Natural history of descending thoracic and thoracoabdominal aortic aneurysms

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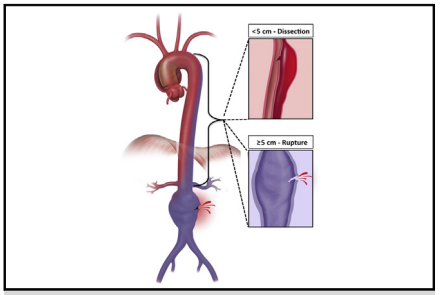
ABSTRACT

Objectives: Elucidating critical aortic diameters at which natural complications (rupture, dissection, and death) occur is of paramount importance to guide timely surgical intervention. Natural history knowledge for descending thoracic and thoracoabdominal aortic aneurysms is sparse. Our small early studies recommended repairing descending thoracic and thoracoabdominal aortic aneurysms before a critical diameter of 7.0 cm. We focus exclusively on a large number of descending thoracic and thoracoabdominal aortic aneurysms followed over time, enabling a more detailed analysis with greater granularity across aortic sizes.

Methods: Aortic diameters and long-term complications of 907 patients with descending thoracic and thoracoabdominal aortic aneurysms were reviewed. Growth rates (instrumental variables approach), yearly complication rates, 5-year event-free survival (Kaplan–Meier), and risk of complications as a function of aortic height index (aortic diameter [centimeters]/height [meters]) (competing-risks regression) were calculated.

Results: Estimated mean growth rate of descending thoracic and thoracoabdominal aortic aneurysms was 0.19 cm/year, increasing with increasing aortic size. Median size at acute type B dissection was 4.1 cm. Some 80% of dissections occurred below 5 cm, whereas 93% of ruptures occurred above 5 cm. Descending thoracic and thoracoabdominal aortic aneurysm diameter 6 cm or greater was associated with a 19% yearly rate of rupture, dissection, or death. Five-year complication-free survival progressively decreased with increasing aortic height index. Hazard of complications showed a 6-fold increase at an aortic height index of 4.2 or greater compared with an aortic height index of 3.0 to 3.5 ($P < .05$). The probability of fatal complications (aortic rupture or death) increased sharply at 2 hinge points: 6.0 and 6.5 cm.

Conclusions: Acute type B dissections occur frequently at small aortic sizes; thus, prophylactic size-based surgery may not afford a means for dissection protection. However, fatal complications increase dramatically at 6.0 cm, suggesting that preemptive intervention before that criterion can save lives. (J Thorac Cardiovasc Surg 2021;161:498-511)



The descending thoracic/thoracoabdominal aorta tends to dissect below and rupture above 5 cm.

CENTRAL MESSAGE

The risk of fatal complications increases dramatically at 6.0 cm in patients with DTTAAs. Preemptive intervention before this size can save lives.

PERSPECTIVE

Natural history knowledge guiding timely prophylactic surgical intervention in patients with DTTAAs is sparse. We find that size thresholds for operative repair in current guidelines do not protect from acute type B dissection. Preemptive operation at a DTTAA size of 5.0 to 5.5 cm can protect from fatal complications (rupture and aortic death).

See Commentaries on pages 512 and 514.

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Abbreviations and Acronyms

AAE = adverse aortic event
AHI = aortic height index
DTTAA = descending thoracic and thoracoabdominal aortic aneurysm
IQR = interquartile range
MRI = magnetic resonance imaging
TAA = thoracic aortic aneurysm

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The normal diameter of the descending thoracic aorta is 2.5 ± 0.2 cm in men and 2.2 ± 0.2 cm in women, with a 1- to 2-mm and 3- to 4-mm decrease in size in both sexes at the diaphragm and infrarenal portion, respectively.[1]

Elucidating the critical size of the descending thoracic and thoracoabdominal aorta at which life-threatening natural complications occur (aortic rupture, aortic dissection, or death, herein termed "adverse aortic events" [AAEs]) is of paramount importance to guide timely prophylactic open or endovascular surgical repair.

Our early thoracic aortic aneurysm (TAA) natural history studies included only a small component of descending and thoracoabdominal aortic aneurysms (DTTAAs). In those studies, we demonstrated a significant increase in the rates of aortic rupture and dissection at a descending thoracic aortic size of 7 cm.[2,3] Accordingly, we advocated operative repair at 6.5 cm.[3] Currently, international guidelines recommend preemptive surgical intervention at an absolute aortic diameter of 5.5 cm to 6.0 cm for DTTAAs.[4,5] However, recent studies have shown that the risk of AAEs in patients with DTTAAs increases at aortic sizes below this guideline-recommended threshold.[6-9] Also, in the years since our early studies, advances in the conduct of open thoracic and thoracoabdominal surgery and the advent of endovascular techniques have increased the safety of intervention for DTTAA.

We have recently provided an update on the natural history of ascending TAAs based on larger patient cohorts compared with our early reports.[10] We aim to do the same for DTTAAs. We focus exclusively on a large number of DTTAAs followed over time, thereby enabling a more detailed analysis with greater granularity across a range of aortic sizes.

MATERIALS AND METHODS

This investigation was approved by the Human Investigation Committee of the Yale University School of Medicine.

Patients

Our database at the Aortic Institute at Yale-New Haven Hospital currently includes 3914 patients with thoracic aortic disease. Among these, for the purpose of our natural history studies, 2384 patients with TAA (ascending or descending) or acute aortic dissection (ascending or descending) comprise a subset in whom all radiologic studies have been re-verified, re-read, and re-analyzed in a standardized manner.[11] Anthropometric, radiologic, and clinical data were manually accrued retrospectively from individual electronic medical records and hospital charts. To permit focused evaluation of the natural history of TAA, we have excluded intramural hematomas, penetrating atherosclerotic aortic ulcers, iatrogenic aortic dissections, Stanford Type A and Type B dissections already chronic at the time of presentation to our center, congenital aortic malformations, and traumatic aortic lesions.

Of these 2384 patients, 907 comprised our study group of descending and thoracoabdominal aneurysms. For inclusion in our study, the descending thoracic aorta needed to exceed 3 cm in diameter. No isolated abdominal aortic aneurysms were included in this study. In our dataset, the occurrence of a descending thoracic aorta less than 3 cm, with an abdominal aortic segment greater than 3 cm, was 0. Thus, these were DTTAAs. In the thoracoabdominal aortic aneurysms, both the descending thoracic and abdominal aortas were greater than or equal to 3 cm in diameter. These patients may have initially entered our database for ascending or descending aortic pathology, or both. These patients had a median radiologic follow-up of 5.7 years (interquartile range [IQR], 2.8-10.1). This cohort includes all descending thoracic and thoracoabdominal aortas 3 cm or greater, inclusive of fusiform, saccular, and thoracoabdominal aneurysms, as well as ectatic descending thoracic aortas that are in the database because of the presence of concomitant ascending aortic dilation. To achieve a more generally representative cohort, we excluded patients with Marfan, Ehlers–Danlos, and Loeys–Dietz syndromes. These syndromic patients numbered 15 in total, and their exclusion did not affect calculations substantially. Additional patient characteristics are listed in Table 1.

The Yale Aortic Institute method for survival analysis, entailing, in addition to clinical follow-up, an additional 4-pronged approach (online database mortality query, hospital IT system clinical and mortality query, referring doctor follow-up, and online obituary search), was used to accomplish long-term follow-up.[12] The follow-up period for analysis for patients who were lost to follow-up (53/907, 5.8%) ended at the date of last proven clinical contact. Exhaustive efforts were undertaken to augment survival follow-up with information from state-issued death certificates, which were obtained and analyzed to ascertain the precise cause of death for each patient. Death certificates were obtained for 141 of the 289 (49%) deceased patients, whereas a confirmed cause of death was obtained from the other aforementioned sources for the remaining 148 patients (51%).

Aortic deaths included "definite" and "possible" descending thoracic and thoracoabdominal aortic–related deaths, per the classification proposed by Lederle and colleagues.[13] Definite aortic deaths included those due to aortic dissection or aortic rupture, as confirmed by radiologic imaging, operation, autopsy, or a death certificate. Possible descending thoracic and thoracoabdominal aortic deaths included patients presenting with symptoms of impending rupture but without objective confirmation of rupture, sudden deaths not due to another cause, and cardiac deaths in which dissection or rupture were not ruled out that were not due to any other "cardiac" cause such as coronary artery disease or heart failure. The detailed cause of death breakdown is provided in Table 2.

ADULT

TABLE 1. Patient characteristics

Variables	Mean (SD)/No. (%)
Age (mean, SD)	68.15 (11.68)
Height (mean, SD)	172.86 (11.92)
Weight (mean, SD)	85.23 (21.75)
Male (%)	615 (67.8)
Family history (%)	
None	443 (48.8)
Proven	152 (16.8)
Likely	43 (4.7)
Possible	46 (5.1)
Unknown	223 (24.6)
Past surgeries (%)	129 (14.2)
Hypertension (%)	568 (62.6)
Smoking (%)	
Unknown	335 (36.9)
Nonsmoker	182 (20.1)
Current/past smoker	385 (43.0)
Dyslipidemia (%)	324 (35.7)
COPD (%)	132 (14.6)
Diabetes mellitus (%)	85 (9.4)
Autoimmune (%)	61 (6.7)
CAD	241 (26.6)
Steroid use (%)	28 (3.1)
Stroke (%)	64 (7.1)
Active malignancy (%)	58 (6.4)
Bovine arch (%)	124 (13.7)
Thoracoabdominal aneurysm (%)	137 (15.1)
Descending TAA (%)	652 (68.9)
Concomitant ascending aortic dilation	
4-4.9 cm	318 (35.1)
≥5 cm	369 (40.7)
AHI (cm/m)	Median, 2.06; IQR, 1.81-2.79

SD, Standard deviation; *COPD*, chronic obstructive pulmonary disease; *CAD*, coronary artery disease; *TAA*, thoracic aortic aneurysm; *AHI*, aortic height index.

TABLE 2. Detailed breakdown of causes of death

Causes	No. (%)
Definite descending aortic*	46 (15.9)
Possible descending aortic†	41 (14.2)
Ascending aortic	21 (7.3)
Perioperative, descending‡	15 (5.2)
Abdominal aortic	6 (2.1)
Descending rupture after repair§	1 (0.3)
Cardiac‖	39 (13.5)
Cancer	27 (9.3)
Respiratory failure	23 (8.0)
Sepsis	11 (3.8)
Dementia	11 (3.8)
Renal failure	10 (3.5)
Multisystem organ failure	8 (2.8)
Intracranial hemorrhage	7 (2.4)
Stroke	7 (2.4)
Gastrointestinal bleed	5 (1.7)
Trauma	5 (1.7)
Pulmonary embolism	2 (0.7)
Liver failure	2 (0.7)
Peripheral vascular disease	1 (0.3)
Encephalopathy	1 (0.3)
Total	289

*Descending aortic dissection or rupture confirmed by imaging, intraoperatively, autopsy, or death certificate. †Sudden death not due to another cause, death after symptomatic presentation, cardiac death without rule out of dissection, or rupture not due to any other cardiac cause. ‡Death due to complications from elective descending thoracic/thoracoabdominal aortic repair. §This patient had a successful elective descending thoracic aortic repair, but a more distal segment ruptured years later. ||Death due to heart failure or coronary artery disease with rule out of dissection or rupture.

DTTAA repair, aortic rupture, acute flap-type Stanford Type B aortic dissection, and death were end points for this study, at which time we ceased charting the natural history of the descending thoracic/thoracoabdominal aorta.

A patient was considered to have a positive family history of TAA if a relative or relatives of the patient had a TAA or aortic dissection confirmed on an imaging study (computed tomography, magnetic resonance imaging [MRI], transthoracic echocardiography, or transesophageal echocardiography), intraoperatively, or on autopsy.

Aortic Imaging

All aortic diameter measurements were doubly confirmed by 2 senior investigators. Official reports from the Department of Radiology at Yale-New Haven Hospital were also consulted. In the event of a discrepancy, scans were reevaluated in a core meeting. All reports lacking accompanying images for our specific review were strictly excluded from the study.

Computed tomography and MRI scans were analyzed to determine aortic sizes. Serial measurements were performed (perpendicular to the long axis of the aorta) at the site of maximal dilation and at the identical level and orientation in sequential scans.[11] Aortic rupture and acute flap-type aortic dissection were confirmed by echocardiography, computed tomography, MRI, autopsy, or operation. A bovine aortic arch was defined as the union of the innominate and left carotid arteries cranial to the plane of the greater curvature of the aortic arch.[14]

Statistical Methods

Statistical analysis and data visualization were performed using R 3.5.1 (R foundation for Statistical Computing, Vienna, Austria) and Excel (Windows Excel 2016, Microsoft, Redmond, Wash).

For continuous variables, the normally distributed data are expressed as the mean ± standard deviation or median with IQR for the skewed data. Continuous data were evaluated for normality using Kolmogorov–Smirnov test. Categoric variables are presented as frequencies with percentages and analyzed by chi-square test or Fisher exact test, as appropriate. Student *t* test was used for normally distributed variables and Mann–Whitney *U* test for non-normally distributed variables.

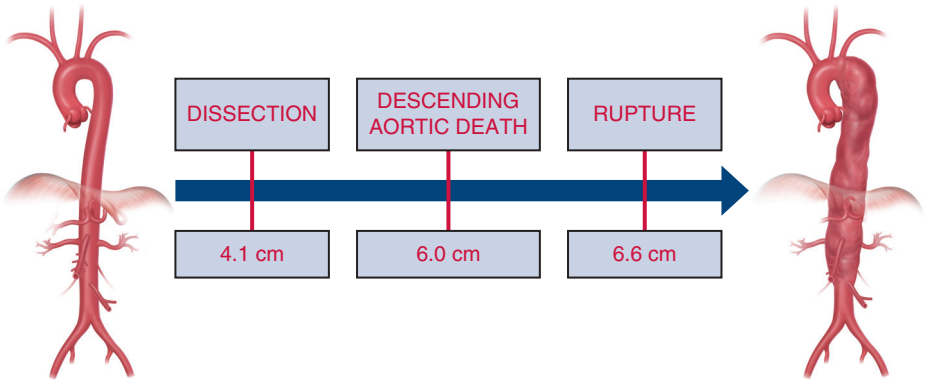


FIGURE 1. Median maximal descending thoracic/thoracoabdominal aortic size at natural complications (acute type B dissection, descending aortic death, and acute aortic rupture). Dissection and rupture occur at different sizes in the descending aorta: dissection in the 4-cm range and rupture in the 6-cm range.

Aortic height index (AHI) was defined as $AHI = \frac{Aortic\ \ Diameter\ \ (cm)}{Height\ \ (m)}$. The AHI was discretized into 6 groups to assess the rate of adverse events at different aortic sizes: less than 1.8; 1.8 to 2.3; 2.4 to 2.9; 3 to 3.5; 3.6 to 4.1; 4.2 or more cm/m. This stratification was based on the distribution of the index to guarantee easy interpretation and a sufficient number of observations within each category, keeping in mind potential patient clinical triage considerations. We tested for nonlinearities with respect to AHI using spline regression and found no evidence of nonlinearities.

DTTAA growth rate estimates were performed using the instrumental variables approach.[15] This approach is designed to mitigate problems of measurement errors inherent in traditional estimates of TAA growth. Briefly, TAAs are assumed to grow at an exponential rate over time. The key idea is to relate a term involving measurement error (size measurement) to one involving little or no measurement error (time measurement, T). The equation illustrating the assumed relationship for aneurysm growth is as follows:

$$\ln(last\ aortic\ size\ measurement) - ln(first\ aortic\ size\ measurement) = \beta_0 \times \mathrm{T} + \beta_1 \times Age \times T \times \beta_2 \times Sex \times T$$

β is estimated using ordinary least squares regression and relates the time interval between diagnostic imaging tests to aneurysm growth.[15] This equation is estimated with no intercept term because as T approaches 0 it must be the case that the first and last sizes converge. Patient age, sex, family history of TAAs, history of cardiac surgery, hypertension, smoking, dyslipidemia, chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, stroke, concurrent active malignancy, autoimmune disease, steroid use, and bovine aortic arch configuration were included in the multivariable linear regression analysis to determine their effect on growth rate. The maximal size of the DTTAA at any level was taken as the aortic "size" for all AAE analyses.

The average annual rate of AAEs (rupture, dissection, and aortic death, in varying combinations) was calculated by number of occurrences over the average duration of observations within each specific size range as follows:

$$Yearly\ Rate_{(Within\ a\ specified\ aortic\ size\ range)} = \frac{\frac{Total\ \ Number\ \ of\ \ Events}{Total\ \ Number\ \ of\ \ Aneurysms}}{Average\ \ Observation\ period\ (Follow{-}up)\ for\ the\ Total\ Number\ of\ Aneurysms}$$

Risk stratification as a function of the AHI was based on the yearly risk of rupture and death and was calculated through the average of the predicted 5-year risk via the Cox proportional hazard model. Complication-free survival was estimated using a Kaplan–Meier analysis and compared with the log-rank test.

The predicted probability for risk of fatal complications (rupture or aortic death) was created from logistic regression and aortic size, age, and sex were included in the analysis. The increase in the risk of rupture and death as a function of aortic size was analyzed. The aortic size groups were divided with 0.5-cm breakdown points (3.0-3.4, 3.5-3.9, 4.0-4.4, 4.5-4.9, 5.0-5.4, 5.5-5.9, 6.0-6.4, 6.5-6.9, and $\geq$7.0), and 4.0 to 4.5 cm was set as the comparison group.

We performed competing-risks regression with Fine–Gray model analysis to explore the effect of AHI on AAE, with 3.0 to 3.5 cm/m as the reference group, controlling for age and sex.

To investigate the risk factors for acute flap type Stanford Type B aortic dissection in the setting of a moderately dilated aorta, dissections were classified into 3 groups (<3.5, 3.5-5, and $\geq$5 cm) and then analyzed with analysis of variance or Wilcoxon rank-sum test.

RESULTS

Aortic Size Distribution Before an End Point and Growth Rates

The median DTTAA size in centimeters before dissection, operation, aortic death, and rupture was 4.1 (IQR, 3.7-4.7), 5.8 (IQR, 4.6-6.6), 6.0 (IQR, 4.7-7.0), and 6.6 (IQR, 5.7-6.9), respectively (Figure 1).

The mean estimated annual growth rate of the DTTAA computed via the instrumental variables approach was 0.19 $\pm$ 0.07 cm/year. The larger the aneurysm, the faster it grew. A 4-cm DTTAA grew at a rate of 0.22 cm/year compared with an 8-cm aneurysm that grew at 0.42 cm/year

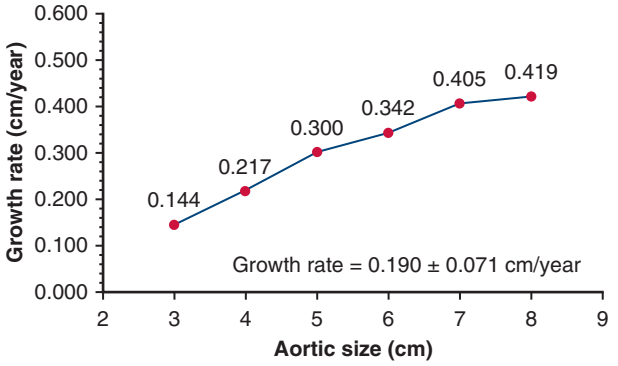


FIGURE 2. Mean yearly growth rate of the descending thoracic and thoracoabdominal aorta based on initial aneurysm size. The larger the aneurysm, the faster it grew.

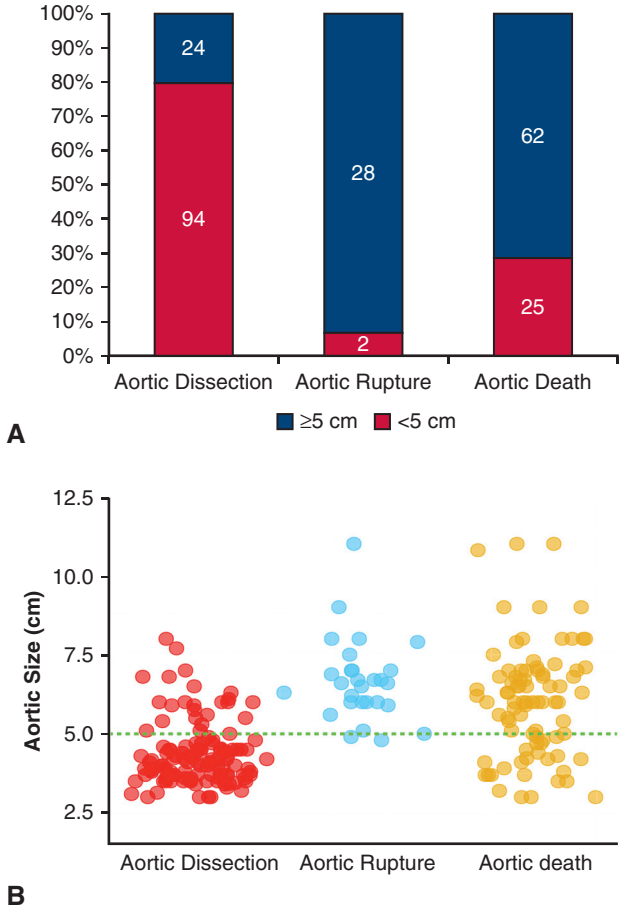


FIGURE 3. Distribution of AAEs (rupture, dissection, and aortic death) above and below a descending thoracic/thoracoabdominal aortic diameter of 5 cm. As depicted in the bar graph and scatter diagram, the majority of acute type B dissections occurred at aortic sizes below 5 cm, whereas the majority of aortic ruptures occurred above 5 cm.

(Figure 2). Multivariable linear regression analysis of the factors affecting growth rate revealed that patient age and chronic obstructive pulmonary disease were associated with a higher growth rate, whereas male sex and bovine aortic arch were associated with a slower growth rate (Table E3) ($P < .05$).

Adverse Aortic Event Rates (Dissection, Rupture, Death) and Complication-Free Survival

There were a total of 289 all-cause deaths among the 907 patients, of which 87 were DTTAA related (46 definite, 41 possible), 27 were deaths due to other aortic causes (ascending and abdominal aortic deaths), and 175 were nonaortic, as confirmed by medical records and death certificates (Table 2).

The distribution of AAEs (rupture, dissection, death) at various DTTAA size ranges is depicted in Table 3 and Figure 3, *A* and *B*. Some 80% (94/118) of acute Stanford Type B dissections occurred at aortic sizes below 5 cm, whereas 93% (28/30) of aortic ruptures occurred at aortic sizes above 5 cm (Table 3 and Figure 3, *A* and *B*). Some 71% (62/87) of aortic deaths occurred above a DTTAA size of 5 cm (Table 3 and Figure 3, *A* and *B*).

The average annual rates of AAEs stratified by aortic size are depicted in Figure 4, demonstrating the impact of increasing DTTAA size on complication rates. The yearly risk of an acute type B dissection was greatest below the 5-cm range and elevated in the 6- to 6.4-cm range. The yearly risk of rupture began to increase in the 5.5- to 5.9-cm range and was greatest in the 6.5- to 6.9-cm range. The risk of aortic death increased incrementally with increasing aortic size, with a sharp increase at 6 cm.

TABLE 3. Distribution of adverse aortic events stratified by aortic size

	Dissection	Rupture	Death
Aortic size (cm)			
3-3.9	48	0	12
4-4.9	46	2	13
5-5.9	11	4	11
6-6.9	10	13	28
≥7	3	11	23
Total	118	30	87

Kaplan–Meier AAE-free survival as a function of the AHI is depicted in Figure 5, *A* and *B*, demonstrating the deleterious effect of DTTAA size on longevity. Larger AHIs were associated with decreased AAE-free survival probability: The 1- and 5-year freedom from AAE were 98.5%, 87.5%, 69.3%, 84.3%, 52.6%, and 49%, and 95.9%, 87.1%, 64.3%, 56.5%, 27.1%, and 26.1% for AHIs (cm/m) less than 1.8, 1.8 to 2.3, 2.4 to 2.9, 3 to 3.5, 3.6 to 4.1, and 4.2 or greater, respectively (Figure 5, *A*). The 1- and 5-year freedom from a composite end point of rupture and aortic death were 99.5%, 98.7%, 87.9%, 90.5%, 59.6%, and 50%, and 96.9%, 98.2%, 81.6%,

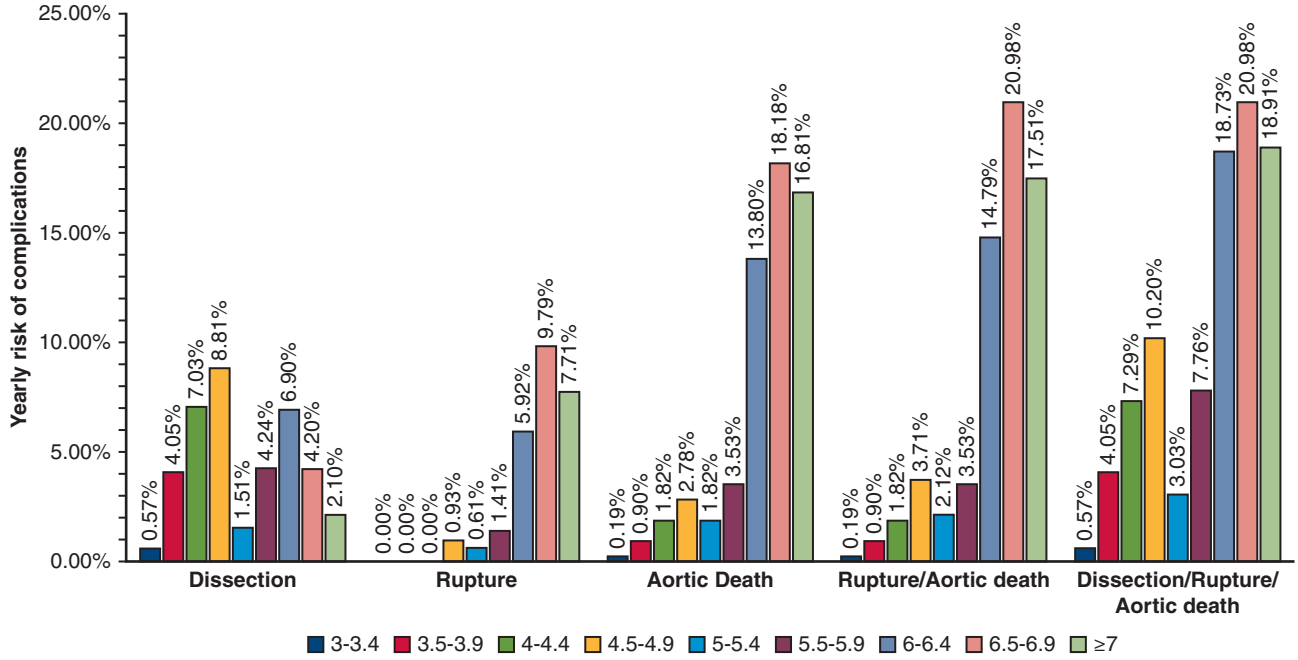


FIGURE 4. Yearly rates of AAEs (acute type B dissection, acute aortic rupture, and descending aortic death, each alone and a composite of rupture and aortic death, and acute type B dissection, acute aortic rupture, and descending aortic death) stratified by descending thoracic/thoracoabdominal aortic size. The overall impact of increasing descending aortic aneurysm size on yearly complication rates is shown. The yearly rate of acute type B dissection was greatest below 5 cm, whereas the risk of rupture and death increased markedly at a size of 6 cm.

60.6%, 30.5%, and 26.7% for AHIs (cm/m) less than 1.8, 1.8 to 2.3, 2.4 to 2.9, 3 to 3.5, 3.6 to 4.1, and 4.2 or greater, respectively (Figure 5, *B*).

Stratified by AHI, the competing-risk regression model revealed an approximately 3-fold increased hazard of AAEs at an AHI of 4.2 cm/m or greater compared with an AHI of 3.0 to 3.5 cm/m ($P < .05$) (Table 4).

The increase in probability of rupture and death as a function of aortic size relative to the 4- to 4.5-cm cohort is depicted in Figure 6. A sharp increase in the risk was observed at 6.0 cm ($P = .014078$) and another at 6.5 cm ($P = .00035$).

Risk Stratification Based on Aortic Height Index

On the basis of the AHI, patients were stratified into 4 categories of yearly risk of a combined end point of rupture and aortic death (Figure 7, *A*). AHIs 2.42 or less, 2.43 to 3.18, 3.21 to 4.00, and 4.05 or greater are associated with yearly risks of less than 2%, 2% to 4%, 4% to 8%, and greater than 8%, respectively. Figure 7, *B* is a similar nomogram but with rupture and all-cause death as an end point.

Characteristics of Patients With Acute Stanford Type B Dissection by Aortic Size

Analysis of acute Stanford Type B aortic dissections in 3 aortic size ranges (<3.5, 3.5-5, and ≥5 cm) revealed a trend of dissections at smaller aortic sizes occurring in significantly younger patients with lower AHIs and a greater prevalence of hypertension ($P < .05$) (Table 5).

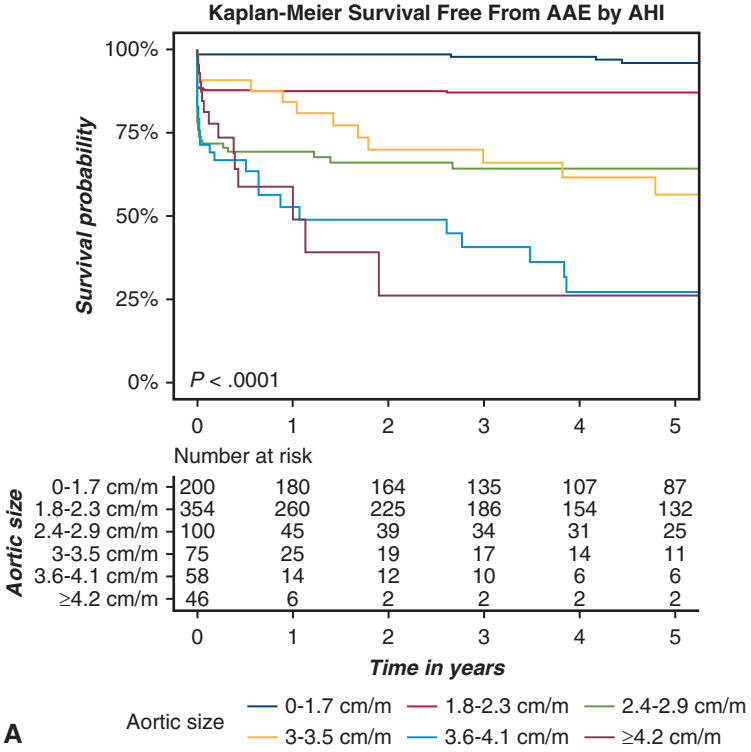
DISCUSSION

The natural history of the descending thoracic and thoracoabdominal aorta remains difficult to elucidate. Our earliest studies, based on 230 patients with ascending or descending TAA, treated the entire thoracic aorta as 1 entity,[3] and current surgical intervention criteria are based in part on this early work.[4,5] Over the last 2 decades, however, it has become apparent that the behavior of the descending thoracic aorta diverges from its ascending counterpart.[16] In the present study, we focused exclusively on the natural history of the descending thoracic and thoracoabdominal aorta, based on data from 907 patients.

Dissection and Rupture Behave Differently

We have found that, unlike the ascending thoracic aorta, in which AAEs (dissection, rupture, and death) manifest primarily at larger sizes, the risk profile of the descending thoracic aorta follows a bimodal distribution, with increased risk of certain adverse events at both small and large diameters.

Our results initially suggested that size may not a reliable predictor of risk in the descending thoracic aorta, because even at smaller diameters, we found a significantly elevated



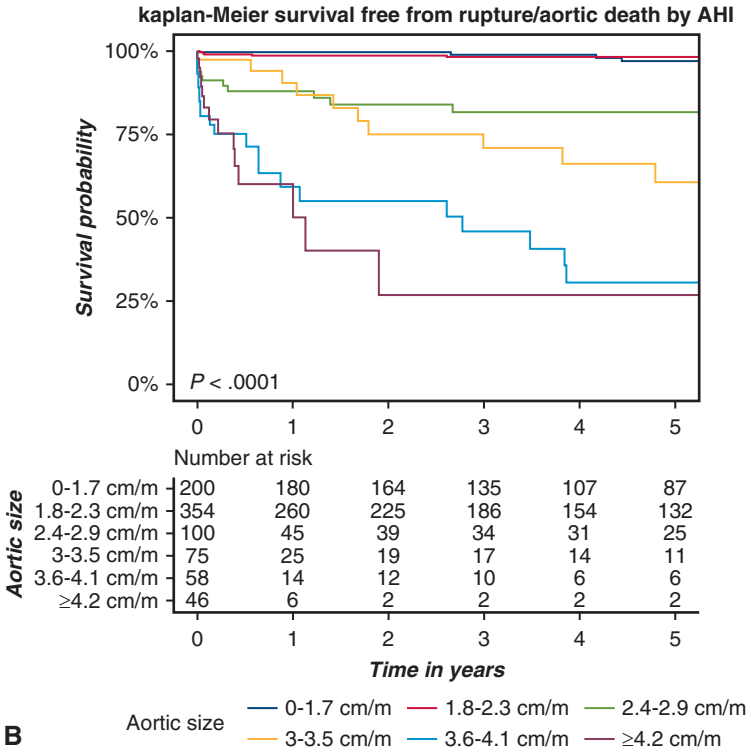


FIGURE 5. Kaplan–Meier analysis of freedom from AAEs stratified by AHI. A, Freedom from a composite end point of rupture, dissection, and aortic death. B, Freedom from a composite end point of rupture and aortic death. This demonstrates the deleterious effect of aneurysm size on longevity. Larger AHIs were associated with decreased complication-free survival. Confidence limits for both Kaplan–Meier curves are provided in Tables E1 and E2.

TABLE 4. Competing-risks model analyzing the effect of aortic height index on adverse aortic events, controlling for age and sex

	Subdistribution HR	SE	P	95% CI, LL	95% CI, UL
AHI (cm/m)					
<1.8	0.06	0.04	.000	0.02	0.20
1.8-2.3	0.10	0.05	.000	0.04	0.27
2.4-2.9	1.06	0.44	.886	0.47	2.39
3.6-4.1	3.44	1.33	.001	1.61	7.33
≥4.2	2.96	1.25	.010	1.29	6.76
Age	0.97	0.01	.020	0.95	1.00
Male	1.03	0.29	.910	0.59	1.80

HR, Hazard ratio; *SE*, standard error; *CI*, confidence interval; *LL*, lower limit; *UL*, upper limit; *AHI*, aortic height index.

risk for AAE. Further analysis demonstrated that the descending aorta tends to dissect at smaller diameters, yet rupture at larger diameters (Table 3 and Figure 3). Specifically, we are able now to document that descending aortic dissection often occurs at small descending sizes (~4 cm range), whereas aortic rupture occurs nearly exclusively at large aortic sizes (>5-6 cm). Fortunately, the majority of acute Stanford Type B dissections in the descending thoracic aorta are not an immediately fatal event. Furthermore, initial management of Stanford Type B dissections consists (arguably) of medical therapy in most cases, not surgical intervention.[17,18]

Slow Growth

The descending thoracic and thoracoabdominal aorta grows slowly at a rate of 0.22 cm/year at 4 cm, with incremental increase in growth rate as diameter continues to enlarge. This mirrors the published growth rates of both the aneurysmal ascending and abdominal aorta, and it reaffirms the indolent nature of this virulent disease.[16,19] Furthermore, existing literature describing the thoracic aorta has focused primarily on aortic diameter and diameter (or cross-sectional area) relative to body surface area or height (first introduced and validated by Dr Svensson) as a predictor for rupture or dissection.[6,20-22] This follows the conventions of risk estimation in both the ascending thoracic aorta, which largely tends to dissect as diameter increases, and the abdominal aorta, which tends to rupture as diameter increases.[10,23,24]

Change in Aortic Size at the Moment of Dissection

It is important to keep in mind that our dissection-related calculations are based on diameter at the time of dissection. Our studies, as well as those of other groups, have shown that in both the ascending and descending thoracic aortas, the diameter increases by 7 to 8 mm at the instant of dissection.[7,9,25] Thus, for example, the diameter immediately before dissection in a 4- to 4.9-cm group was likely closer to the 3- to 3.9-mm range. As the diameter of descending aortic complications decreases toward 3 cm, however, this is nearing the territory of the upper limit of normal aortic diameter. This makes surgical intervention for prevention of descending aortic dissection conceptually problematic. The propensity of the descending thoracic and thoracoabdominal aorta to dissect in the absence of significant aortic dilation also highlights the ineffectiveness of current guidelines for prophylactic surgery of DTTAA (at 5.5-6.0 cm),[4,5] and perhaps surgery altogether, in protecting patients from acute Type B dissection.

Hinge Points

Figure 6 depicts the increasing probability of a lethal aortic event, rupture or aortic death, with increasing size

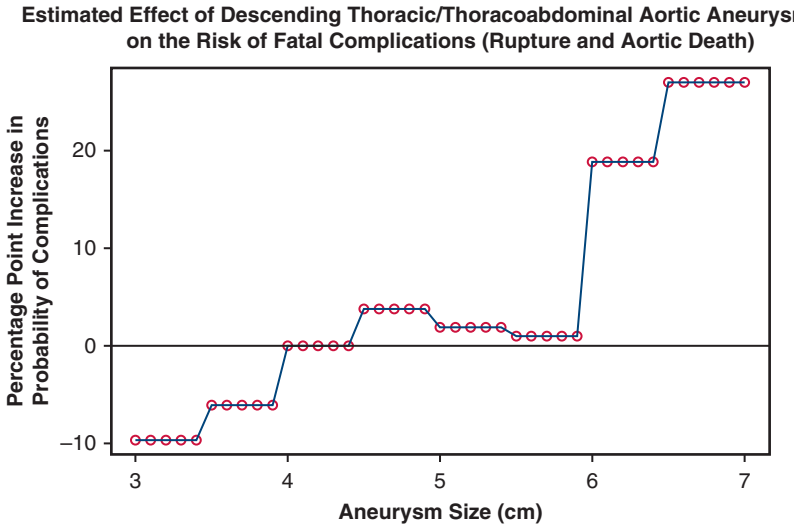


FIGURE 6. Probability of rupture or aortic death of the descending thoracic/thoracoabdominal aorta by aneurysm size. Analysis of the predicted probability of fatal complications (ie, rupture or aortic death) revealed that the risk increased sharply at 2 hinge points: 6.00 cm and 6.50 cm.

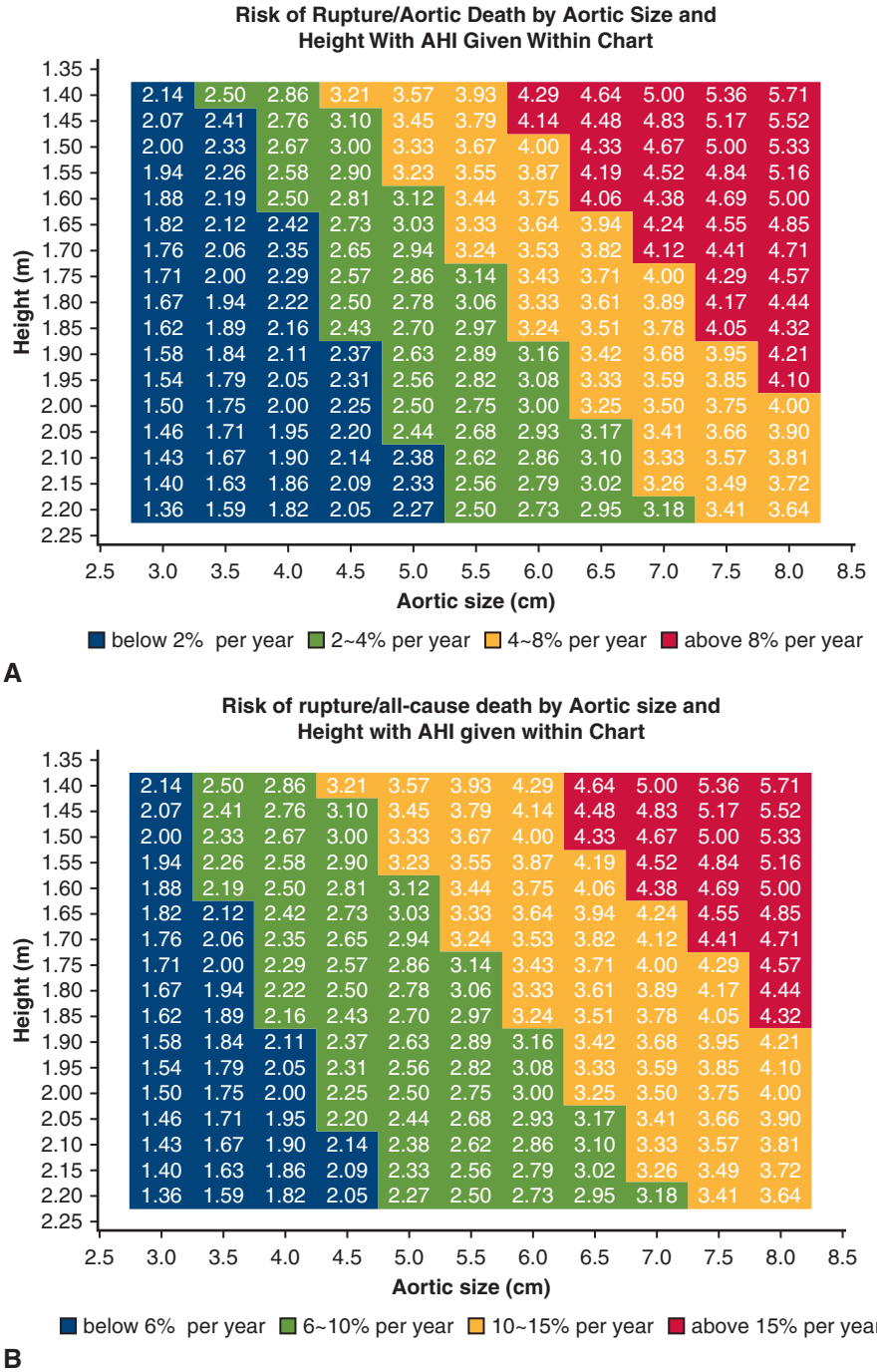


FIGURE 7. A, Risk of fatal complications (aortic rupture and death) in patients with DTTAA as a function of aortic diameter (*horizontal axis*) and height (*vertical axis*), with the AHI shown. B, Risk of fatal complications (aortic rupture and all-cause death) in patients with DTTAA as a function of aortic diameter (*horizontal axis*) and height (*vertical axis*), with the AHI shown. On the basis of the AHI, patients are stratified into 4 categories of yearly risk of complications, depicted as a color-coded 4-tier warning system of escalating risk. This can assist clinicians with the surgical decision-making process. *AHI*, Aortic height index.

of the descending thoracic and thoracoabdominal aorta. There are 2 critical hinge points, at 6.0 cm and 6.5 cm, at which the risk of fatal events increases significantly. Although descending aortic dissection is not usually immediately lethal, on the other hand, rupture of the descending thoracic and thoracoabdominal aorta is an

TABLE 5. Characteristics of acute type B dissection cases by aortic size

	<3.5 cm	3.5-4.9 cm	≥5 cm	P
n	12	82	24	
Age (mean, SD)	59.25 (13.53)	63.95 (13.70)	70.42 (12.19)	.040
Height (mean, SD)	172.75 (7.72)	172.30 (10.74)	169.39 (10.78)	.546
Weight (mean, SD)	92.00 (29.22)	89.51 (27.16)	75.17 (13.09)	.087
AHI (mean, SD)	1.86 (0.17)	2.36 (0.25)	3.53 (0.41)	<.001
Male (%)	7 (58.3)	48 (58.5)	13 (54.2)	.929
Family history (%)				.488
None	10 (83.3)	45 (54.9)	15 (62.5)	
Proven	2 (16.7)	10 (12.2)	1 (4.2)	
Likely	0 (0.0)	1 (1.2)	0 (0.0)	
Possible	0 (0.0)	2 (2.4)	1 (4.2)	
Unknown	0 (0.0)	24 (29.3)	7 (29.2)	
Past cardiac surgeries (%)	2 (16.7)	10 9.8)	3 (12.5)	.561
Hypertension (%)	12 (100.0)	69 (84.1)	15 (62.5)	.012
Smoking (%)				.091
Unknown	4 (33.3)	36 (43.9)	17 (70.8)	
Nonsmoker	2 (16.7)	18 (22.0)	4 (16.7)	
Current/past smoker	6 (50.0)	28 (34.1)	3 (12.5)	
Dyslipidemia (%)	6 (50.0)	25 (30.5)	8 (33.3)	.406
COPD (%)	5 (41.7)	12 (14.6)	6 (25.0)	.065
Diabetes mellitus (%)	2 (16.7)	8 (9.8)	3 (12.5)	.749
Autoimmune (%)	0 (0.0)	9 (11.0)	3 (12.5)	.459
CAD (%)	3 (25.0)	20 (24.4)	6 (25.0)	.997
Steroid use (%)	2 (16.7)	5 (6.1)	0 (0.0)	.136
Stroke (%)	0 (0.0)	10 (12.2)	3 (12.5)	.437
Active malignancy (%)	0 (0.0)	10 (12.2)	0 (0.0)	.091
Bovine arch (%)	1 (8.3)	12 (14.6)	2 (8.3)	.639

SD, Standard deviation; *AHI*, aortic height index; *COPD*, chronic obstructive pulmonary disease; *CAD*, coronary artery disease.

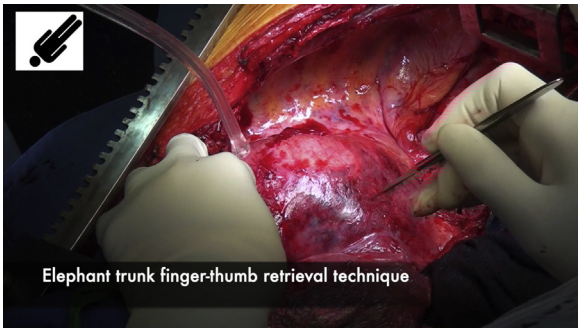
almost uniformly fatal event (unless successful emergency surgical [open or endovascular] repair is undertaken). However, surgical intervention (open and endovascular) for ruptured DTTAA is associated with a significantly higher morbidity and mortality than elective repair of unruptured DTTAA,[26,27] underlining the importance of prophylactic surgery (Video 1) to obviate rupture and its sequelae. The hinge points identified in this graph suggest that the current guidelines of 5.5 to 6.0 cm for preemptive surgical intervention of DTTAA should be reevaluated, especially for high-volume specialized aortic centers that can deliver elective surgery safely. With the knowledge that the majority of ruptures and aortic deaths occur above an aortic size of 5 cm and that 6.0 cm is a critical point, a "left-shift" down to the 5.0 to 5.5 cm range may be more appropriate when it comes to surgical decision-making. Interestingly, this is also the recommended range for surgical intervention in the abdominal aorta (5.0 cm for women, 5.5 cm for men).[24]

Aortic Height Index Risk Stratification Table

On the basis of the results of this study, we provide an AHI-based risk stratification nomogram to aid with surgical decision-making (Figure 7, *A* and *B*). For the reasons explained, we excluded the risk of acute type B dissection from this analysis, and therefore risk in this nomogram specifies a natural risk of fatal complications, aortic rupture and death. We hope that the table in Figure 7, *A* and *B*, will be useful to clinicians.

Study Limitations

This study is largely limited by its retrospective nature and inherently biased sample population. Every patient in our database was referred to our center for evaluation of suspected or confirmed aortic pathology; thus, it is impossible to make comparisons with the general population. Additionally, our dataset includes patients



VIDEO 1. Elephant trunk finger-thumb retrieval technique. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32517-6/fulltext.

who underwent descending thoracic aortic surgery for their respective pathologies. That is, we have intervened surgically to prevent AAEs when we thought it was appropriate; in other words, we prevented the natural history from expressing itself based on surgical judgment. Although the surgical patients are appropriately censored in time-to-event analyses, surgical intervention likely distorts our description of the natural history because after aortic intervention, no further AAEs will occur. Of course, there is no conscionable alternative to intervention to prevent patient death. One cannot simply observe a lethal disease to determine its completely natural outcomes.

The inclusion of "possible" aortic deaths in our accounting likely overestimates the true number of aortic deaths. However, to neglect these "possible" aortic deaths (many of which are likely to be bona fide) would incur error in the opposite direction, namely, underestimation. It is simply not possible to know conclusively the exact mode of death for every patient. By requesting, awaiting, and incorporating Death Certificate information, we think we have exhaustively addressed this matter.

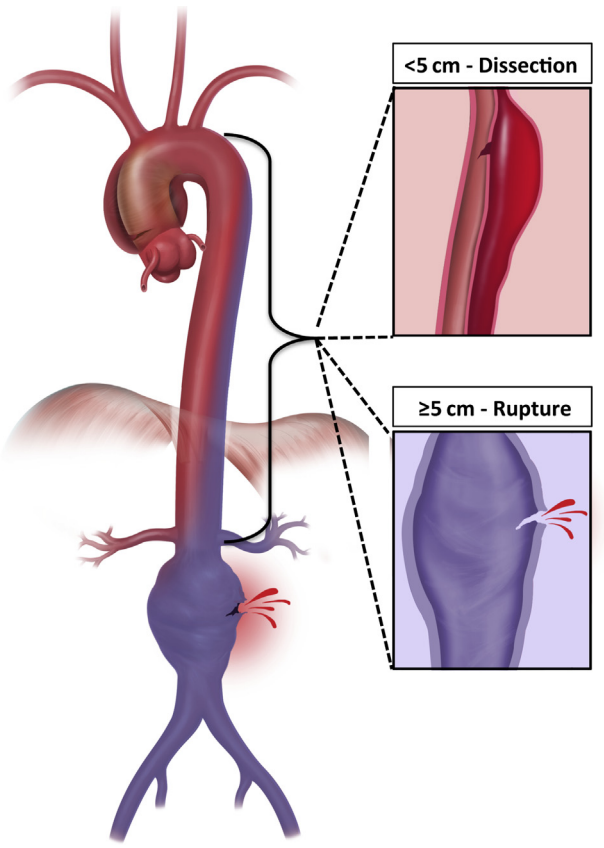


FIGURE 8. By putting the findings of this study in context with other segments of the aorta, we note the following: The ascending aorta dissects above 5 cm but rarely ruptures without dissection. The abdominal aorta ruptures above 5 cm but rarely dissects. The descending thoracic and thoracoabdominal aorta is a mélange and dissects at small diameters below 5 cm but does not rupture until 5 cm or more.

CONCLUSIONS

This study of the natural history of DTTAA permits the following conclusions (Figure 8):

1. The descending thoracic and thoracoabdominal aorta grows slowly at 0.19 cm/year.
2. Descending aortic dissection and rupture occur primarily at very different aortic sizes: dissection at dimensions in the 4-cm range and rupture at dimensions above 5 cm.
3. The aortic size thresholds for operative repair in the current guidelines would not be expected to afford protection from dissection of the descending thoracic and thoracoabdominal aorta.
4. The natural risk of rupture/aortic death based on aortic size increases sharply at 2 hinge points: 6.0 cm and 6.5 cm.
5. On the basis of these data, we conclude that we cannot currently define intervention criteria that can protect from descending aortic dissection. Fortunately, descending aortic dissection is not usually lethal.
6. On the basis of these data, we recommend intervention on the descending or thoracoabdominal aorta at 5.0 to 5.5 cm to prevent aortic-related rupture and consequent death.
7. The general size recommendations for aortic intervention can be made more precise for individual patients by referring to the nomogram displaying complication risk based on aortic size and patient height (Figure 7, *A* and *B*).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Sunday_May5/205BD/205BD/S51%20-%20Arch%20and%20descending%20aorta/S51_4.mp4.

Conflict of Interest Statement

Dr Elefteriades reports the following: Coolspine, principal; Terumo and Jarvik Heart, data monitor safety board member; Cryolife, consultant; DuraBiotech, consultant. All other authors have nothing to disclose with regard to commercial support.

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Key Words: thoracic aortic aneurysm, descending thoracic aorta, thoracoabdominal aorta, natural history, aortic dissection, aortic rupture, intervention criteria

ADULT

Discussion

Dr Lars G. Svensson *(Cleveland, Ohio)*. You don't document in the article how many of your patients had aortic dissection that you were actually following. In other words, how many patients had dissection already at the beginning when you were following this group of 907, and how many then later dissected? We know that some patients have a higher incidence of redissecting after initial dissection, such as in patients with Marfan. How many of these patients were there?

How do you measure the size? As you know, there are a lot of standards, and the thoracic guidelines recommended for MRI and computed tomography to measure the external diameter. Did you use a different standard for computed tomography angiography or magnetic resonance angiography and did you measure the sizes differently? Could you comment on the fact that 70% of your patients had enlarged ascending aortas or roots; in fact, 40% of were larger than 5 cm. Why were they not operated on?

Dr Mohammad A. Zafar *(New Haven, Conn)*. In response to your first question, you are correct, few patients who we actually observe at the Aortic Institute have dissection. The majority are patients who presented to our institution with an acute type B dissection.

Dr Svensson. No, I am going back to your original 907. According to your methods, that included patients who had previously dissected. Isn't that the case?

Dr Zafar. No. We did not include chronic dissections. If the dissection was acute at presentation, we included these patients. If the patient had dissection previously and a chronic dissection at presentation to our institution, we did not include such patients.

Dr Svensson. All right. Well, the way I understood your methods, you had included patients with acute aortic dissection in your initial denominator that you were following.

As to your other findings, I think this is important to recognize that the prediction of dissection is not very good based on size. There are a lot of data on that. We know that in the aortic root and the ascending aorta this varies. There are data from U Penn and the International Registry of Acute Aortic Dissections that show that dissection is difficult to predict on the basis of size.

However, we looked at our 870 patients who had received reimplantations, up to the end of last year, and Bentalls, and what was disturbing was that 1.4% of those patients had dissection, mainly in the descending aorta with a normal-sized aorta. So the question is, can we tease out these patients and identify who is at risk of dissection?

I would submit, just looking at your data, there is an opportunity of emphasizing diameter to look at other parameters, such as relation to height, aortic length, and MRI of the aortic wall. The ideal would be that all of us who perform aortic surgery would combine our data and use machine learning from all the countries and get a predictive formula for dissection. I would submit that if you look into our historical knowledge about dissections, that is, steroids, obesity, hypertension, smoking, cocaine abuse, chronic obstructive pulmonary disease, and volume calculations, and if we put that all into a formula, we would have a better predictive model.

I think we have various upcoming opportunities from MRI and magnetic resonance angiography to look at the aortic wall. We are looking at proteoglycans and matrix metalloproteinases; maybe we will get to the point to be able to identify what is happening to the collagen versus elastic ratios, and we will have a better predictive idea.

I applaud what you are doing, and this adds to our knowledge. I think the calculation of risk of rupture based on size is something that we do not fully understand because it is not that predictive. Please keep up your great work.

Dr Thomas J. Gleason *(Pittsburgh, Pa)*. Along Lars' line there, I think another point to inquire about with respect to your database is were these assumed to all be optimally medically managed throughout that time period? Is there any auditing of the degree of medical management? Because as Marc Moon pointed out yesterday, there is a dramatic difference in long-term outcome when we include patients who are optimally medically managed and those who aren't. How does that play into your modeling?

Dr Zafar. We are not sure if there is any mode of medical management that is truly effective for aneurysms. The patients with uncomplicated type B dissection are on strict anti-impulse therapy, but as far as the aneurysms are concerned, that is not a factor that we looked at. We do not really think, based on our extensive published reviews of the literature, that medical management, at least in aortic aneurysms at this point in time, is efficacious.

Dr D. Craig Miller *(Stanford, Calif)*. How did you measure your aortic size? You know there is a major fire fight going on about your ascending work, because John feels that the multiplanar reformat— or true orthonormal 3-dimensional measurements—are bogus, whereas most of us believe that these 3-dimensional orthogonal dimensions are the best we have. But in your ascending group you used echocardiography estimates or your regular 2-dimensional axial measurements, which frequently may be erroneous. How did you measure the aorta in this descending trial?

Dr Zafar. We made every effort to measure perpendicular to the long axis of the aorta using MRI and computed tomography scans. The majority were computed tomography scans, but MRI was also included. We also tried to reconcile the radiologist's measurements with our own measurements, so there was sort of a double verification process. In case of a discrepancy, we sat down and sorted it out.

Dr Miller. I interpret your answer to say you used 2-dimensional aortic diameter measurements. So John Elefteriades and your group still do not believe in the 3-dimensional orthonormal measurements derived from multiplanar reformatted images for the descending aorta? Many of us believe deriving true 3-dimensional orthonormal aortic dimensions from ultiplanar reformation computed tomography angiography reconstructions is just as important for

the descending thoracic aorta as it is for the ascending aorta because the descending aorta can become quite tortuous and ''loopy'' as the patients age and the aorta elongates.

Dr Zafar. That's probably a question for Dr Elefteriades.

Dr Miller. Yes, that's a tricky one. John is right here. Stand up and defend yourself.

Dr John Elefteriades *(New Haven, Conn)*. I think the descending aorta is easy to measure, because it is predominantly vertical, and there is good agreement on measurement between the 2 modalities. The problem comes up in the aortic root mostly, and the ascending aorta, when it is very elongated, makes that C-curve we are all familiar with. But the descending aorta is not the primary source of discrepancy here between the 2 methods. We are currently analyzing that thoroughly, and we are 3-dimensionally printing some of these aortas and measuring them. We are working hard regarding that issue.

Dr Maral Ouzounian *(Toronto, Ontario, Canada)*. Congratulations on another important study from the Yale aortic group. You reported rates of rupture and dissection during follow-up. What proportion received elective surgery during the study period, what thresholds were you using, and are you recommending different thresholds for patients who would be repaired with a straightforward thoracic endovascular aortic repair compared with open distal aortic or thoracoabdominal repair?

Dr Zafar. I think approximately 200 patients underwent elective surgery in our cohort. It is a balancing act between the risk of surgery and the risk of natural complications; thus, we provide the nomogram. For each institution, the rates of complications, be it thoracic endovascular aortic repair or open repair, should be kept in context when operating.

Dr Steven Lansman *(Valhalla, NY)*. Is there a time bias here in the sense that when we first started keeping databases, 25 years ago, we were more cautious about operating on patients because of high mortality. With time we got better and are operating on patients with smaller aortas while not observing patients with 7-cm aneurysms. So smaller aortas are being included and larger ones excluded from our databases. Can that account for the left shift?

Dr Zafar. I think so. Thank you for bringing up this important point, which is a limitation of this study. The bigger aneurysms with faster growth are being selected out for operation more routinely now than 10 to 15 years ago.

TABLE E1. Kaplan–Meier analysis of freedom from adverse aortic events (composite end point of rupture, dissection, and aortic death) stratified by aortic height index

	Survival free from AAE by AHI		
AHI	**1 y**	**3 y**	**5 y**
0-1.7 cm/m	98.5% (95% CI, 96.8-100.0)	97.8% (95% CI, 95.8-100.0)	95.9% (95% CI, 92.7-99.3)
1.8-2.3 cm/m	87.5% (95% CI, 84.2-91.0)	87.1% (95% CI, 83.6-90.7)	87.1% (95% CI, 83.6-90.7)
2.4-2.9 cm/m	69.3% (95% CI, 60.6-79.1)	64.3% (95% CI, 54.9-75.3)	64.3% (95% CI, 54.9-75.3)
3-3.5 cm/m	84.3% (95% CI, 74.4-95.5)	66.0% (95% CI, 51.4-84.7)	56.5% (95% CI, 40.6-78.6)
3.6-4.1 cm/m	52.6% (95% CI, 38.8-71.2)	40.7% (95% CI, 26.7-62.0)	27.1% (95% CI, 14.5-50.7)
≥4.2 cm/m	49.0% (95% CI, 30.1-79.7)	26.1% (95% CI, 9.3-73.5)	26.1% (95% CI, 9.3-73.5)

AAE, Adverse aortic event; *AHI*, aortic height index; *CI*, confidence interval.

ADULT

TABLE E2. Kaplan–Meier analysis of freedom from fatal aortic events (a composite endpoint of rupture and aortic death), stratified by aortic height index

	Survival free from rupture/aortic death by AHI		
AHI	**1 y**	**3 y**	**5 y**
0-1.7 cm/m	99.5% (95% CI, 98.5-100.0)	98.8% (95% CI, 97.2-100.0)	96.9% (95% CI, 93.9-100.0)
1.8-2.3 cm/m	98.7% (95% CI, 97.4-100.0)	98.2% (95% CI, 96.6-99.8)	98.2% (95% CI, 96.6-99.8)
2.4-2.9 cm/m	87.9% (95% CI, 80.7-95.7)	81.6% (95% CI, 72.3-92.0)	81.6% (95% CI, 72.3-92.0)
3-3.5 cm/m	90.5% (95% CI, 81.2-100.0)	70.8% (95% CI, 55.6-90.2)	60.6% (95% CI, 43.8-83.9)
3.6-4.1 cm/m	59.2% (95% CI, 44.4-78.9)	45.8% (95% CI, 30.4-69.0)	30.5% (95% CI, 16.5-56.6)
≥4.2 cm/m	50.0% (95% CI, 30.8-81.3)	26.7% (95% CI, 9.5-75.0)	26.7% (95% CI, 9.5-75.0)

AHI, Aortic height index; *CI*, confidence interval.

TABLE E3. Multivariable linear regression analysis for aortic growth

	Coefficient	**SE**	**P**	**95% CI, LL**	**95% CI, UL**
Age	0.002	0.000	.000	0.001	0.002
Male	−0.066	0.005	.000	−0.077	−0.055
COPD	0.055	0.008	.000	0.039	0.070
Bovine arch	−0.203	0.006	.003	0.035	−0.006

SE, Standard error; *CI*, confidence interval; *LL*, lower limit; *UL*, upper limit; *COPD*, chronic obstructive pulmonary disease.