaging studies. In total, 438 patients with aneurysm (182 with concomitant dissection) and 72 patients with dissection alone were collected prospectively.

All Patients

In total 668 patients have been identified and compiled into the database (414 with TAA in the absence of dissection and 254 with dissection—of these, 26 patients with PAU were identified and 23 were identified with IMH).

A hospital chart review was then conducted on identified patients (chart review on the initial group of patients was performed primarily by the authors of the initial paper,[66] although additional data on all patients was collected subsequent to the author joining the project by a variety of researchers including the author, Dr. Michael Coady, Dr. Lee Goldstein, and others). Specifically, the author (Mr. Davies) performed data collection on 314 patients. Data recovered from hospital records and computer files were cross-checked by Dr. Rizzo with hospital discharge abstract data monitored by the Connecticut Hospital Association and Connecticut State Mortality Records. Risk factors for vascular disease were assessed (tobacco use, diabetes mellitus, hypertension, lipid profile, cardiac disease and renal dysfunction), as were a variety of other risk factors for morbidity and mortality (pulmonary disease, cancer). Where possible, risk factors were graded as mild, moderate, or severe according to the suggested standards for reports pertaining to lower extremity ischemia as formulated by the Ad Hoc Committee on Reporting Standards of the Society of Vascular Surgery and the International Society of Cardiovascular Surgery of North America.[115] Where severity could not be established, we conservatively graded the disease as mild.

In defining the type and extent of aneurysmal disease at presentation, presentation with aortic disease was considered to occur at the *first* presentation to *any* medical professional with the symptoms of *thoracic* aortic disease (or in the case of asymptomatic disease, the presentation at which the disease was discovered). When a patient's first presentation occurred outside of Yale-New Haven Hospital, data was recovered from other health care providers where possible. Otherwise, the unavailable information was coded as such in the database, and those patients were excluded from analyses requiring unavailable information.

Periodic re-review of computerized hospital records—particularly imaging studies—was also performed. This re-review (performed by the author) occurred on a bimonthly basis for a selected group of

active charts so that each chart was examined at least once per year. A computerized database was maintained initially in Microsoft Excel as part of ongoing studies at the Yale Center for Thoracic Aortic Disease, a major referral center for New England. Subsequently, this database was converted to a relational database designed by the author in Microsoft Access2000 (©2000, Microsoft, Inc., Redmond, WA) and continues to be maintained by the author at the Yale Center.

The database includes 3115 radiographic studies (985 CT scans, 418 MRI scans, 139 TEE studies, 1344 TTE studies, and 229 angiographic studies) and 20 intra-operative size measurements performed on patients with thoracic aortic disease, all compiled by the author. Dinsmore, et al.[116] have reported a high-degree of correlation between CT, MRI and echocardiography, so measurements from these modalities were combined (they continue to be maintained separately in the database so that with larger sample sizes, we may be able to examine the differences between them). Size measurements during aortic angiography are less accurate, and often result in significant magnification of the aneurysmal aortic diameter; therefore, although angiographic data was used to identify the presence or absence and type of aortic disease in these patients, size measurements made at angiography were excluded from analysis. The thoracic aorta was considered aneurysmal if it attained a maximal diameter of 3.5 cm or greater.

During the 15-year period, a total of 397 patients out of the 668 underwent surgical treatment of the thoracic aorta. There were 259 elective procedures, and 138 emergency procedures. Operations included 283 procedures on the ascending aorta or aortic arch (93 emergent and 190 elective), and 114 procedures on the descending or thoracoabdominal aorta (45 emergent and 69 elective). Operations on the ascending aorta were performed with the use of cardiopulmonary bypass with myocardial preservation by systemic hypothermia, topical hypothermia with iced saline solution, and cold crystalloid or blood cardioplegia. Deep hypothermia and circulatory arrest were used uniformly for arch replacements and liberally for the distal anastomosis of ascending aortic replacements. Since 1987, operations on the descending aorta have been performed routinely with the use of left atrial-femoral artery bypass with a centrifugal pump without an oxygenator, except when the patient's condition was not stable enough for cannulation; in this case, the operation was done by the "clamp-and-sew" technique.

Recent data from our group has identified stroke as a common complication in operations on both the ascending and descending operation.[117] The majority of strokes resulted from embolic sources; there-

fore, since 1999, additional protective techniques have been employed, including: care in the mobilization of the descending aorta, debridement of atherosclerotic aortic cuffs, TEE-guided location of cannulation and perfusion sites, CO_2 flooding of the operative field, placement of the proximal clamp prior to the institution of femoral perfusion in descending operations, and avoidance of cannulating a fibrillating left atrium.

Growth Rates

Of the 668 patients with thoracic aortic disease, there was a core group of 332 patients who were observed with serial imaging studies. Serial imaging consisted of 2 or more size measurements separated in time. This group of 332 patients consisted of 190 individuals with aneurysms of the ascending aorta, 24 of the aortic arch, 40 of the descending aorta, and 78 of the thoraco-abdominal aorta. Dissection was present in 129 patients and absent in 203. The period of serial radiological follow-up prior to surgery ranged from 0 to 171.7 months, with a median of 19.1 months. These patients were followed longitudinally and this sample was used to estimate aneurysm growth rates and to identify risk factors affecting aneurysm growth in a multivariable model.

Analysis of Complication Rates in Thoracic Aortic Aneurysms

Of the 668 patients in the database, 304 patients met the inclusion criteria for the analysis of complication rates. Inclusion criteria were as follows: aortic size ≥ 3.5 cm and age > 6 years at presentation, absence of congenital aortic malformations (for example, aortic coarctation), absence of chronic dissection at presentation, and at least one size measurement prior to operative repair.

Table 2. Distribution of 92 end-points.*

Events	*# patients*
dissection, rupture & death	2
dissection, rupture (no death)	2
dissection, death (no rupture)	5
rupture, death (no dissection)	4
rupture alone	5
dissection alone	15
death alone	44

* Some patients satisfied multiple end-points, leading to the total of 92 specific events

These 304 patients form the basis for the analysis of complication rates. Patient characteristics are shown in Table 5 on page 29. There were 178 males and 126 females. Mean age in this population was 59.8 years and ranged from 8.8 to 93.7. Available radiologic follow-up in these patients ranged from 0 to 262 months with a median of 31.6 months. There were 28 patients with Marfan syndrome and no patients identified with other inherited systemic connective tissue diseases. Among the 92 hard end-points (rupture, dissection or death) realized in serial follow-up of these patients, were 55 deaths, 13 documented ruptures and 24 new, acute aortic dissections (Table 2). We examined the mortality records of all patients. Ten mortalities could be attributed definitively (based on death certificates and autopsy records) to causes

other than aortic aneurysms (for example, metastatic lung cancer or pancreatic cancer). It is likely that some of the remaining mortality represented aneurysm rupture and that the true incidence of rupture in this population was even higher than in our tabulation.

In contrast to most studies of the natural history thoracic aortic aneurysms, we did not limit our analysis to patients excluded from surgery. Instead, we followed patients from diagnosis until they were lost to follow-up or were treated surgically. Although this will lower the cumulative rates of complications by including patients who were followed for only a single month, it provides a more accurate picture of risk over time, and a more accurate picture of the entire population of patients with thoracic aortic disease.

Statistical Analysis

Growth Rate Analysis

Traditional methods for the estimation of aneurysm growth rates have been prone to measurement error.[62,118,119] Consequently we have used the IV approach to growth rate estimation as described by Rizzo, et al.[118,119] Specifically, we used SAS 6.12 (©1996, SAS Institute, Inc., Cary, NC) to calculate growth rate estimates and 95% confidence intervals (CI) for patients and sub-groups with varying risk factors. The estimates were obtained by means of multivariable regression analysis in which aneurysm growth followed an exponential path. In particular, the natural logarithm of the last measured size and the first measure size was related to the time interval between the two tests and interactions between this time variable and risk factors.

The multivariable models for aneurysm growth rates are estimated as follows:

Equation 3

$$S_l = S_f \cdot e^{(\alpha \cdot Time + \beta \cdot Time \cdot RISK' + \theta \cdot Time \cdot RISK'')}$$

where S_l = last size measurement, S_f = first size measurement, *Time* = the duration between the last and first size measurement and *RISK'* and *RISK''* are coefficients indicating the presence or absence of particular risk factors being analyzed (chronic dissection, hypertension, size, etc...). Taking the natural logarithm of each side of Equation 3 yields:

Equation 4

$$\ln S_l = \ln S_f + \alpha \cdot Time + \beta \cdot Time \cdot RISK' + \theta \cdot Time \cdot RISK''$$

Subtracting $\ln S_f$ from both sides of Equation 4 we get:

Equation 5

$$\ln \frac{S_l}{S_f} = \alpha \cdot Time + \beta \cdot Time \cdot RISK' + \theta \cdot Time \cdot RISK''$$

Equation 5 is the equation we estimate for the full sample of 332 patients where *RISK'* = 1 if a dissection is present and 0 if absent. *RISK''* was eliminated from the overall estimation but was added for the separate regressions described below. This equation is estimated without an intercept term because when *Time* = 0, we must have $S_l = S_f$. The estimated regression was:

Equation 6

$$\ln \frac{S_l}{S_f} = 0.017791 \cdot Time + 0.011298 \cdot Time \cdot RISK'(DISSECTION)$$

Separate regressions were estimated for ascending versus descending aneurysms, as well as for the interaction where *RISK''* was included as a measure of initial aortic size.

Growth rates were calculated using the above terms, starting with:

Equation 7

$$Growth = S_l - S_f$$

Combining Equation 3 and Equation 7 yields:

Equation 8

$$Growth = S_f \cdot e^{(\alpha \cdot Time + \beta \cdot Time \cdot RISK' + \theta \cdot Time \cdot RISK'')} - S_f$$

Or:

Equation 9

$$Growth = S_f (e^{(\alpha \cdot Time + \beta \cdot Time \cdot RISK' + \theta \cdot Time \cdot RISK'')} - 1)$$

Confidence intervals were obtained using the upper and lower estimates of each parameter in the regression model. Dr. Rizzo provided consultation in the methods of IV estimation, but all statistical analysis was performed by the author.

Analysis of Complication Rates in Thoracic Aortic Aneurysms

Statistical methods were used to identify and estimate risk factors for the following outcomes: cumulative incidence of major complications, survival free from major complications, and overall long-term survival. Results are not shown for the analyses with stratified levels because they did not provide

any additional information. All analyses were performed by the author with consultative assistance from Dr. Rizzo.

The methods of statistical analysis included: χ^2 test for comparisons of dichotomous risk factors (history of coronary artery disease, congestive heart failure, abdominal aortic aneurysm, etc...) with negative outcomes (rupture, dissection, death), Mantel-Haenszel χ^2 test for comparisons taking into consideration ranked scores of disease severity (cardiac disease, pulmonary disease, increasing aortic size, etc...), the Wilcoxon test for one-way analysis of variance between means for comparisons between two groups (for multiple groups, Bonferonni's test was used). The criteria for statistical significance was $p < 0.05$ for all univariate tests.

Logistic regression analysis of the cumulative incidence was used to generate multivariable models predicting increased incidence of complications. Life table estimates (Kaplan-Meier) were calculated using the LIFETEST procedure of SAS 6.12 for PowerPC (©1996, SAS Institute, Cary, NC) with the log-rank test for difference between strata. The Cox regression model (using the PHREG procedure, SAS 6.12), in a forward stepwise manner, was used to identify the most predictive variables in the analysis of survival and complication rates over time.

Multivariable regression analyses (both logistic regression and Cox proportional hazards regression) was performed under two models in order to assess: (1) the most conservative estimate of multivariate predictors of rupture or dissection and (2) all factors which might (if the sample size were large enough to demonstrate statistical significance) influence the incidence of rupture or dissection. Forward selection was used for both, with the threshold for entry $p < 0.05$ for the conservative model and $p < 0.70$ for the other model. Both models are reported, along with statistics describing their accuracy.

Determination of Family History and Genetic Analysis

Patient Collection and Data Analysis

Of the 668 patients described above, 60 patients had a history of Marfan syndrome, 608 patients had no history of MFS, MFS-related disease, or any other inherited systemic connective tissue disorder. Five patients were excluded from further analysis because their aneurysm was found to be due to congenital disease of the aorta (eg. post-stenotic dilatation after aortic coarcatation). Of the 603 patients remaining,

534 had confirmed TAA (171 with concomitant dissection) and 69 had aortic dissection in the absence of TAA. Four interviewers attempted to contact 450 patients; 117 patients were lost to follow-up. Complete medical and family histories on 278 patients (60 with MFS, 218 without—142 males and 76 females) were obtained. All telephone screening was carried out consistently by the four trained interviewers (including the author, who contacted 79 of the 278 patients). Responses were recorded on standardized forms. Pedigree analysis was performed on families in which more than one member had an aortic aneurysm.

We defined nMFS familial thoracic aortic disease as either aneurysm or dissection occurring in patients with 1 or more first-degree relatives with aneurysm or dissection and no history of MFS or other inherited systemic connective tissue defect. For the purposes of this study, patients with family members known to have AAA or cerebral aneurysms were included in the family history group. This was done, in part, because some families with multiple individuals affected by TAA also had family members with AAA or cerebral aneurysms, suggesting a possible connection between these forms of aneurysmal disease. We defined sporadic cases as those occurring in patients with no family history of aortic disease and no history of Marfan syndrome or any other inherited systemic connective tissue defect. Patients with a family history of sudden death (although included in other studies of familial risk of aneurysmal disease)[107] were <u>not</u> considered to have a family history and were included with the sporadic cases. Patients with a diagnosis of Marfan syndrome met the revised criteria for the diagnosis as outlined by DePaepe, et al.[90]

Statistical methods were used to compare the 3 categories of aortic disease: nMFS familial, sporadic, and MFS-associated. Separate analysis was carried out for the 3 categories of patients, additionally those patients in whom a positive or negative family history was obtained were compared to the 344 patients for whom family history was not known, in order to assess the impact of the patient collection method. All statistical analysis was performed by the author.

Serial follow-up was available for 41 patients in the familial non-syndromic group, 174 patients in the sporadic group, and 47 patients in the MFS group. Mean follow-up time for the 3 categories was 49.6 months (median 33.3, range 0.0 to 317.7 months) for patients with familial non-syndromic TAA, 43.9 months (median 31.8, range 0.0 to 224.2 months) for sporadic TAA, and 101.9 months (median 91.3, range 0.0 to 415.5 months) for patients with MFS. As described above, subsets of patients were used for the various analyses. When growth rates were calculated, the exclusion criteria detailed under *Growth Rates*

on page 21 were used. Sample sizes were not sufficient to perform separate complication rate analyses for each group: sporadic, familial-nMFS, and MFS-related, nor were they sufficient to use the presence of a family history as a risk factor for the analysis of complication rates.

Genetic Analysis

Patients identified as having a non-syndromic family history were contacted and blood samples were collected after appropriate informed consent was signed. Blood samples were provided to the laboratory of Richard P. Lifton, MD, PhD, in the Department of Genetics and the Howard Hughes Medical Institute. Personnel in the laboratory performed the following work:

Genomic DNA was obtained from whole blood samples by standard procedures.[120] Genotyping of a total of 6 polymorphic loci spanning a region surrounding *FBN1* was performed by PCR with a customized set of primers in a single collected family. PCR products were labeled by incorporation of fluorescent end-labeling of oligonucleotide primers with analysis performed on an ABI 377 instrument equipped with GENESCAN 2.1 and GENOTYPER 1.1.1 software (Applied Biosystems). Genotypes were scored by a single investigator blinded to infection status. Marker order was obtained from databases at the Whitehead Institute for Biomedical Research/MIT Center for Genome Research, The Cooperative Human Linkage Center, and The Genome Database, and analysis of linkage was performed by use of the GENEHUNTER program[121] on a SUN SparcStation.

RESULTS

Characteristics of the Entire Study Population

Demographic characteristics and the incidence of risk factors for the entire study population are given in Table 3. The male:female ratio was 1.6:1. Other comorbidities—especially vascular comorbidities—abounded. In particular, 347 patients (63.6%) had a history of hypertension. There were 30 patients (12.0%) with a history of AAA (defined as a previously diagnosed, but not necessarily repaired abdominal aortic aneurysm).

Table 3. Demographic characteristics of 668 patients with thoracic aortic disease

Variable	*N*	*%*	*Mean*	*Median*	*Range*
Sex (male)	414	62.0 %			
Age at presentation (yrs)	604		60.4	67.1	7 days to 95.2 years
Aortic diameter at presentation (cm)	488		5.0	4.7	3.5 to 11.0
Hypertension (n = 546)	347	63.6 %			
Cardiac Disease(n = 496)	196	39.5 %			
Pulmonary Disease (n = 512)	98	19.1 %			
Renal Disease (n = 496)	56	11.3 %			
Carotid Disease (n = 472)	61	12.9 %			
Tobacco Use(n = 492)	193	39.2 %			
CAD	159	23.7 %			
CHF	63	9.4 %			
CVA/TIA	53	7.9 %			
AAA	80	12.0 %			
Marfan syndrome	60	9.0 %			

Aneurysm Growth Rates

Aneurysm growth rates were calculated as described earlier. Table 4 shows the average growth rate according to initial aneurysm size and risk factor status. Aneurysms in the descending or thoracoabdominal region had substantially higher growth rates (0.19 cm/yr) than those in the ascending aorta or aortic arch (0.07 cm/yr). This information is presented graphically in Figure 15. A similar difference in growth rates was found with dissected (0.14 cm/yr) versus non-dissected (0.09 cm/yr) aortas. Patients with Marfan syndrome and those with a history of

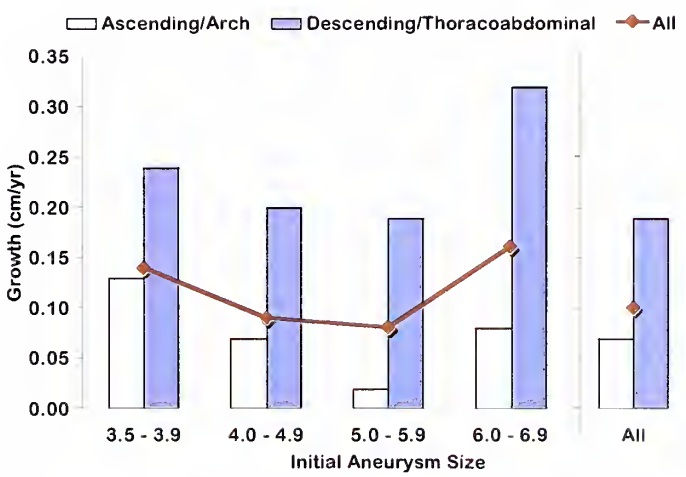


Figure 15. Multivariable estimates of aneurysm growth rates by initial aortic size and location. The blue bar indicates the growth rates of descending and thoraco-abdominal aneurysms, the white bar rates for ascending/arch aneurysms. The red line is the average for aneurysms independent of location.

Table 4. Multivariate estimates of aneurysm growth rates.*

	Annual growth rate (cm/yr) according to initial aneurysm size†				
Patient Category	*< 4.0*	*4.0 – 4.9*	*5.0 – 5.9*	*> 6.0*	*All*
All (n = 332)	0.14 cm/yr	0.09 cm/yr	0.08 cm/yr	0.16 cm/yr	0.10 cm/yr
	(0.04 to 0.23)	(0.02 to 0.16)	(-0.01 to 0.16)	(0.00 to 0.32)	(0.08 to 0.13)
Location of Aneurysm					
Ascending or arch (n = 214)	0.13 cm/yr	0.07 cm/yr	0.02 cm/yr	0.08 cm/yr	0.07 cm/yr
	(-0.02 to 0.28)	(-0.05 to 0.20)	(-0.06 to 0.18)	(-0.13 to 0.37)	(-0.03 to 0.16)
Descending or thoraco-abdominal (n = 118)	0.24 cm/yr	0.20 cm/yr	0.19 cm/yr	0.32 cm/yr	0.19 cm/yr
	(0.10 to 0.37)	(0.08 to 0.32)	(0.05 to 0.33)	(0.09 to 0.55)	(0.11 to 0.26)
Comorbidities					
Hypertension (n = 186)	0.14 cm/yr	0.09 cm/yr	0.07 cm/yr	0.15 cm/yr	0.09 cm/yr
	(0.0 to 0.30)	(-0.04 to 0.21)	(-0.08 to 0.22)	(-0.08 to 0.40)	(0.01 to 0.17)
Pulmonary Disease (n = 47)	0.20 cm/yr	0.13 cm/yr	0.14 cm/yr	0.18 cm/yr	0.13 cm/yr
	(0.04 to 0.36)	(0.0 to 0.27)	(-0.03 to 0.31)	(-0.06 to 0.43)	(0.04 to 0.21)
History of Coronary Artery Disease (n = 95)	0.13 cm/yr	0.08 cm/yr	0.07 cm/yr	0.11 cm/yr	0.07 cm/yr
	(-0.01 to 0.27)	(-0.04 to 0.20)	(-0.08 to 0.22)	(-0.11 to 0.35)	(0.00 to 0.15)
Marfan Syndrome (n = 42)	0.14 cm/yr	0.11 cm/yr	0.10 cm/yr	0.20 cm/yr	0.13 cm/yr
	(0.01 to 0.29)	(-0.01 to 0.24)	(-0.04 to 0.25)	(-0.02 to 0.44)	(0.05 to 0.20)
AAA (n = 46)	0.09 cm/yr	0.04 cm/yr	0.01 cm/yr	0.07 cm/yr	0.04 cm/yr
	(-0.06 to 0.24)	(-0.09 to 0.18)	(-0.15 to 0.17)	(-0.16 to 0.32)	(-0.05 to 0.13)
Chronic Dissection					
Present (n = 119)	0.17 cm/yr	0.12 cm/yr	0.12 cm/yr	0.21 cm/yr	0.13 cm/yr
	(0.04 to 0.31)	(0.01 to 0.21)	(-0.03 to 0.26)	(-0.02 to 0.44)	(0.05 to 0.20)
Absent (n = 93)	0.13 cm/yr	0.07 cm/yr	0.06 cm/yr	0.14 cm/yr	0.08 cm/yr
	(0.03 to 0.23)	(0.00 to 0.11)	(-0.03 to 0.15)	(-0.03 to 0.30)	(0.06 to 0.11)

† Values indicate aortic growth rate based on regression analysis for patients with serial imaging studies. The regression model used to calculate each value includes the variables indicated in the row and column headings, as well as the time between studies. 95% confidence intervals are given in parentheses.

pulmonary disease also had higher growth rates. Growth rate differences between ascending and descending and dissected and non-dissected aneurysms persisted when we controlled for initial aortic size. Although the differences in growth rates were strong trends, the sample sizes were not large enough to assess statistical significance.

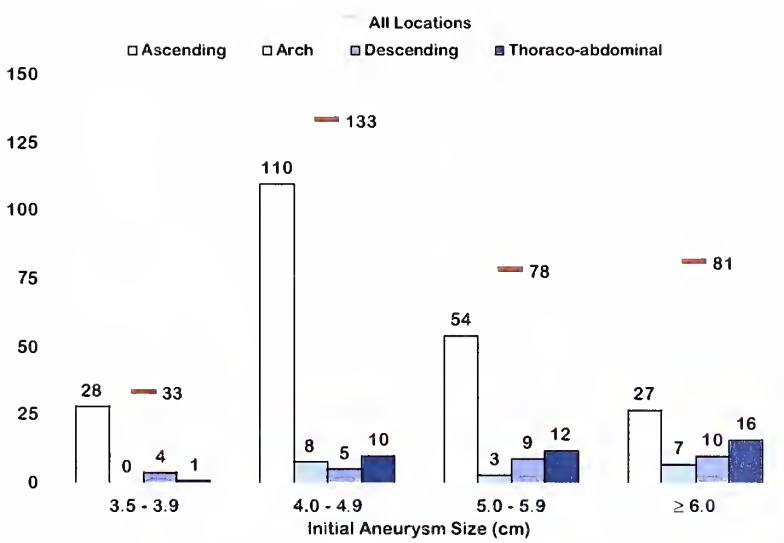


Figure 16. Histogram of initial aortic size and aneurysm location.

Analysis of complications

Demographic and Clinical Characteristics of the Study Population

Demographic characteristics and the prevalence of risk factors for the 304 patients included in the analysis of complication rates are given in Table 5. In this population, 142 patients (39.1%) had a history of hypertension. Again, the prevalence of vascular comorbidities was particularly high. The distribution of aneurysms by initial size is shown in Figure 17 and Figure 16. Aneurysms of the ascending aorta were substantially more common than the others. The mean initial aortic size for each aneurysm location is shown in Table 6. Aneurysms of the ascending aorta and aortic arch had smaller initial sizes than those in the descending or thoracoabdominal region ($p = 0.0001$)

Table 5. Demographic information on 304 patients included in analysis of complications.*

Variable	*Mean*	*Range*
Initial aortic size (cm)	5.0	3.5 to 11.0
Radiologic follow-up (mths)	43.1	0.0 to 262.6
Age at presentation (yrs)	59.8	8.8 to 93.7
Variable	**N**	**%**
Sex (male)	178	58.9 %
Marfan syndrome	28	9.2 %
Aneurysm Size		
3.5 to 3.9 cm	33	10.9 %
4.0 to 4.9 cm	133	43.8 %
5.0 to 5.9 cm	78	25.7 %
≥ 6.0 cm	60	19.7 %
Aneurysm Location		
Ascending	219	72.0 %
Arch	18	5.9 %
Descending	28	9.2 %
Thoracoabdominal	39	12.8 %
Hypertension (n = 225)	142	59.1 %
Cardiac Disease (n = 219)	96	43.8 %
Tobacco Use (n= 220)	81	36.8 %
Pulmonary Disease (n = 225)	47	20.9 %
Carotid Disease (n = 209)	23	11.0 %
Renal Disease (n = 220)	30	13.6 %
CAD (n = 304)	82	24.6 %
CHF (n = 304)	34	10.2 %
CVA (n =304)	25	7.5 %
AAA (n = 304)	31	9.3 %

* percentages may not sum to 100 due to rounding.
AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CHF = congestive heart failure, CVA = cerebrovascular accident

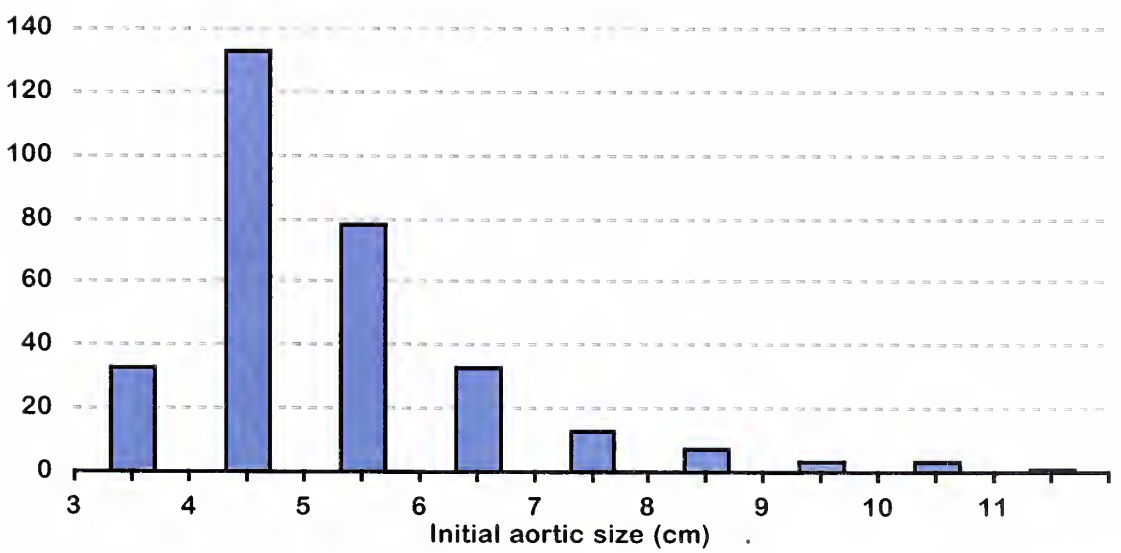


Figure 17. Histogram of initial aortic size in 304 patients.

Table 6. Initial aortic size (cm) in 304 patients with thoracic aortic aneurysms.

	Non Marfan syndrome (n = 276)		*Marfan syndrome (n = 28)**	
	Mean	*Range*	*Mean*	*Range*
Ascending (n = 219)	4.8†	3.5 to 10.5	4.5	3.5 to 7.0
Arch (n =18)	5.9†	4.0 to 11.0	N/A	N/A
Descending (n = 28)	5.3	3.5 to 7.5	N/A	
Thoraco-Abdominal (n = 39)	5.7†	3.8 to 9.8	8.3	8.3 to 8.3
Ascending/arch (n = 237)	4.9‡	3.5 to 11.0	4.5	3.5 to 7.0
Descending/thoracoabdominal (n = 67)	5.5‡	3.5 to 9.8	8.3	8.3 to 8.3
ALL PATIENTS (n = 304)	5.1‡*		4.6*	

* Differences between patients with Marfan syndrome and those without were not statistically significant at $p \leq 0.05$
† $p < 0.005$ for the comparison of initial aortic size in ascending versus arch or thoracoabdominal, Bonferroni's test
‡ $p = 0.0001$, Wilcoxon test.

Complication Rates

Cumulative Incidence

Figure 18 illustrates the cumulative incidence of rupture and dissection during follow-up stratified by initial aortic size. The incidence increases with increasing aortic size ($p = 0.0003$). Patients with the largest aneurysms (≥ 6.0 cm) had complication rates more than seven times as high as those with the smallest aneurysms (< 4.0 cm) (21.7% versus 3%). Similar increases were observed for rupture alone ($p = 0.0006$) and acute dissection alone (p = NS), as shown in Figure 19 and Figure 20.

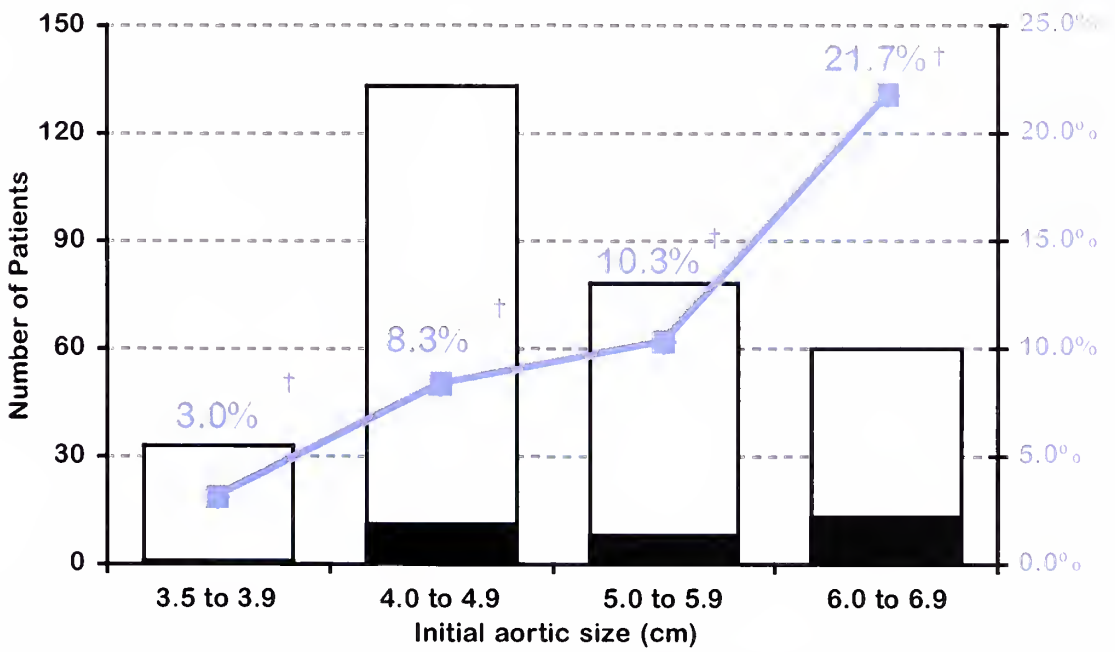


Figure 18. Incidence of acute dissection or rupture as a function of initial aneurysm size. The entire column indicates the total number of patients with thoracic aortic aneurysms in each size range. The *black area* indicates the number of patients who incurred an acute dissection or rupture of the aneurysm. The line graph and associated percentages indicates the percentage of patients in each category who incurred an acute dissection or rupture of the aneurysm and corresponds to the axis on the right.
† Statistically significant increase in complication rates with increasing initial aortic size, $p = 0.003$. (Mantel-Haenszel χ^2 test)

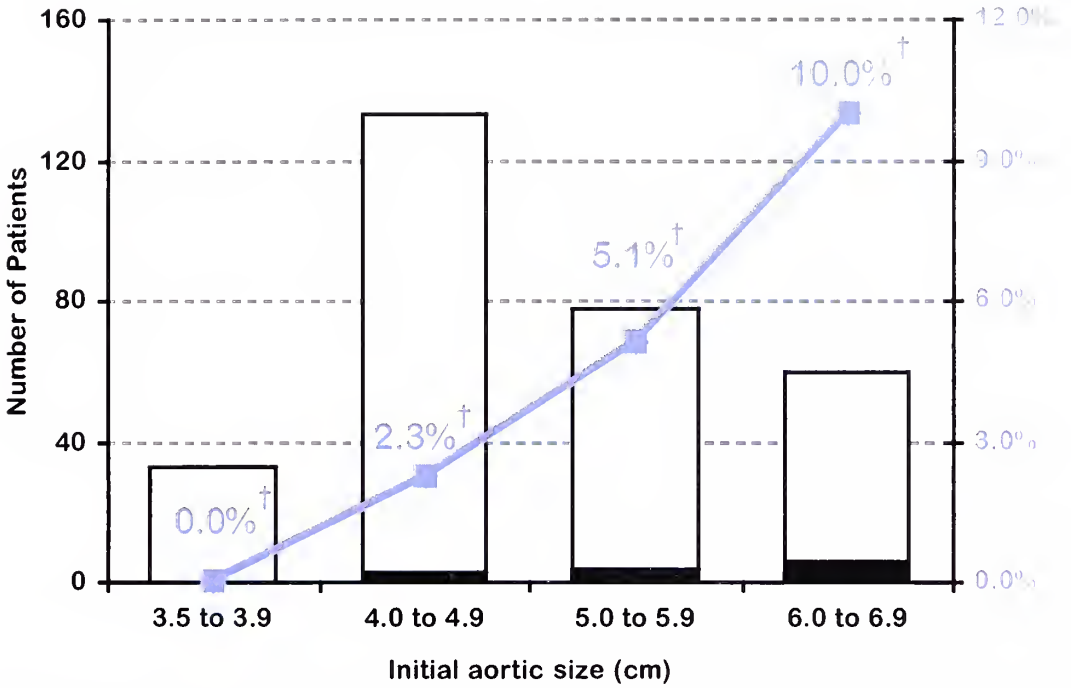


Figure 19. Incidence of rupture as a function of initial aneurysm size. The entire column indicates the total number of patients with thoracic aortic aneurysms in each size range. The *black area* indicates the number of patients who incurred a rupture of the aneurysm. The line graph and associated percentages indicates the percentage of patients in each category who incurred a rupture of the aneurysm and corresponds to the axis on the right.
† Statistically significant increase in complication rates with increasing initial aortic size, $p = 0.006$. (Mantel-Haenszel χ^2 test)

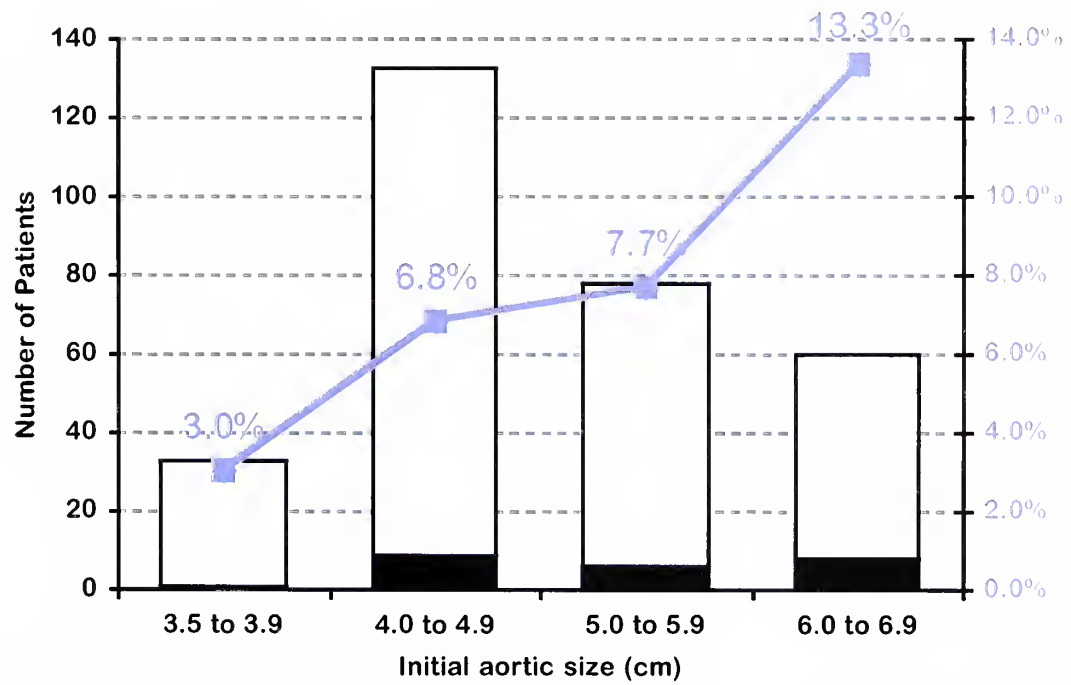


Figure 20. Incidence of acute dissection as a function of initial aneurysm size. The entire column indicates the total number of patients with thoracic aortic aneurysms in each size range. The black area indicates the number of patients who incurred an acute dissection of the aneurysm. The line graph and associated percentages indicates the percentage of patients in each category who incurred an acute dissection of the aneurysm and corresponds to the axis on the right.

Table 7. Aneurysm size (cm) at the time of complication.

	All Patients			*Non Marfan syndrome (n = 28)*			*Marfan syndrome (n = 5)*		
	*Mean**	*Median*	*Range*	*Mean**	*Median*	*Range*	*Mean**	*Median*	*Range*
All ruptures or acute dissections (n = 33)	5.7 cm (5.2 to 6.2)	5.5	4.0 to 9.3	5.8 (5.3 to 6.3)	5.8	4.0 to 9.3	5.2 cm (3.0 to 7.4)	4.4	4.2 to 8.3
All dissections (n = 24)†	4.6 cm (5.1 to 6.1)	5.4	4.0 to 8.0	5.7 (5.2 to 6.2)	5.7	4.0 to 8.0	4.2 cm	4.2	4.2 to 4.2
All ruptures (n = 13)†	5.9 cm (5.0 to 6.9)	5.8	4.0 to 9.3	5.9 (4.8 to 7.0)	5.9	4.0 to 9.3	5.9 cm (0.68 to 11.2)	5.0	4.4 to 8.3
Ascending /arch (n = 22)	5.7 cm (5.0 to 6.3)	5.2	4.0 to 9.3	5.9 cm (5.2 to 6.8)	5.8	4.0 to 9.3	4.5 cm (3.8 to 5.1)	4.3	4.2 to 5.0
Descending/ thoracoabdominal (n = 11)	5.9 cm (5.0 to 6.7)	6.0	4.0 to 8.3	5.6 cm (4.9 to 6.4)	5.8	4.0 to 7.2	8.3 cm	8.3	8.3 to 8.3

*95% Confidence intervals for the mean are given in parentheses
†The sum of all acute dissections and all ruptures is more than 33 because some patients incurred both acute dissections and ruptures.

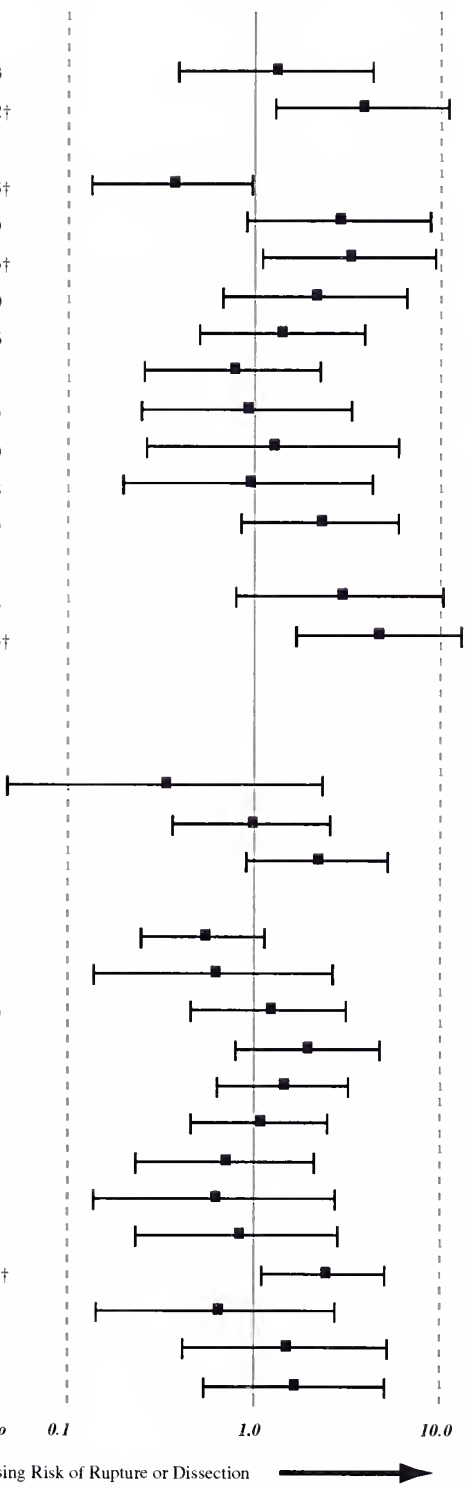
The mean and median thoracic aortic sizes at the time of rupture or dissection are shown in Table 7. Mean size at dissection was 4.6 cm, while the mean size at rupture was 5.9 cm. Sample sizes were not adequate to demonstrate statistical significance, but trends suggest that complications occur at larger aortic sizes in the descending and thoracoabdominal aorta versus the ascending aorta, and at smaller sizes in patients with Marfan syndrome than in those without.

Univariate analysis of risk factors predictive of rupture and dissection is shown in the top of Table 8. Initial aortic size ≥ 6.0 cm was associated with a nearly four-fold increase in the incidence of rupture. Other significant univariate predictors of rupture included location of the aneurysm in the descending or thoraco-abdominal aorta and a history of abdominal aortic aneurysm. In addition, male gender conferred significant protection from rupture. The bottom of Table 9 shows risk factors for dissection. A history of coronary artery disease was the only statistically significant univariate predictor of dissection.

The incidence of rupture and dissection was analyzed together at the top of Table 9. Size was a powerful predictor of these complications. The protective effect of male gender was consistent, as was the increased risk associated with the presence of other vascular diseases including coronary artery disease, abdominal aortic aneurysm, or a history of stroke. The bottom of Table 9 also indicates that nearly all comorbidities, but particularly vascular diseases, were associated with an increased incidence of death prior to surgical correction in this population. Increasing aortic size showed a trend toward increased preoperative mortality with an odds ratio of 1.911.

Table 8. Univariate analysis of risk factors predictive of rupture or dissection.

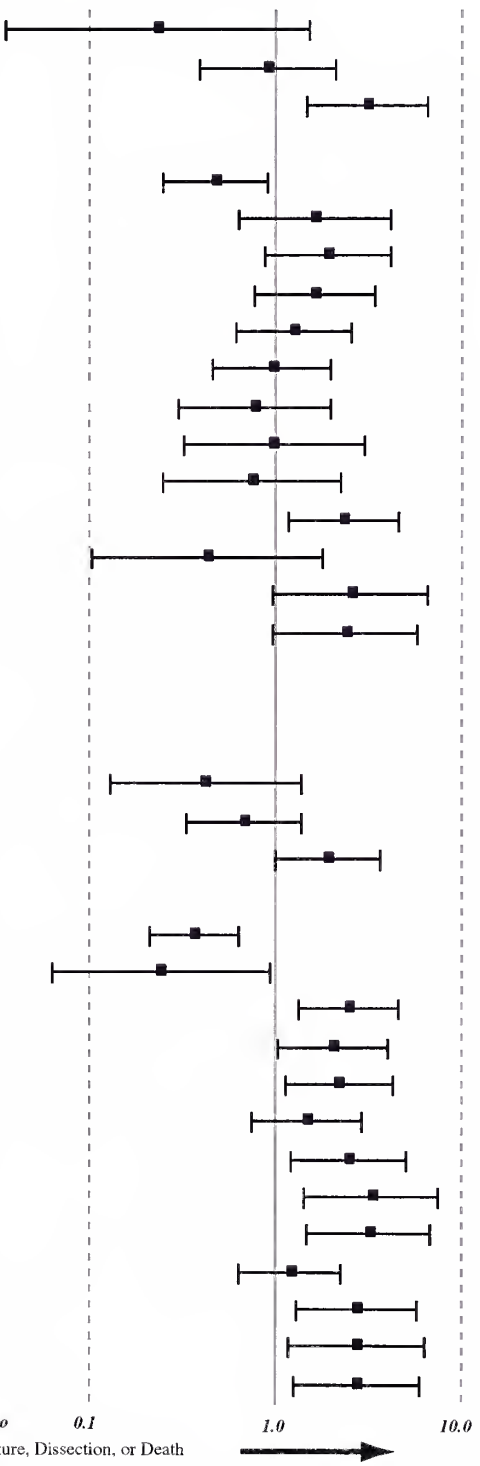
Risk Factor		*Complication Rate*	*Odds Ratio*	*Odds Ratio (with 95% CI)*	*P value*
Risk Factors for Rupture					
Initial Aortic Size	3.5 to 3.9 cm	0/33 (0.0%)			0.198
	5.0 to 5.9 cm	4/78 (5.1%)	1.303		0.666
	≥ 6.0 cm	6/60 (10.0%)	3.762†		0.014†
	Gender (male)	6/96 (3.1%)	0.365†		0.044†
	Marfan syndrome	4/35 (11.4%)	2.839		0.071
	Aneurysm location (desc/TA)	6/66 (9.1%)	3.243†		0.032†
	Hypertension	12/162 (9.1%)	2.100		0.201
	Cardiac Disease	8/104 (7.7%)	1.396		0.518
	Tobacco History	5/86 (5.8%)	0.761		0.623
	Pulmonary Disease	3/51 (5.9%)	0.909		0.085
	Carotid Disease	2/28 (7.1%)	1.250		0.778
	Renal Disease	2/35 (5.7%)	0.928		0.924
	CAD	7/82 (8.5%)	2.259		0.102
	CHF	0/34 (0.0%)			0.154
	Prior CVA	3/25 (12.0%)	2.873		0.102
	AAA	5/31 (16.1%)	4.663†		0.003†
Risk Factors for Dissection					
Initial Aortic Size	3.5 to 3.9 cm	1/33 (3.0%)	0.337		0.272
	5.0 to 5.9 cm	6/78 (7.7%)	0.963		0.939
	≥ 6.0 cm	8/60 (13.3%)	2.192		0.081
	Gender (male)	13/196 (6.6%)	0.542		0.113
	Marfan syndrome	2/35 (5.7%)	0.611		0.510
	Aneurysm location (desc/TA)	6/66 (9.1%)	1.200		0.711
	Hypertension	18/162 (11.1%)	1.936		0.416
	Cardiac Disease	13/104 (12.5%)	1.418		0.399
	Tobacco History	10/91 (11.0%)	1.073		0.870
	Pulmonary Disease	4/51 (7.8%)	0.696		0.522
	Carotid Disease	2/28 (7.1%)	0.615		0.523
	Renal Disease	3/35 (8.6%)	0.810		0.743
	CAD	7/82 (8.5%)	2.370†		0.028†
	CHF	2/34 (5.9%)	0.632		0.541
	Prior CVA	3/25 (12.0%)	1.484		0.540
	AAA	4/31 (12.9%)	1.647		0.381



† = Statistically significant results. Bars on graph indicate 95% confidence intervals, odds ratios cannot be calculated when the incidence of the measured outcome is zero. AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CHF = congestive heart failure, CVA = cerebrovascular accident or stroke, desc = descending, TA = thoraco-abdominal.

Table 9. Univariate analysis of risk factors predictive of rupture or dissection and death.

Risk Factor		*Complication Rate*	*Odds Ratio*	*P value*
Risk Factors for Rupture or Dissection				
Initial Aortic Size	3.5 to 3.9 cm	1/33 (3.0%)	0.233	0.126
	5.0 to 5.9 cm	8/78 (10.3%)	0.919	0.844
	6.0 cm	13/60 (21.7%)	3.098	0.003†
Gender (male)		17/196 (8.7%)	0.475	0.027†
Marfan syndrome		6/35 (17.1%)	1.613	0.472
Aneurysm location (desc/TA)		11/66 (16.7%)	1.927	0.096
Hypertension		25/162 (15.4%)	1.626	0.204
Cardiac Disease		17/104 (16.3%)	1.265	0.516
Tobacco History		13/91 (14.3%)	0.957	0.906
Pulmonary Disease		6/51 (11.8%)	0.764	0.573
Carotid Disease		4/28 (14.3%)	0.983	0.977
Renal Disease		4/35 (11.4%)	0.753	0.616
CAD		16/82 (19.5%)	2.303	0.016†
CHF		2/34 (5.9%)	0.431	0.248
Prior CVA		6/25 (24.0%)	2.554	0.054
AAA		7/31 (22.6%)	2.386	0.056
Risk Factors for Mortality				
Initial Aortic Size	3.5 to 3.9 cm	3/33 (9.1%)	0.421	0.155
	5.0 to 5.9 cm	11/78 (14.1%)	0.679	0.288
	6.0 cm	16/60 (26.7%)	1.911	0.054
Gender (male)		24/196 (12.2%)	0.367	0.001†
Marfan syndrome		2/35 (5.7%)	0.241	0.039†
Aneurysm location (desc/TA)		20/66 (30.3%)	2.472	0.004†
Hypertension		35/162 (21.6%)	2.035	0.041†
Cardiac Disease		24/104 (23.1%)	2.206	0.021†
Tobacco History		18/91 (19.8%)	1.491	0.252
Pulmonary Disease		15/41 (36.6%)	2.486	0.011†
Carotid Disease		10/28 (35.7%)	3.278	0.005†
Renal Disease		12/35 (34.3%)	3.165	0.003†
CAD		17/82 (20.7%)	1.203	0.561
CHF		12/34 (35.3%)	2.727	0.008†
Prior CVA		9/25 (36.0%)	2.717	0.020†
AAA		11/31 (35.5%)	2.718	0.011†



† = Statistically significant results. Bars on graph indicate 95% confidence intervals, odds ratios cannot be calculated when the incidence of the measured outcome is zero. AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CHF = congestive heart failure, CVA = cerebrovascular accident or stroke, desc = descending, TA = thoraco-abdominal.

The results of a multivariable regression analysis examining risk factors predictive of rupture or dissection prior to surgical correction are given in Table 10. The only risk factor remaining in the model following stringent selection criteria ($p \leq 0.05$) was aneurysm size ≥ 6.0 cm. At that size, the risk of incurring a rupture or dissection was nearly three times as high as for aneurysms of 4.0 to 4.9 cm. When a less stringent selection criteria ($p < 0.70$) was used, the model again demonstrates the importance of vascular comorbidities in predicting rupture or dissection in this population. Table 10 indicates that the odds of incurring a rupture or acute dissection are 2.0 times greater (95% CI 0.515 to 5.039) for patients with coronary artery disease, and 1.6 times greater (95% CI 0.850 to 5.5051) for those with a history of abdominal aortic aneurysm.

Table 10. Logistic regression of risk factors for rupture or dissection (dependent variables)§

Regression Analysis	*Conservative Model*	*Entry at*	*p < 0.05**		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Odds Ratio†*
Intercept term	-2.2267	0.2476	0.0001		
Aortic Size ≥ 6.0 cm‡	1.0557‡	0.4234	0.0126‡	2.874‡	(1.253 – 6.589)
Regression Analysis	***Liberal Model***	***Entry at***	***p < 0.7*****		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Odds Ratio†*
Intercept term	-2.2267	0.2476	0.0001		
Aortic Size					
< 4.0 cm	-0.9107	1.0884	0.4027	0.402	(0.048 – 3.396)
5.0 – 5.9 cm	0.2362	0.5341	0.6583	1.266	(0.445 – 3.607)
≥ 6.0 cm‡	1.0994‡	0.5127	0.0320‡	3.002‡	(1.099 – 8.201)
Age at presentation (risk per year)	-0.00757	0.0122	0.5335	0.992	(0.969 – 1.016)
AAA	0.4769	0.5818	0.4123	1.611	(0.515 – 5.039)
CAD	0.7283	0.4548	0.1093	2.071	(0.850 – 5.051)
CHF	-0.9483	0.7786	0.2233	0.387	(0.084 – 1.782)

§ This variable equals 1 if the patient incurred a rupture or acute dissection and 0 otherwise.
*Criteria for assessing model fit: -2 Log L: intercept only: 176.919; intercept and covariates: 171.147; χ^2 for covariates: 6.629 with 1 DF ($p = 0.001$).
**Criteria for assessing model fit: -2 Log L: intercept only: 176.919; intercept and covariates: 164.400; χ^2 for covariates: 12.826 with 7 DF ($p = 0.0765$).
† 95% confidence intervals on odds ratios are given in parentheses.
‡ Statistically significant at $p < 0.05$ level.

Incidence of Rupture, Dissection and Death Over Time

The incidence of rupture or dissection over time as a function of initial aneurysm size is given in Figure 21. The rate of ruptures and dissections was significantly higher in patients with higher initial aortic size ($p = 0.006$). At aortic sizes ≥ 6.0 cm, there is a marked step-up in the average yearly rate of complications to 6.9% per year (Figure 22). Proportional hazards regression demonstrates that the hazard function is more than 2.7 times worse for patients with size ≥ 6.0 cm than for those with size between 4.0 to 4.9 cm, again male sex confers some relative protection from adverse events (Table 11). When less stringent criteria are used to create a proportional hazards model, the importance of size can clearly be seen, in

Table 11. Proportional hazards regression of factors predicting increased rates of rupture or dissection. (dependent variables)§

Regression Analysis	*Conservative Model*	*Entry at*	*p < 0.05**		
Variable	*Parameter estimate*	*Standard error*	*p Value*	*Odds Ratio†*	
Size ≥ 6.0 cm‡	1.002336‡	0.38378	0.0090‡	2.725‡	(1.284 – 5.781)
Gender (male)†	-0.904492††	0.39089	0.0207††	0.405††	(0.188 – 0.871)
Regression Analysis	***Liberal Model***	***Entry at***	***p < 0.70*** **		
Variable	*Parameter estimate*	*Standard error*	*p Value*	*Odds Ratio†*	
Initial Aortic Size					
3.5 – 3.9 cm	-0.429173	1.06710	0.6875	0.651	(0.080 - 5.271)
5.0 – 5.9 cm	0.815989	0.51781	0.1151	2.261	0.820 - 6.239
≥ 6.0 cm‡	1.489282‡	0.49997	0.0029‡	4.434‡	(1.664 - 11.813)
Location (Desc/TA)	-0.202180	0.44746	0.6514	0.817	(0.340 - 1.964)
Gender (male)†	-1.010436††	0.41804	0.0156††	0.364††	(0.160 - 0.826)
Pulmonary Disease	-0.220534	0.53700	0.3242	0.802	(0.471 - 1.365)
AAA	0.529420	0.21731	0.5594	1.698	(0.593 - 4.864)
HTN	-0.126842	0.18055	0.1457	0.881	(0.575 - 1.349)
Cardiac Disease	0.262694	0.27112	0.4160	1.300	(0.913 - 1.853)

§ This variable equals 1 if the patient incurred a rupture or dissection and 0 otherwise.
*Criteria for assessing model fit: -2 Log L: without covariates: 274.596; with covariates: 262.811; χ^2 for covariates: 11.785 with 2 DF (p = 0.0028).
** Criteria for assessing model fit: -2 Log L: without covariates: 274.596; with covariates: 256.536; χ^2 for covariates: 18.060 with 9 DF (p =0.0345).
† 95% confidence intervals on odds ratios are given in parentheses.
‡ Statistically significant at the 1% level.
†† Statistically significant at the 5% level.

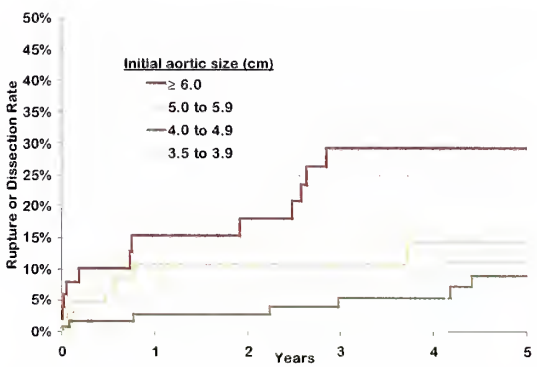


Figure 21. Kaplan-Meier cumulative incidence of rupture or dissection. Five-year hazard estimates are illustrated for patients as a function of initial aneurysms size, p = 0.006.

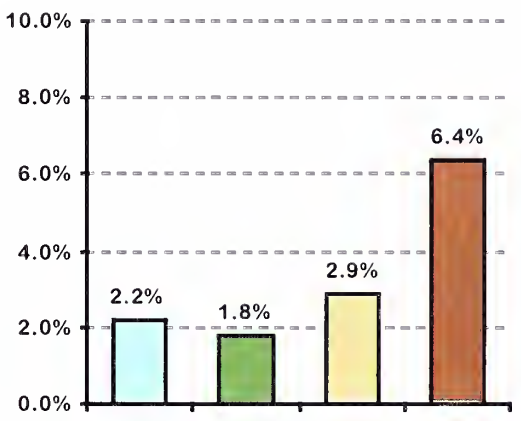


Figure 22. Average yearly rate of rupture or dissection by initial aortic size.

addition, a history of hypertension or pulmonary disease both show a trend toward increasing rates of rupture or disseetion (risk ratios: 1.300 and 1.698, $p = 0.14$ and 0.32, respectively).

The importance of size is vividly apparent when rupture is analyzed alone (Figure 23 and Figure 24). Under the most conservative proportional hazards model the rate of rupture is five times worse with aortic size of 5.0 to 5.9 cm and nearly ten times worse with size ≥ 6.0 cm when each is compared with aneurysms of size < 4.0 cm (Table 12). Under the less conservative model, size has an even greater impact,

Table 12. Proportional hazards regression of factors predicting increased rates of rupture (dependent variables).§

Regression Analysis	*Conservative Model*	*Entry at*	*p < 0.05**		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Odds Ratio†*
Initial Aortic Size					
5.0 – 5.9 cm	1.595365	0.86744	0.0659	4.930	(0.901 – 26.991)
≥ 6.0 cm‡	2.256365‡	0.81758	0.0058‡	9.548‡	(1.923 – 47.408)
Regression Analysis	***Liberal Model***	***Entry at***	***p < 0.70*** **		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Odds Ratio†*
Initial Aortic Size					
3.5 – 3.9 cm	-13.536449	1554	0.9930	0.000	(N/A)
5.0 – 5.9 cm††	1.984684††	0.99127	0.0453††	7.277††	(1.043 – 50.782)
≥ 6.0 cm‡	2.715466‡	0.94503	0.0041‡	15.112‡	(2.371 – 96.321)
Gender (male)††	-1.487251††	0.72427	0.0400††	0.226††	(0.055 – 0.935)
Age at presentation (risk/year)	-0.012866	0.01927	0.5044	0.987	(0.951 – 1.025)
AAA	0.531282	0.71240	0.4558	1.701	(0.421 – 6.873)
HTN	-0.565626	0.42697	0.1853	0.568	(0.246 – 1.312)
Cardiac Disease	0.552271	0.29030	0.0571	1.737	(0.983 – 3.069)

§ This variable equals 1 if the patient incurred a rupture and 0 otherwise.
* Criteria for assessing model fit: -2 Log L: without covariates: 112.877; with covariates: 103.063; χ^2 for covariates: 9.814 with 2 DF ($p = 0.0074$).
** Criteria for assessing model fit: -2 Log L: without covariates: 112.877; with covariates: 93.424; χ^2 for covariates: 19.453 with 7 DF ($p = 0.0069$).
† 95% confidence intervals on odds ratios are given in parentheses.
‡Statically significant at the 1% level.
†† Statistically significant at the 5% level.

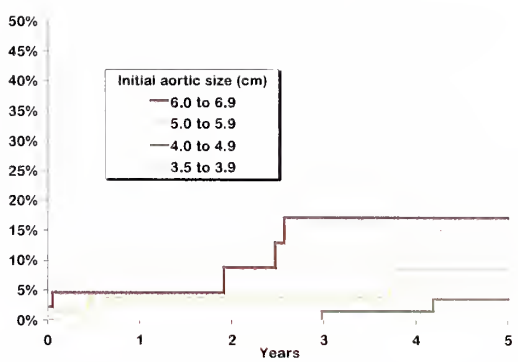


Figure 24. Kaplan-Meier cumulative incidence of rupture. Five-year hazard estimates are illustrated for patients as a function of initial aneurysm size, $p = 0.0045$.

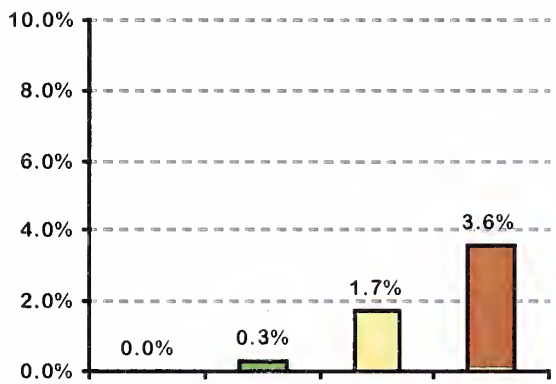


Figure 23. Average yearly rate of rupture by initial aortic size. In this graph and those on succeeding pages, the colors consistently indicate the same size: blue = 3.5 to 3.9 cm, green = 4.0 to 4.9 cm, yellow = 5.0 to 5.9 cm, and red = ≥ 6.0 cm.

and other important risk factors predictive of worse outcomes become visible, including a history of abdominal aortic aneurysm and a history of cardiae disease. Male gender again confers a relative protective effect ($p = 0.04$). Similar risk with increased aortic size is seen when dissection is analyzed alone (Figure 25 and Figure 26).

As described above, nearly all risk factors were predictive of increased risk of death prior to operation in a univariate analysis (Table 9). However, when analyzing the survival of these patients prior to operative repair with proportional hazards, only a history of abdominal aortie aneurysm (risk ratio 2.218, 95% CI 0.985 to 4.597) and inereasing age at presentation (risk ratio 1.072 per year, 95% CI 1.038 to 1.106) were predictive of poor survival (data not shown). Increasing aortic size was associated with de-

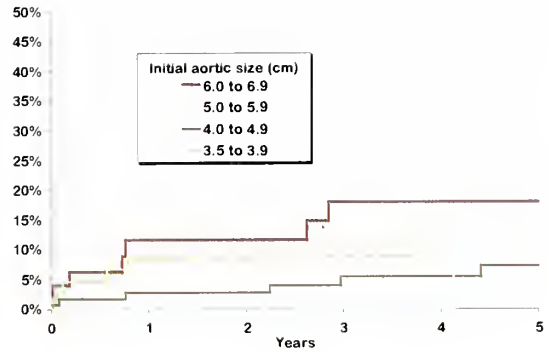


Figure 25. Kaplan-Meier cumulative incidence of dissection. Five-year hazard estimates are illustrated for patients as a function of initial aneurysms size, $p = 0.1878$.

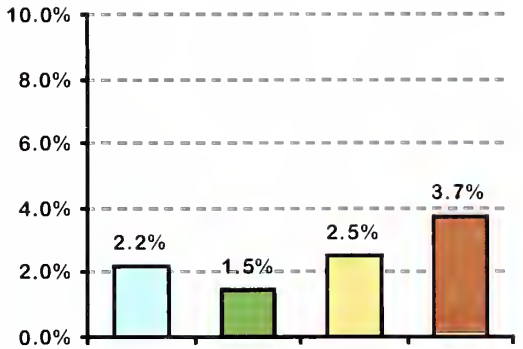


Figure 26. Average yearly rate of dissection by initial aortic size.

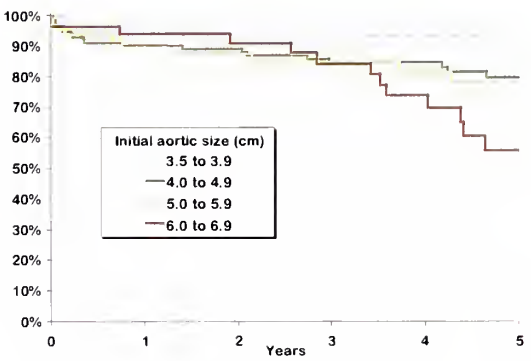


Figure 27. Kaplan-Meier cumulative survival prior to operative repair. Five-year survival estimates are illustrated for patients as a function of initial aneurysm size, $p = 0.0671$.

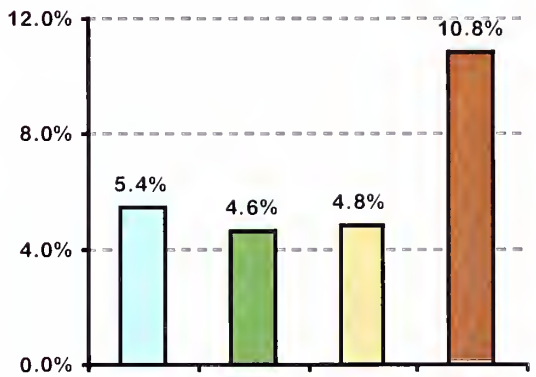


Figure 28. Average yearly rate of death by initial aortic size.

creasing survival ($p = 0.067$) (Figure 27). The yearly rates demonstrate dramatic increases at sizes ≥ 6.0 cm (Figure 28).

This step-up in the risk is clearly evident when rupture, dissection and death prior to surgical repair are considered as endpoints together (Figure 29), with a mean yearly rate twice as high in patients with size greater than 6 cm than in those with smaller aneurysms. Proportional hazards regression of this combined end-point confirmed

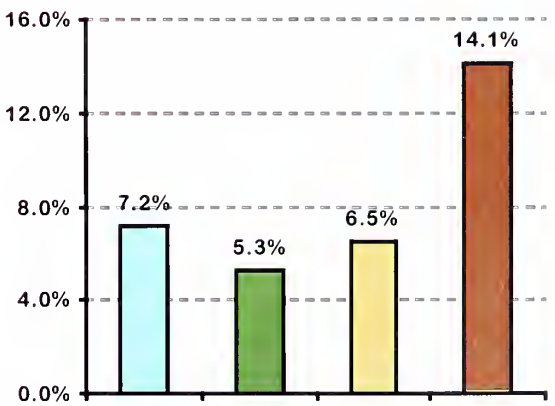


Figure 29. Average yearly rate of rupture, dissection or death based on initial aortic size.

Table 13. Proportional hazards regression of factors predicting increased rates of complications (rupture, dissection or death) prior to surgery (dependent variables).§

Regression Analysis	*Conservative Model*	*Entry at*	*p < 0.05**		
Variable	*Parameter estimate*	*Standard error*	*p Value*	*Odds Ratio†*	
Size ≥ 6.0 cm††	0.589408††	0.28672	0.0398††	1.803††	(1.028 – 3.163)
Age at presentation (risk/year)†	0.034516†	0.00908	0.0001†	1.035†	(1.017 – 1.054)
Regression Analysis	***Liberal Model***	***Entry at***	***p < 0.70*****		
Variable	*Parameter estimate*	*Standard error*	*p Value*	*Odds Ratio†*	
Size ≥ 6.0 cm††	0.624428††	0.31478	0.0473††	1.867††	(1.007 – 3.460)
Location (Desc/TA)	-0.263983	0.31120	0.3963	0.768	(0.417 – 1.413)
Gender (male)	-0.367578	0.28381	0.1953	0.692	(0.397 – 1.208)
Age at presentation (risk/year)†	0.028269†	0.00969	0.0035†	1.029†	(1.009 – 1.048)
AAA	0.555504	0.36834	0.1315	1.743	(0.847 – 3.587)
Pulmonary Disease	0.233892	0.33102	0.4798	1.264	(0.660 – 2.417)
Cardiac Disease	0.226279	0.28009	0.4192	1.254	(0.724 – 2.171)

§ This variable equals 1 if the patient ruptured, dissected or died prior to surgical correction and 0 otherwise.
*Criteria for assessing model fit: -2 Log L: without covariates: 522.849; with covariates: 496.325; $\chi 2$ for covariates: 26.524 with 2 DF ($p = 0.0001$).
** Criteria for assessing model fit: -2 Log L: without covariates: 522.849; with covariates: 490.231; $\chi 2$ for covariates: 32.618 with 7 DF ($p = 0.0001$).
† 95% confidence intervals on odds ratios are given in parentheses.
†Statistically significant at the 1% level.
†† Statistically significant at the 5% level.

the impact of larger aortic size on poor outcome prior to surgical correction (Table 13). Patients with aneurysms of the descending or thoraco-abdominal aorta were less likely to rupture (odds ratio 0.768, 95% CI 0.417 to 1.413) in this model, but otherwise the model contained similar predictors of complications as previously described. The yearly rates for all endpoints are summarized graphically in Figure 30.

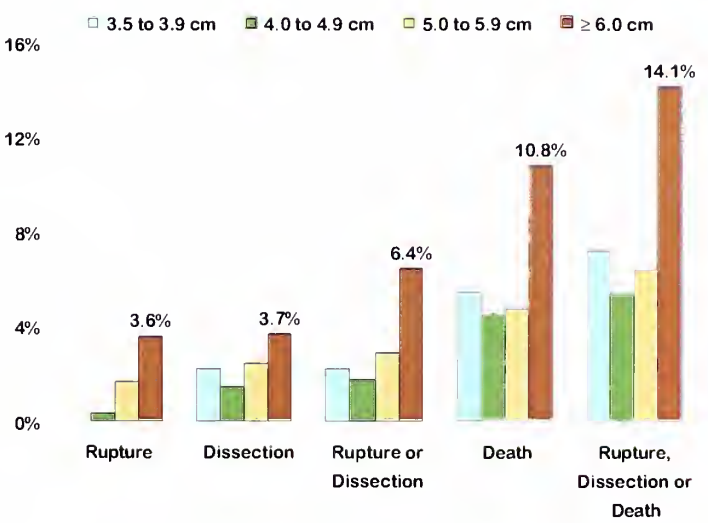


Figure 30. Average yearly rates of all negative outcomes by initial aortic size.

Long-Term Survival

Overall long-term survival for all patients, independent of surgical correction, as a function of initial aortic size is shown in Figure 31. Larger aneurysms are associated with decreased long-term survival ($p = 0.0039$). Five-year survival in patients with aneurysms ≥ 6.0 cm is only 56%. Overall, for all patients in the database, survival was better for the ascending than for the descending aorta (Figure 32), which may

reflect the larger size of descending aneurysms at presentation (Figure 16 and Table 6) and higher growth rates (Table 4). Survival was also better for non-dissected than for dissected aortas (Figure 33). Long-term survival is better in patients treated with elective surgery than in those who require emergent surgery or those maintained on medical therapy (Figure 34). Postoperative survival for patients treated emergently remains poor in this population when compared to those treated electively (Figure 35). Elective surgery restores a flat survival curve indistinguishable from that of the normal population.

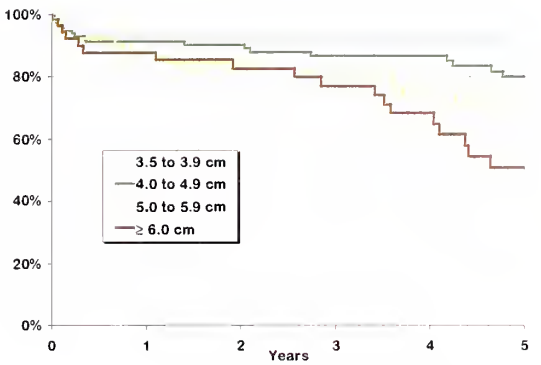


Figure 31. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of initial aortic size, $p = 0.0671$

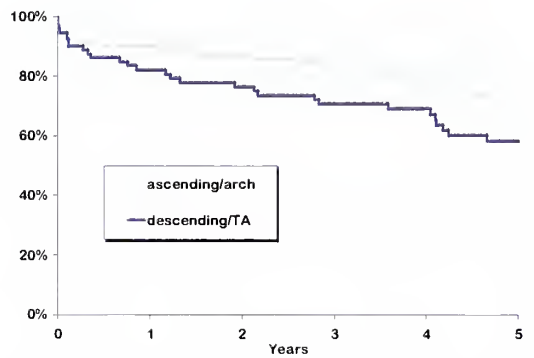


Figure 32. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of aneurysm location, $p = 0.0023$.

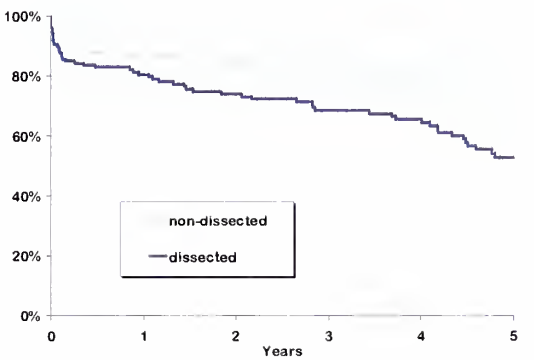


Figure 33. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function dissection status, $p = 0.0002$.

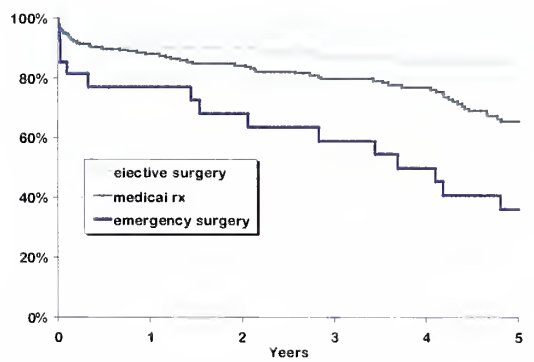


Figure 34. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of the treatment received, $p = 0.002$.

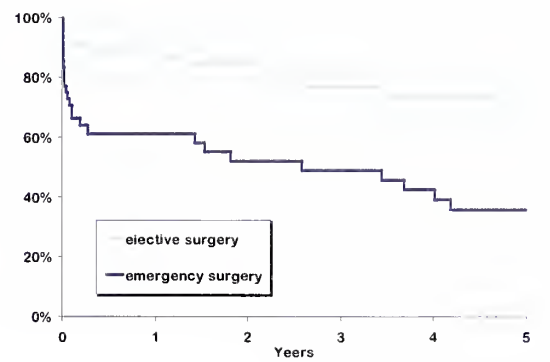


Figure 35. Kaplan-Meier cumulative survival. Five-year post-operative survival estimates are illustrated for patients as a function of the urgency of the surgical procedure, $p = 0.0004$.

The Impact of Genetic Factors on Natural History

Demographic and Clinical Characteristics of the Study Population

Table 11 indicates the baseline characteristics in the 218 patients without MFS for whom we were able to ascertain the presence or absence of a family history. These patients are compared to the 344 patients in whom we were not able to obtain a family history. Overall, the two populations are similar in terms of aneurismal disease. However, patients we contacted were more likely to have a type B dissection (p = 0.003) and an aneurysm in the 4.0 to 4.9 cm range at presentation (p = 0.037), as well as a history of pulmonary disease (p = 0.007) or stroke (p =0.035).

Table 14. Comparison of demographic characteristics in patients between patients with known (+ or -) family history and those with unknown family history. (Numbers are percentages unless otherwise indicated)

	Known (n = 218)	*Unknown (n = 344)*	*p value*
Sex (male) (n = 562)	65.2	59.2	0.137
Age at presentation (n = 560)	63.7 yrs	64.1 yrs	0.820
Initial aortic size (n =562)			
Mean (cm) (n = 441)	5.01 cm	5.07 cm	0.644
< 3.5 cm	23.5	27.8	0.280
3.5 to 3.9 cm	6.9	10.8	0.104
4.0 to 4.9 cm	35.6	27.8	0.037†
5.0 to 5.9 cm	19.3	18.1	0.711
6.0 to 6.9 cm	6.0	9.2	0.160
≥ 7.0 cm	8.6	6.8	0.406
Aneurysm Location			
Ascending/Arch (n =275)	77.2	71.8	0.242
Descending/thoracoabdominal (n = 97)	22.8	28.2	0.242
Dissection (n = 562)			
Any	45.5	35.2	0.024†
Type A	23.6	21.5	0.517
Type B	26.6	16.5	0.003†
Number of Aneurysms (n =562)‡			
None	9.9	12.4	0.071‡
Single	61.4	65.1	0.071‡
Multiple	28.8	22.4	0.071‡
Comorbidities			
Hypertension (n = 493)	67.2	69.8	0.540
Cardiac History (n = 449)	39.8	44.2	0.351
Carotid History (n = 429)	13.9	14.4	0.894
Renal History (n = 450)	11.4	13.1	0.578
Tobacco Use (n = 445)	42.4	39.9	0.599
Pulmonary Disease (n = 465)	26.8	16.3	0.006†
CAD (n = 603)	25.3	26.0	0.864
CVA (n = 603)	5.6	10.5	0.035†
AAA (n = 603)	12.5	12.2	0.918
CHF (n = 603)	8.2	11.1	0.242

† Statistically significant difference between groups (T-test for difference between means in analysis of variance).
‡ p value for Mantel-Haenszel χ^2 for increasing frequency of multiple aneurysms in patients with known history.

Two hundred thirty-three patients without MFS were interviewed. Of the 233 patients, 44 (29 men, 15 women) (18.9%) were found to have at least 1 first-degree relative with aneurismal disease, and were considered non-MFS-related familial (nMFS familial); the remaining cases were considered sporadic. Table 15 summarizes the demographic and clinical characteristics of these 44 patients with nMFS familial aortic disease (two patients P557A, P557B, were determined to be in the same family). Patients with nMFS familial aortic disease had a similar incidence of dissection when compared with sporadic cases (52.3% vs. 43.9%, p = 0.316), and a similar frequency of aortic disease in the ascending aorta (76.7% vs. 77.3%, p = 0.940). In

contrast, the patients with MFS had a lower incidence of dissection (20.0% $p = 0.001$) and were much more likely to have disease in the ascending aorta (97.1%, $p = 0.029$).

There was a statistical trend toward younger presentation in patients with nMFS familial aortic disease than in sporadic cases (58.7 years vs. 65.0 years), and both groups were significantly older than patients with MFS (26.0 years, $p = 0.0001$). Patients with MFS had a significantly lower prevalence of nearly all comorbidities as shown in Table 16 and depicted graphically in Figure 36. In particular, the rates of hypertension and vascular diseases were markedly lower in patients with MFS than in the other two groups: *no* patients with MFS had renal or carotid disease, and only 15.1% had a history of hypertension (versus 60.8% of nMFS familial and 68% of sporadic, $p = 0.001$). Patients with nMFS familial aneurysms did not differ significantly from those with sporadic aortic disease, although there was a slight trend toward a reduced incidence of hypertension. Data is not shown for the analysis of comorbidities based on the stratified severity scores because no difference was statistically significant.

Table 15. Demographics and clinical characteristics of patients with non-MFS-related familial thoracic aortic disease.*

Pedigree	Age, y/ Sex	Tobacco Use	HTN	Pulmonary Disease	Cardiac Disease	Initial Aortic Size (cm)	Site	Dissection
P026	58/M	none	none	mild	none	5.4	Asc	—
P030	38/M	none	none	none	none	4.5	Asc	—
P041	76/F	none	none	none	mild	3.9	Asc	—
P042	58/M	severe	severe	mild	moderate	7.5	Desc	—
P090	61/F	mild	none	none	moderate	3.5	Desc	—
P091	35/M	none	mild	none	none	.	—	Type A
P098	35/M	none	none	none	none	4.0	Asc	—
P107	80/F	moderate	mild	moderate	moderate	7.2	Asc	Type A
P111	49/M	mild	mild	none	none	.	.	—
P141	52/M	severe	.	none	severe	4.6	Asc	—
P145	24/M	none	none	none	none	4.8	Asc	Type A
P167	58/F	severe	moderate	none	none	9.8	TA	—
P184	73/F	severe	mild	mild	none	6.0	TA	—
P188	58/M	none	none	mild	moderate	4.1	Asc	—
P190	36/M	none	none	none	none	4.0	Arch	Type A
P211	47/M	none	severe	none	none	3.8	Arch	Type B
P256	65/M	.	.	.	.	7.5	Arch	.
P265	75/M	severe	mild	moderate	none	5.0	Asc	—
P271	74/M	severe	none	none	.	4.0	.	—
P286	64/F	severe	mild	moderate	.	4.0	.	—
P324	79/F	none	moderate	none	moderate	6.0	Asc	—
P330	15/F	none	none	none	.	4.5	Asc	—
P335	82/F	moderate	severe	none	moderate	5.9	Asc	Type B
P345	57/F	.	.	.	.	.	.	.
P366	66/M	.	moderate	none	moderate	4.0	Asc	Type B
P422	48M	.	.	.	.	4.0	Asc	—
P422	/M	none	mild	none	none	.	.	Type A
P470	38/M	none	severe	mild	.	4.2	Asc	Type B
P511	65/M	none	none	none	none	.	.	Type A
P518	76/F	none	moderate	none	none	5.5	Asc	—
P546	69/M	none	mild	mild	moderate	4.2	Desc	Type B
P547	75/M	mild	mild	none	mild	4.2	Asc	—
P557A	/F	.	.	.	.	4.1	Asc	—
P557B	59/M	none	mild	none	.	.	—	Type A
P563	72/F	none	moderate	mild	severe	5.0	Asc	—
P565	64/M	none	mild	none	none	6.0	TA	Type B
P571	/M	.	.	.	.	7.3	Desc	—
P572	60/M	mild	none	none	mild	.	.	—
P591	81/F	none	mild	none	moderate	.	—	Type B
P604	47/F	moderate	none	mild	moderate	4.1	Asc	—
P666	60/F	none	none	mild	none	5.3	Asc	Type A
P703	68/M	none	none	mild	none	4.5	Asc	—
P906	86/M	.	mild	.	.	6.2	Asc	—
P933	64/M	mild	moderate	severe	none	5.0	TA	—

* . indicates that the information was not available for a specific patient (this occurred when presentation occurred to an outside hospital and data related to the patient's presentation could not be reliably retrieved in a format consistent with that retrieved for patients seen at Yale-New Haven, — indicates that the patient did not have a particular type of aortic disease.

Table 16. Comparison of patients with sporadic, nMFS familial, and MFS-related thoracic aortic disease.*

Variable	*Sporadic*	*nMFS familial*	*MFS related*
No. of patients (sex)	189 (123 M, 66 F)	44 (29 M, 15 F)	60 (40 M, 20 F)
Age (yrs)	65.0 (62.7 to 67.4)†	59.7 (54.8 to 64.7)†	26.0 (21.8 to 30.3)†
Initial aortic diameter (cm)	5.1 (4.6 to 5.6)	5.1 (4.8 to 5.3)	4.8 (4.3 to 5.2)
Comorbidities			
Hypertension	108 (68.8%)‡	23 (60.5%)‡	8 (15.1%)‡
Cardiac Disease	53 (38.4%)‡	15 (45.5%)‡	5 (10.6%)‡
Carotid Disease	16 (12.5%)§	6 (20.0%)§	0 (0.0 %)§
Renal Disease	17 (12.2%)§	3 (8.1%)§	0 (0.0%)§
Pulmonary Disease	58 (43.0%)	15 (40.5%)	11 (23.4%)
Tobacco Use	35 (24.1%)¶	14 (36.8%)¶	3 (6.4%)¶
CAD	47 (24.9%)¶	12 (27.7%)¶	3 (5.0%)¶
AAA	22 (11.6%)	7 (15.9%)	6 (10.0%)
CVA	10 (5.3%)	3 (6.8%)	1 (1.7%)
CHF	12 (6.4%)§	7 (15.9%)§	3 (5.0%)§
Growth rate (cm/yr)	0.08 (-0.02 to 0.18)	0.13 (0.04 to 0.22)	0.13 (0.06 to 0.21)

* Values are given as N (%), or as mean with 95% confidence intervals in parentheses where appropriate. The Bonferonni test for differences between means was used in the analysis of variance procedure. χ^2 test was used to evaluate difference in prevalence of comorbidities between groups. Percentages and N values may not correspond across rows because some patients were excluded from each analysis because of incomplete information.
† $p < 0.0001$
‡ $p < 0.001$
§ $p < 0.05$
¶ $p < 0.005$

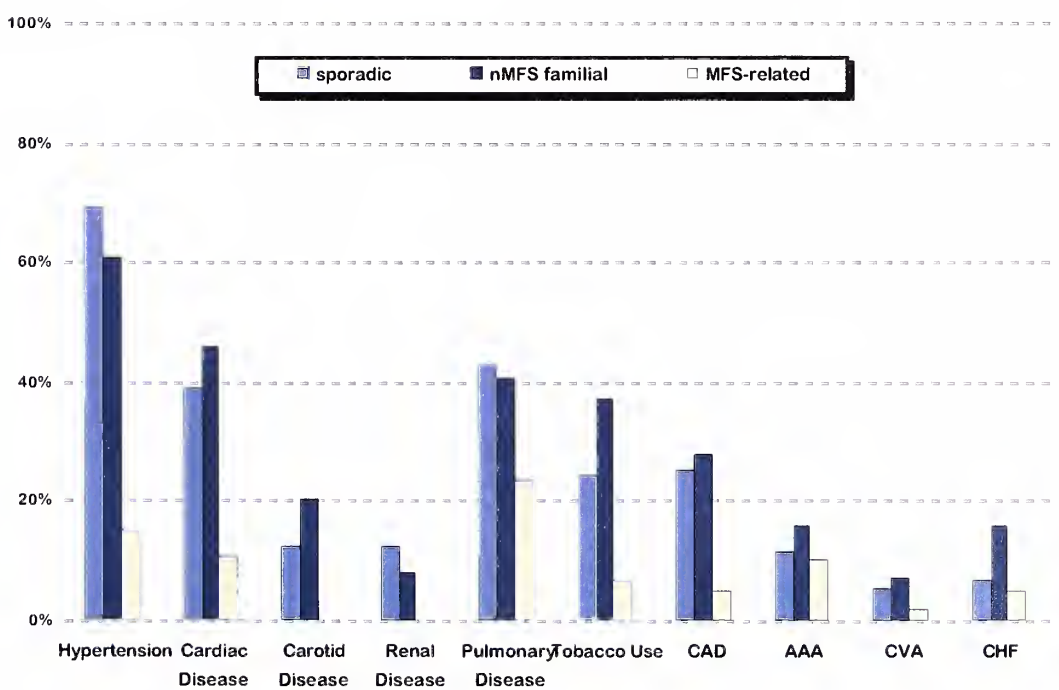


Figure 36. Prevalence of comorbidities analyzed by the presence of a family history.

Pedigree Analysis

Figure 37 displays the family pedigrees of a representative group of 26 out of the 44 patients and their first-order relatives. All pedigrees are consistent with autosomal dominant transmission with reduced penetrance. Some pedigrees (for example P286, P546, P271) are consistent with autosomal recessive; however, the high frequency of affected individuals in the affected generation (50%) suggests that this simply represents incomplete penetrance of the disease phenotype, rather than a distinct mode of inheritance. Some pedigrees may also be consistent with X-linked inheritance (for example, P141, P167, P184).

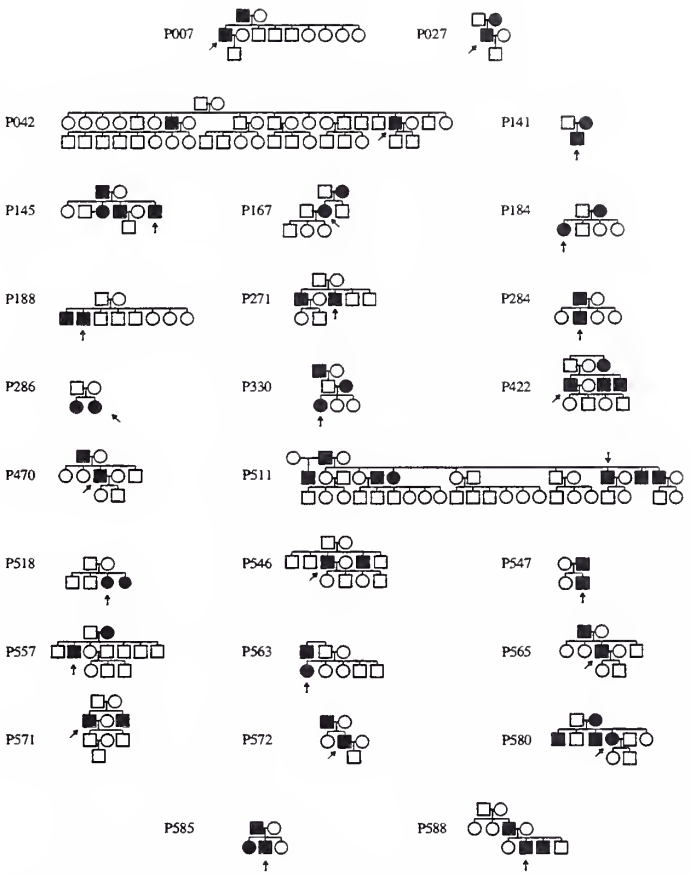


Figure 37. Pedigrees for 26 families with nMFS familial aortic disease. Squares represent men and circles women. An arrow indicates the proband with thoracic aortic disease. Blackened squares or circles represent affected patients with aortic aneurysms.

Aneurysm Growth Rates

The initial aortic diameter at the time of diagnosis was the same for patients with sporadic disease and those with nMFS familial aortic disease (Table 16). Patients with MFS tended to have smaller aortic diameter at presentation. Aortic aneurysm growth rates for the sporadic, nMFS familial, and MFS-related TAA are displayed in Table 15 and Table 17. Although sample sizes were not sufficient to dem-

Table 17. Comparison of aortic growth rate according to dissection status in patients with sporadic, nMFS familial, and MFS-related thoracic aortic aneurysms.*

	Aortic Dissection	*No Dissection*
Sporadic	0.09	0.06
	(-0.06 to 0.26)	(-0.04 to 0.17)
nMFS familial	0.16	0.13
	(-0.01 to 0.34)	(0.03 to 0.24)
MFS related	0.18	0.13
	(0.05 to 0.32)	(0.04 to 0.21)
Overall†	0.13	0.08
	(0.05 to 0.20)	(0.06 to 0.11)

* Values indicate aortic growth rate based on regression analysis for patients with and without aortic dissection. 95% confidence intervals for the mean are given in parentheses

† Includes patients in whom the family history status is not known.

onstrate statistical significance, patients with nMFS familial disease, and those with MFS had higher growth rates for both dissected and non-dissected aneurysms. Growth rates for dissected aneurysms were 0.16 cm per year in nMFS familial patients, and 0.18 cm per year in patients with MFS. Sporadic patients with dissection had growth rates of only 0.06 cm per year.

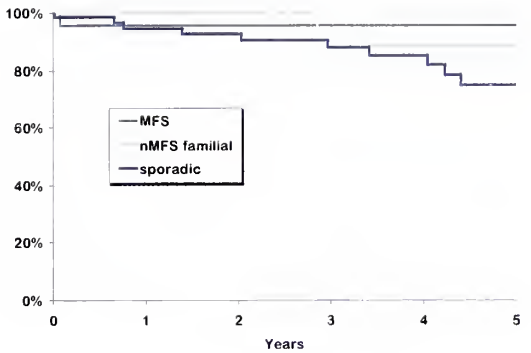


Figure 38. Kaplan-Meier cumulative survival prior to operative repair. Five-year survival estimates are illustrated for patients as a function of familial history. ($p = 0.997$)

Long-Term Survival

The survival prior to operative repair was not significantly different between patients with a family history and those without ($p = 0.997$, Figure 38). Predictors of preoperative death were similar in this population to the entire population, and the presence or absence of a family history did not enter into a proportional hazards model which continued to

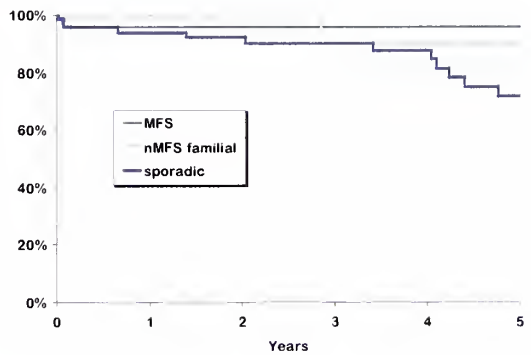


Figure 39. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of familial history. ($p = 0.0902$)

Table 18. Proportional hazards regression of factors predicting decreased long-term survival when familial history is included as a risk factor (dependent variables).§

Regression Analysis	***Conservative Model***	***Entry at***	***p < 0.05****		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Risk Ratio†*
Size ≥ 6.0 cm‡	1.204503‡	0.46678	0.0099‡	3.335‡	(1.336 – 8.326)
Cardiac Disease††	1.125778††	0.46606	0.0157††	3.083††	(1.237 – 7.685)
Regression Analysis	***Liberal Model***	***Entry at***	***p < 0.70****		
Variable	*Parameter estimate*	*Standard error*	*p Value*		*Risk Ratio†*
Initial Aortic Size					
3.5 – 3.9 cm	-14.54718	1715	0.4559	0.000	N/A
≥ 6.0 cm	0.909644	0.47785	0.0570	2.843	(0.973 – 6.336)
nMFS familial history	0.466472	0.71212	0.5124	1.594	(0.395 – 6.438)
Age at presentation (per year)	0.023342	0.01736	0.1789	1.024	(0.989 – 1.059)
Location (Desc/TA)	0.566817	0.69088	0.4120	1.763	(0.455 – 6.827)
Pulmonary Disease	-0.675778	0.60925	0.2673	0.509	(0.154 – 1.679)
AAA	0.820452	0.70731	0.2461	2.483	(0.973 – 6.336)
Cardiac Disease††	1.129986††	0.57202	0.0482††	3.096††	(1.009 – 9.498)

§ This variable equals 1 if the patient incurred died and 0 otherwise.

*Criteria for assessing model fit: -2 Log L: without covariates: 138.583; with covariates: 125.499; χ^2 for covariates: 13.084 with 2 DF ($p = 0.0014$).

** Criteria for assessing model fit: -2 Log L: without covariates: 138.583; with covariates: 118.030; χ^2 for covariates: 20.552 with 8 DF ($p = 0.0084$).

† 95% confidence intervals on odds ratios are given in parentheses.

‡ Statistically significant at the 1% level.

†† Statistically significant at the 5% level.

demonstrate similar predictors of decreased survival as noted above (Table 13).

Long-term survival between groups (independent of operative repair) did not differ significantly in a life-table analysis ($p = 0.0902$)(Figure 38), and the conservative proportional hazards model demonstrated only that size ≥ 6.0 cm and a history of cardiac disease predicted poor long-term survival (Table 18). However, under the less conservative multivariable model (Table 18) there was a trend toward an increased risk of death over time in patients with nMFS familial disease (odds ratio 1.594, 95% CI 00.395 – 6.438). Other predictors of earlier mortality in this population included location of the aneurysm in the descending or thoraco-abdominal aorta, increasing age at presentation, and a history of cardiac disease.

However, a serious limitation of long-term survival analysis in this population becomes evident when the survival function of patients included in the analysis is compared to survival in those in whom we were unable to ascertain a family history. Mortality in the group we were able to contact (independent of family history status) was significantly lower than in the group with unknown family history ($p = 0.0003$) (Figure 40).

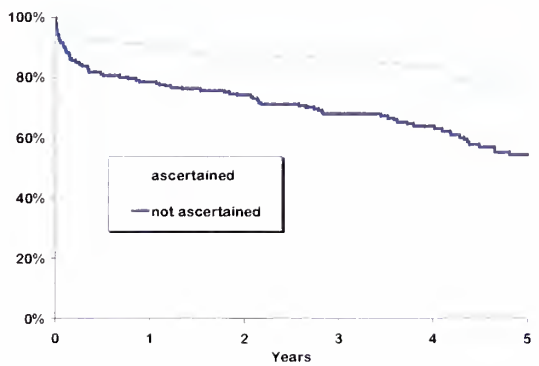


Figure 40. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of whether or not we were able to ascertain a family history. ($p = 0.0003$)

Analysis of linkage was performed on a single family with nMFS familial aortic disease in order to assess the potential for linkage in this family to the genetic locus containing the *FBN1* gene. Affected individuals in this family did not share *any* alleles at the *FBN1* locus, excluding defects in fibrillin as a potential cause in this family.

DISCUSSION

Aneurysm Growth Rates

Growth rates in this population were consistent with previous estimates.[4,60,64] The mean aortic growth rate was 0.10 cm per year. Sample sizes in the groups analyzed were not sufficient to assess statistical significance; however, some trends can be noted. The largest aneurysms (≥ 6.0 cm) grew at higher rates than smaller aneurysms. Surprisingly, the smallest aneurysms (< 4.0 cm) grew at particularly high rates, even when the incidence of concomitant dissection and Marfan disease were accounted for. This high rate may reflect the inclusion of aneurysms in the aortic root where the sinuses can dilate rapidly and asymmetrically. Because we used maximal aortic diameter, rather than cross-sectional area as our measurement of aortic size, the size and growth rates of these aneurysms may have been over-estimated. Consistent with previous reports,[4,60,64] aneurysms in the descending or thoraco-abdominal aorta, those with concomitant dissection and those in patients with a history of pulmonary disease or with Marfan syndrome also tended to grow faster.

Analysis of Complications

Examining the natural history of thoracic aortic aneurysms is complicated by a number of issues specific to the disease which make scientific assessments of risks difficult. Patients with large aneurysms, high rates of growth between imaging studies, and those with significant symptoms are usually selected for surgical intervention. Those who were not selected for surgery may have been excluded as operative candidates because of significant comorbidities. Therefore, studies of risk factors for complications require large sample sizes. This is the first report from our center in which data is robust enough (1383 years of patient follow-up before surgical intervention) to permit statistically valid calculation of yearly rates of rupture or other complications for aneurysms of different sizes.

This study confirms that thoracic aortic aneurysm is intrinsically a lethal disease and that aneurysm size has a *profound* impact on rupture, dissection and death. In the conservative proportional hazards models, size is the *only* predictor of increased risk of rupture and one of two factors predicting increased risk for the compound end-points of rupture or dissection and rupture, dissection or death.

We find that the mean rate of rupture or dissection is only 2% per year for small aneurysms, rises to 3% for aneurysms 5.0 to 5.9 cm, and jumps to 6.9% for aneurysms greater than 6.0 cm in diameter. The risk of rupture alone is near zero for small aneurysms, rises to 1.7% per year for aneurysms 5.0 to 5.9 cm, and jumps to 3.6% per year for aneurysms greater than 6.0 cm in diameter. Using a multivariable proportional hazards model, we estimate a 15-fold increase in risk with aortic size ≥ 6.0 cm versus that for aneurysms 4.0 to 4.9 cm. The risk of rupture, dissection or death from all causes is 6.5% at aneurysm size 5.0 to 5.9 cm and jumps to 14.1% per year for aneurysms greater than 6.0 cm. These data confirm the devastating prognosis associated with aneurysms ≥ 6.0 cm which we identified in our previous work.[66]

It is anticipated that these size-specific rates may be of use in counseling individual patients presenting for consideration of elective pre-emptive surgical extirpation of asymptomatic aneurysms. These data confirm that thoracic aortic aneurysm is a highly lethal condition and support pre-emptive surgical correction. It is important to emphasize that this data is for asymptomatic aneurysms and that symptomatic aneurysms require extirpation regardless of size. The general thrust of this data suggests intervention before aneurysm size reaches 6.0 cm, consonant with findings and recommendations from our earlier report on a smaller number of patients.[66]

For individual patients at specific centers, the center's surgical risk can be factored into the decision-making. At our institution, for experienced operators, hospital mortality is 2.5% for elective ascending and arch and 10.9% for elective descending and thoraco-abdominal aortic operations.[117] This indicates that surgical repair done electively promises lifetime protection at a mortality "cost" comparable to, or less than, a single year's natural rupture or dissection rates. The very flat survival curve (Figure 35) following pre-emptive surgical repair approaches that of a normal age and sex matched population and confirms vividly that surgical repair protects life long-term.

Certain limitations of these data can be enumerated. Definition of rupture, dissection, and aneurysm-related death was strict, as we required in-hospital documentation by imaging studies, surgical findings, or post-mortem examination. The mortality calculations are immune from this factor and represent true rates. Second, patients we followed were operated on electively when they reached size criteria, thus eliminating them from susceptibility to rupture or dissection. The only patients with very large aneurysms followed without surgery were those cared for elsewhere before referral to us, those refusing

surgery, or those felt to be non-operative candidates. These two factors—strict definition of aneurysm-related events, and limitation of patients at risk by pre-emptive surgery—imply that the yearly rates we have presented represent minimum lower limits of the actual rates. Some out of hospital deaths were certainly aneurysm-related. Thus, in decision-making and counseling, we can presume that the risk of rupture or dissection is *at least* 6.4% per year for 6 cm aneurysms. On the other hand, the rupture rate cannot exceed the combined endpoint rate of 14.1%, as unidentified/unrepaired rupture is a lethal event.

Two interesting and not anticipated findings of our study are that comorbid vascular disease increased the risk of rupture (odds ratio > 2-fold) and that male sex provides some relative protection (odds ratio 0.365). The former implicates complex processes of vascular biology in the growth of aneurysms and their subsequent rupture. The latter suggests that women require closer scrutiny, possibly because a specific size aneurysm represents proportionately greater aortic dilatation in smaller patients of female sex. That is, female sex may be a surrogate for low body surface area in this report.

Another issue has to do with the influence of concomitant pulmonary disease on aortic events. Multiple prior studies have shown such correlation.[51,60,65] We found an adverse impact of pulmonary disease on the rate of growth of the aorta, but did not confirm an impact on rupture or dissection. Regarding hypertension, like Griepp's group,[65] we did not uncover a direct increase in rupture or dissection. As previously described[65] it is likely that this indicates adequate treatment of hypertension, rather than a lack of effect of high blood pressure on aortic growth and rupture. A prospective study with serial blood pressure measurements would be required to fully assess the impact of high blood pressure (as opposed to merely a history of hypertension) in this population.

As would be expected, we found increasing size is more strongly associated with an increased risk of rupture, rather than an increased risk of dissection. Dissection may occur at smaller sizes due to other factors (such as connective tissue disease from Marfan syndrome or bicuspid aortic valve), whereas rupture appears to be a predominantly size-related event.

The Impact of Genetic Risk Factors

The initial results from our analysis of familial patterns of TAA were published in 1999.[3] Since that time we have identified an additional 18 patients with nMFS familial aortic disease. Consistent with our previous publication and that of Biddinger et al.[107] in 1997, we report a familial aggregation of thoracic

aortic disease in 19% of patients. Ascertainment bias likely explains the trend toward younger presentation in patients with nMFS familial disease and those with MFS. That is, patients with a close relative with an aneurysm may seek medical attention earlier than patients with sporadic TAA, and patients with MFS are screened for asymptomatic disease.

Hypertension is significantly associated with thoracic aortic disease in both familial and sporadic patients (68.8% and 60.5%), but not in patients with MFS. Although it is well known that hypertension is associated with aortic aneurysms, aneurysm formation cannot be ascribed to elevated blood pressure alone.[107] The low rate of hypertension in patients with MFS suggests that inherent vessel weakness due to the genetic defect in the fibrillin gene may represent the greatest influence on aneurysm formation in these patients. Differing levels of genetic susceptibility to aneurysm formation may be reflected in the trend toward increased aortic growth rates seen in patients with familial disease despite similar levels of hypertension.

It was surprising to find the incidence of comorbidities to be similar in the nMFS familial and the sporadic cases. This may reflect the heterogeneous nature of the population described as nMFS familial. Some of these patients may have severe genetic defects similar to those in MFS, while others may have very mild genetic defects. This is consistent with the pattern seen with defects in fibrillin, since a number of reports have described patients with well-characterized genetic defects in fibrillin who do not manifest the full-spectrum of MFS.[108,122]

Pedigree analysis suggests a dominant mode of inheritance with reduced penetrance. This is consistent with a complex disease in which disease genotype is associated with an increased susceptibility to as-yet-undefined environmental effects (for example, hypertension or chronic infection or inflammatory processes). Linkage analysis in a single family with familial nMFS disease has excluded FBN1 as a potential candidate gene indicating that other genes are involved in the predisposition toward aortic aneurysm formation.

Several limitations of this study should be mentioned. Long-term survival in the patients in whom we were able to ascertain a family history is significantly better than those who we were not able to contact. This suggests that we have interrogated a population with less severe disease on average. The prospective identification of patients following our initial publication should mitigate this effect as we continue to

gather patients. Because this study includes only families with previously diagnosed disease, it is likely that we failed to include some families with undiagnosed asymptomatic TAA and AAA. Likewise a relative may have died before aneurysms became symptomatic. Because we proceeded conservatively and did not include patients with a history of sudden death in the family, our estimate of 19% prevalence of familial aggregation should be taken as a lower limit of the true prevalence.

In order to minimize non-inclusion of asymptomatic disease, we hope to screen all first-degree family members of our pedigrees to identify additional patients with undetected aneurysm and to confirm or refute absence of aortic disease in other family members.

Summary

This report confirms that 19% of families demonstrate familial aggregation of thoracic aortic disease. While sample sizes were too small to assess statistical significance in this population, it appears that patients with non-Marfan-related familial thoracic aortic disease have similar clinical and demographic characteristics as sporadic cases. In addition, they may have higher growth rates and a worse long-term survival. Larger, prospective studies need to be performed in order to assess the true risk associated with a family history of thoracic aortic disease. Whole genome analysis of linkage using families with a significant number of living, affected individuals will likely be required in order to establish the nature of genetic risk in this population.

Our review of the natural history of thoracic aortic aneurysms prior to surgical repair permits the following conclusions. Thoracic aortic aneurysm is a lethal disease. Forty-six percent of patients with large aneurysms will die within 5 years. Aneurysm size has a profound impact on rupture, dissection, and death. For counseling purposes, the patient with an aneurysm exceeding 6 cm in diameter can expect a yearly rate of rupture or dissection of at least 6.4% and a death rate of 10.8% per year. Elective surgery eliminates the risk of rupture and restores survival to near normal. Elective surgical repair can be accomplished at a "cost" of less than a single year's expected natural mortality. Careful follow-up of patients with thoracic aortic aneurysms is essential, with pre-emptive extirpation before the dangerous diameter criterion of 6 cm. It is hoped that these data will permit concrete estimation of the natural history side of the balance of relative risks and benefits of medical management versus surgical intervention for specific patients.

REFERENCES

1. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture/dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2000; [in press].
2. Coady MA, Davies RR, Hammond GL, Kopf GS, Elefteriades JA. Familial inheritance of thoracic aortic aneurysms [abstract]. *Circulation* 1999; 98 Suppl S.
3. Coady MA, Davies RR, Hammond GL, Rizzo JA, Elefteriades JA. Familial patterns of thoracic aortic aneurysms [abstract]. *Transactions of the New England Surgical Society* 1998; 79.
4. Coady MA, Davies RR, Roberts M, et al. Familial patterns of thoracic aortic aneurysms. *Arch Surg* 1999; 134:361-7.
5. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Cell junctions, cell adhesion, and the extracellular matrix. *Molecular Biology of the Cell*. New York NY: Garland Publishing, 1994:949-1009.
6. Dobrin PB. Vascular mechanics. In: Shepherd JT, Abboud FM, eds. *The Cardiovascular System Handbook of Physiology*. Vol. 3. Washington, D.C.: American Physiological Society, 1983:65-102.
7. Dobrin PB. Mechanics of normal and diseased blood vessels. *Ann Vasc Surg* 1988; 2:283-294.
8. Barnes MJ. Collagens of normal and diseased blood vessel wall. In: Nimni ME, ed. *Collagen I Biochemistry*. Boca Raton, FL: CRC Press, 1988:271-291.
9. Kivirikko KI. Collagens and their abnormalities in a wide spectrum of diseases. *Ann Med* 1993; 25:113-26.
10. Pereira L, Andrikopoulos K, Tian J, et al. Targetting of the gene encoding fibrillin-1 recapitulates the vascular aspect of Marfan syndrome. *Nat Genet* 1997; 17:218-22.
11. Mecham RP, Davies E. Elastic fiber structure and assembly. In: Yurchenco PD, Birk DE, Mecham RP, eds. *Extracellular Matrix Assembly and Structure*. New York, NY: Academic Press, 1994:281-314.
12. Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent *de novo* missense mutation in the fibrillin gene. *Nature* 1991; 352:337-9.
13. Wolinsky H, Glagov S. A lamellar unit of aortic medial structure and function in mammals. *Circ Res* 1967; 20:99-111.
14. Wolinsky H, Glagov S. Comparison of abdominal and thoracic aortic medial structure in mammals. Deviation of man from the usual pattern. *Circ Res* 1969; 25:677-86.
15. Wolinsky H. Comparison of medial growth of human thoracic and abdominal aortas. *Circ Res* 1970; 27:531-8.
16. Coady MA, Rizzo JA, Goldstein LJ, Elefteriades JA. Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. *Cardiol Clin* 1999; 17:615-35; vii.
17. Dobrin PB. Mechanical properties of arteries. *Physiol Rev* 1978; 58:397-460.
18. Patel DJ, Greenfield JC, Fry PL. The in vivo pressure-length radius relationship to certain blood vessels in man and dog. In: Attinger O, ed. *Pulsatile Blood Flow*. New York, NY: McGraw-Hill, 1964.
19. Patel DJ, Janicki JS, Carew TE. Static anisotropic elastic properties of the aorta in living dogs. *Circ Res* 1969; 25:765-79.
20. Borst HG, Heinemann MK, Stone CD. Pathogenesis. In: Borst HG, Heinemann MK, Stone CD, eds. *Surgical Treatment of Aortic Dissection*. New York, NY: Churchill Livingstone, 1996:47-54.
21. Garfield RE, Chacko S, Blose S. Phagocytosis by muscle cells. *Lab Invest* 1975; 33:418-27.
22. White JV, Scovell SD. Etiology of abdominal aortic aneurysms: the structural basis for aneurysm formation. In: Calligaro KD, Dougherty MJ, Hollier LH, eds. *Diagnosis and Treatment of Aortic and Peripheral Arterial Aneurysms*. Philadelphia, PA: Saunders Co., 1999.
23. White JV. Role of adventitial defects in the pathogenesis of aortic aneurysms. In: Veith F, ed. *Current Critical Problems in Vascular Surgery*. Vol. 5. St. Louis, MO: Quality Medical Publishing, 1993:293-301.

24. Burton AC. Relation of structure to function of tissues of wall of blood vessels. *Physiol Rev* 1954; 34:619.
25. Wolinsky H, Glagov S. Structural basis for the static mechanical properties of the aortic media. *Circ Res* 1964; 14:400.
26. White JV, Mazzacco SL. Formation and growth of aortic aneurysms induced by adventitial elastolysis. *Ann N Y Acad Sci* 1996; 800:97-120.
27. Crawford ES, DeNatale RW. Thoracoabdominal aortic aneurysm - natural history and treatment. *J Thorac Cardiovasc Surg* 1986; 79:489-98.
28. Pitt MP, Bonser RS. The natural history of thoracic aortic aneurysm disease: an overview. *J Card Surg* 1997; 12:270-8.
29. Bickerstaff LK, Pairolero PC, Hollier LH, et al. Thoracic aortic aneurysms: a population-based study. *Surgery* 1982; 92:1103-8.
30. Ergin MA, Griepp RB. Dissections of the Aorta. In: Baue AE, Geha AS, Hammond GL, Laks H, Naunhelm KS, eds. *Glenn's Thoracic and Cardiovascular Surgery*. Norwalk, CT: Appleton & Lange, 1996:2273-2298.
31. Cooke JP, Kazmier FJ, Orszulak TA. The penetrating aortic ulcer: pathologic manifestations, diagnosis, and management. *Mayo Clin Proc* 1988; 63:718-25.
32. Stanson AW, Kazmier FJ, Hollier LH, et al. Penetrating atherosclerotic ulcers of the thoracic aorta: natural history and clinicopathologic correlations. *Ann Vasc Surg* 1986; 1:15-23.
33. Welch TJ, Stanson AW, Sheedy PFd, Johnson CM, McKusick MA. Radiologic evaluation of penetrating aortic atherosclerotic ulcer. *Radiographics* 1990; 10:675-85.
34. Coady MA, Rizzo JA, Elefteriades JA. Pathologic variants of thoracic aortic dissections. Penetrating atherosclerotic ulcers and intramural hematomas. *Cardiol Clin* 1999; 17:637-57.
35. Roberts WC. Aortic dissection: anatomy, consequences, and causes. *Am Heart J* 1981; 101:195-214.
36. Coady MA, Rizzo JA, Hammond GL, Pierce JG, Kopf GS, Elefteriades JA. Penetrating ulcer of the thoracic aorta: what is it? How do we recognize it? How do we manage it? *J Vasc Surg* 1998; 27:1006-15; discussion 1015-6.
37. Hirst AEJ, Johns VJ, Kime SWJ. Dissecting aneurysm of the aorta: A review of 505 cases. *Medicine* 1958; 37:217-271.
38. Sterpetti AV, Hunter WJ, Feldhaus RJ, al. e. Inflammatory aneurysms of the abdominal aorta: incidence, pathologic, and etiologic considerations. *J Vasc Surg* 1989; 9:643-650.
39. Goldstone J, Malone JM, Moore WS. Inflammatory aneurysm of the abdominal aorta. *Surgery* 1983; 83:425-430.
40. Sethia B, Darke SG. Abdominal aortic aneurysm with retroperitoneal fibrosis and ureteric entrapment. *Br J Surg*; 70:434-436.
41. Movat HZ, More RH, Haust MD. The diffuse internal thickening of the human aorta with aging. *Am J Pathol* 1958; 34:1023-1031.
42. Schlatmann TJM, Becker AE. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. *Am J Cardiol* 1977; 39:13-20.
43. Doll R, Peto R. Mortality in relation to smoking: 20 years observations in male British doctors. *BMJ* 1976; ii:1525-36.
44. Hammond EC, Garfinkel L. Coronary artery disease, stroke, and aortic aneurysm. Factors in etiology. *Arch Environ Health* 1969; 19:167-182.
45. Kahn H. The Dorn study of smoking and mortality among US veterans: report on 8.5 years of observation. *National Cancer Institute Monographs* 1966; 19:1-125.
46. George PM, Travis J, Vissers MCM, Winterbourn CC, Carrell RW. A genetically engineered mutant of alpha-1-antitrypsin protects connective tissue from neutrophil damage and may be useful in lung disease. *Lancet* 1984; ii:1426-1428.
47. Carrell RW. Alpha-1-antitrypsin: molecular pathology, leucocytes, and tissue damage. *J Clin Invest* 1986; 78:1427-1431.
48. Gardner RJ, Lancaster JR, Tarnay TJ, Warden HE, Currie RA. Five year history of surgically treated abdominal aortic aneurysms. *Surg Gynecol Obstet* 1970; 130:981-7.
49. Gwathmey O, Adkins PC, Blades B. Emergency and elective treatment of abdominal aortic aneurysms. *Postgrad Med J* 1959; 25:677-684.

50. Gore I, Hirst AE, Jr. Arteriosclerotic aneurysms of the abdominal aorta: a review. *Progress in Cardiovascular Diseases* 1973; 16:113-50.
51. Cronenwett JL, Murphy TF, Zelencock GB, al. e. Actuarial analysis of variables associated with rupture of small aortic aneurysms. *Surgery* 1985; 98:472-483.
52. Cronenwett JL, Sargent SK, Wall MH, et al. Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg* 1990; 11:260-8; discussion 268-9.
53. MacSweeney ST, Powell JT, Greenhalgh RM. Pathogenesis of abdominal aortic aneurysm. *Br J Surg* 1994; 81:935-41.
54. Osler W. Aneurysm of the abdominal aorta. *Lancet* 1905; 2:1089-1096.
55. Maniglia R, Gregory JE. Increasing incidence of arteriosclerotic aortic aneurysms. Analysis of six thousand autopsies. *Arch Pathol* 1952; 54:298-305.
56. Svensjo S, Bengtsson H, Bergqvist D. Thoracic and thoracoabdominal aortic aneurysm and dissection: an investigation based on autopsy. *Br J Surg* 1996; 83:68-71.
57. Pressler V, McNamara JJ. Thoracic aortic aneurysm: natural history and treatment. *J Thorac Cardiovasc Surg* 1980; 79:489-98.
58. DeBakey ME, Noon GP. Aneurysms of the thoracic aorta. *Mod Concepts Cardiovasc Dis* 1975; 44:53-8.
59. Joyce JW, Fairbairn J, Kincaid OW, al. e. Aneurysms of the thoracic aorta - A clinical study with special reference to prognosis. *Circulation* 1964; 29:176-181.
60. Cambria RA, Gloviczki P, Stanson AW, et al. Outcome and expansion rate of 57 thoracoabdominal aortic aneurysms managed nonoperatively. *Am J Surg* 1995; 170:213-7.
61. Dapunt OE, Galla JD, Sadeghi AM, et al. The natural history of thoracic aortic aneurysms. *J Thorac Cardiovasc Surg* 1994; 107:1323-32; discussion 1332-3.
62. Rizzo JA, Darr U, Fischer M, et al. Multi-modality serial follow-up of thoracic aortic aneurysms. *Int J Angiol* 1997; 6:153-156.
63. Hirose Y, Hamada S, Takamiya M, Imakita S, Naito H, Nishimura T. Aortic aneurysms: growth rates measured with CT. *Radiology* 1992; 185:249-52.
64. Masuda Y, Takanashi K, Takasu J, Morooka N, Inagaki Y. Expansion rate of thoracic aortic aneurysms and influencing factors. *Chest* 1992; 102:461-6.
65. Juvonen T, Ergin MA, Galla JD, et al. Prospective study of the natural history of thoracic aortic aneurysms. *Ann Thorac Surg* 1997; 63:1533-45.
66. Coady MA, Rizzo JA, Hammond GL, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg* 1997; 113:476-91.
67. Darling RC. Ruptured arteriosclerotic abdominal aortic aneurysms. A pathologic and clinical study. *Am J Surg* 1970; 119:397-401.
68. Cronenwett JL. Variables that affect the expansion rate and rupture of abdominal aortic aneurysms. *Ann N Y Acad Sci* 1996; 800:56-67.
69. Szilagyi DE, Elliott JP, Smith RF. Clinical fate of the patient with asymptomatic abdominal aortic aneurysm and unfit for surgical treatment. *Arch Surg* 1972; 104:600-6.
70. Foster JH, Bolasny BL, Gobbel WG, Jr., Scott HW, Jr. Comparative study of elective resection and expectant treatment of abdomianl aortic aneurysm. *Surg Gynecol Obstet* 1969; 129:1-9.
71. Sterpetti AV, Cavallaro A, Cavallari N, et al. Factors influencing the rupture of abdominal aortic aneurysms. *Surg Gynecol Obstet* 1991; 173:175-8.
72. Strachan DP. Predictors of death from aortic aneurysm among middle-aged men: the Whitehall study. *Br J Surg* 1991; 78:401-4.
73. Boyd LJ. A study of four thousand reported cases of aneurysm of the thoracic aorta. *Am J Med Sci* 1924; 168:654-668.
74. Johansson G, Markstrom U, Swedenborg J. Ruptured thoracic aortic aneurysms: a study of incidence and mortality rates. *J Vasc Surg* 1995; 21:985-8.
75. Kampmeier RH. Saccular aneurysm of the thoracic aorta: a clinical study of 633 cases. *Ann Intern Med* 1938; 12:624-651.
76. Masuda Y, Takanashi K, Takasu J, et al. Unoperated thoracic aortic aneurysms: survival rates of the patients and determinants of prognosis. *Intern Med* 1992; 31:1088-93.

77. Kouchoukos NT. Aneurysms of the ascending aorta. In: Baue AE, Geha AS, Hammond GL, Laks H, Naunhelm KS, eds. *Glenn's Thoracic and Cardiovascular Surgery*. Norwalk, CT: Appleton & Lange, 1996:2225-2237.
78. Majumder PP, St. Jean PL, Ferrell RE, Webster MW, Steed DL. On the inheritance of abdominal aortic aneurysm. *Am J Hum Genet* 1991; 48:164-70.
79. LaRoy LL, Cormier PJ, Matalon TA, Patel SK, Turner DA, Silver B. Imaging of abdominal aortic aneurysms. *AJR Am J Roentgenol* 1989; 152:785-92.
80. Clouse WD, Hallett JW, Jr., Schaff HV, Gayari MM, Ilstrup DM, Melton LJ, 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA* 1998; 280:1926-9.
81. Lilienfeld DE, Gunderson PD, Sprafka JM, Vargas C. Epidemiology of aortic aneurysms: I. Mortality trends in the United States, 1951 to 1981. *Arteriosclerosis* 1987; 7:637-43.
82. Svensson LG, Crawford ES. Aortic dissection and aortic aneurysm surgery: clinical observations, experimental investigations, and statistical analyses. Part II. *Curr Probl Surg* 1992; 29:913-1057.
83. Waller BF, Catellier MJ, Clark MA, Hawley DA, Pless JE. Cardiac pathology in 2007 consecutive forensic autopsies. *Clin Cardiol* 1992; 15:760-5.
84. Pressler V, McNamara JJ. Aneurysm of the thoracic aorta. Review of 260 cases. *J Thorac Cardiovasc Surg* 1985; 89:50-4.
85. Crawford ES, DeNatale RW. Thoracoabdominal aortic aneurysm: observations regarding the natural course of the disease. *J Vasc Surg* 1986; 3:578-82.
86. Cohn LH, Rizzo RJ, Adams DH, et al. Reduced mortality and morbidity for ascending aortic aneurysm resection regardless of cause. *Ann Thorac Surg* 1996; 62:463-8.
87. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome [see comments]. *N Engl J Med* 1994; 330:1335-41.
88. Groenink M, de Roos A, Mulder BJ, Spaan JA, van der Wall EE. Changes in aortic distensibility and pulse wave velocity assessed with magnetic resonance imaging following beta-blocker therapy in the Marfan syndrome. *Am J Cardiol* 1998; 82:203-8.
89. Collod-Beroud G, Beroud C, Ades L, et al. Marfan database (third edition): new mutations and new routines for the software. *Nucleic Acids Res* 1998; 26:229-33.
90. De Paepe AD, Devereux RB, Dietz HC, Hennekam RCM, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996; 62:417-26.
91. Tsipouras P, Devereux RB. Marfan syndrome: genetic basis and clinical manifestations. *Semin Dermatol* 1993; 12:219-28.
92. Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. *N Engl J Med* 1979; 300:772-7.
93. Tsipouras P, Silverman DI. The genetic basis of aortic disease. Marfan syndrome and beyond. *Cardiol Clin* 1999; 17:683-96.
94. Aoyama T, Francke U, Gasner C, Furthmayr H. Fibrillin abnormalities and prognosis in Marfan syndrome and related disorders. *Am J Med Genet* 1995; 58:169-76.
95. Davies MJ, Treasure T, Richardson PD. The pathogenesis of spontaneous arterial dissection. *Heart* 1996; 75:434-5.
96. Dietz HC. New insights into the genetic basis of aortic aneurysms. In: Schoen FJ, Gimbrone MA, eds. *Monographs in Pathology: Cardiovascular Pathology, Clinicalpathologic Correlations and Pathogenetic Mechanisms*. Vol. 37. Baltimore: Williams and Wilkins, 1995:144-55.
97. Herskowitz I. Functional inactivation of genes by dominant negative mutations. *Nature* 1987; 329:219-22.
98. Chakravorty B, Gleadhill CA. Familial incidence of cerebral aneurysms. *BMJ* 1966; 5480:147-8.
99. Tilson MD, Seashore MR. Fifty families with abdominal aortic aneurysms in two or more first-order relatives. *Am J Surg* 1984; 147:551-3.
100. Norrgard O, Rais O, Angquist KA. Familial occurrence of abdominal aortic aneurysms. *Surgery* 1984; 95:650-6.
101. Tilson MD, Seashore MR. Human genetics of the abdominal aortic aneurysm. *Surg Gynecol Obstet* 1984; 158:129-32.

102. Johansen K, Koepsell T. Familial tendency for abdominal aortic aneurysms. *JAMA* 1986; 256:1934-6.
103. Powell JT, Greenhalgh RM. Multifactorial inheritance of abdominal aortic aneurysm. *Eur J Vasc Surg* 1987; 1:29-31.
104. Nicod P, Bloor C, Godfrey M, et al. Familial aortic dissecting aneurysm. *J Am Coll Cardiol* 1989; 13:811-9.
105. Hanley WB, Jones NB. Familial dissecting aortic aneurysm. A report of three cases within two generations. *Br Heart J* 1967; 29:852-8.
106. Toyama M, Amano A, Kameda T. Familial aortic dissection: a report of rare family cluster. *Br Heart J* 1989; 61:204-7.
107. Biddinger A, Rocklin M, Coselli J, Milewicz DM. Familial thoracic aortic dilatations and dissections: a case control study. *J Vasc Surg* 1997; 25:506-11.
108. Milewicz DM, Michael K, Fisher N, Coselli JS, Markello T, Biddinger A. Fibrillin-1 (FBN1) mutations in patients with thoracic aortic aneurysms. *Circulation* 1996; 94:2708-2711.
109. Francke U, Berg MA, Tynan K, et al. A Gly1127Ser mutation in an EGF-like domain of the fibrillin-1 gene is a risk factor for ascending aortic aneurysm and dissection. *Am J Hum Genet* 1995; 56:1287-96.
110. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med* 1972; 286:804-8.
111. Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol* 1995; 75:157-60.
112. von Kodolitsch Y, Simic O, Nienaber CA. Aneurysms of the ascending aorta: diagnostic features and prognosis in patients with Marfan's syndrome versus hypertension. *Clin Cardiol* 1998; 21:817-24.
113. Darling RCI, Brewster DC, Darling RC, et al. Are familial abdominal aortic aneurysms different? *J Vasc Surg* 1989; 10:39-43.
114. Webster MW, St. Jean PL, Steed DL, Ferrell RE, Majumder PP. Abdominal aortic aneurysms: results of a family study. *J Vasc Surg* 1991; 13:366-72.
115. Rutherford RB, Flanigan DP, Gupta SK, et al. Suggested standards for reports dealing with lower extremity ischemia. *J Vasc Surg* 1986; 4:80-94.
116. Dinsmore RE, Liberthson RR, Wismer GL, et al. Magnetic resonance imaging of thoracic aortic aneurysms: comparison with other imaging methods. *AJR Am J Roentgenol* 1986; 146:309-14.
117. Goldstein LJ, Davies RR, Davila JJ, et al. Stroke in thoracic aortic surgery: incidence, impact,, etiology, and prevention. *J Thorac Cardiovasc Surg* 2001; [in press].
118. Rizzo JA, Coady MA, Elefteriades JA. Procedures for estimating growth rates in thoracic aortic aneurysms. *J Clin Epidemiol* 1998; 51:747-54.
119. Rizzo JA, Coady MA, Elefteriades JA. Interpreting data on thoracic aortic aneurysms. Statistical issues. *Cardiol Clin* 1999; 17:797-805, x.
120. Sambrook J, Fritsch EF, Maniatis T. Molecular cloning. A laboratory manual. Vol. 2. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 1989.
121. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* 1996; 58:1347-63.
122. Milewicz DM, Chen H, Park E-S, et al. Reduced penetrance and variable expressivity of familial thoracic aortic aneurysms/dissections. *Am J Cardiol* 1998; 82:474-9.

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