Risk of Rupture or Dissection in Descending Thoracic Aortic Aneurysm

Running title: Kim et al.; Descending thoracic aneurysms

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Journal Subject Term: CV surgery: aortic and vascular disease
Abstract

**Background**—Current practice guidelines recommend surgical repair of large thoracic aortic aneurysms (TAA) to prevent fatal aortic dissection (AD) or rupture, but limited natural history data exist to support clinical criteria for timely intervention.

**Methods and Results**—Of 3,247 TAA patients registered in our institutional Thoracic Aortic Center Database, we identified and reviewed 257 non-syndromic patients (age 72.4±10.5 years, 143 females) with descending thoracic or thoracoabdominal aortic aneurysm (DTA/TAAA) without history of AD in whom surgical intervention was not undertaken. The primary endpoint was a composite of AD/rupture and sudden death. Baseline mean maximal aortic diameter was 52.4±10.8mm with 103 patients having diameters ≥ 55mm. During a median follow-up of 25.1 months (Quartile 1-3, 8.3-56.4 months), definite and possible aortic events occurred in 19 (7.4%) and 31 patients (12.1%), respectively. On multivariable analyses, maximal aortic diameter at baseline emerged as the only significant predictor of aortic events (HR=1.12; 95% CI, 1.08-1.15). Estimated rates of definite aortic events within 1 year were 5.5%, 7.2% and 9.3% at the aortic diameters of 50mm, 55mm and 60mm, respectively. Receiver operating characteristic for discriminating aortic events were higher for indexed aortic sizes referenced by body size (areas under curve [AUC]=0.832 to 0.889), but not significantly different to absolute maximal aortic diameter (AUC=0.805).

**Conclusions**—Aortic size was the principle factor related to aortic events in unrepaired DTA/TAAA. Although the risk of aortic events started to increase with a diameter above 5.0-5.5cm, it is uncertain if repair of TAAAs in this range leads to overall benefit and the threshold for repair requires further evaluation.

**Key words:** aorta; aneurysm; surgery; prognosis; risk factor
Introduction

Aneurysm of the descending thoracic and thoracoabdominal aorta (TAA) is a life-threatening disorder given risks of aortic dissection (AD) or rupture and their associated high mortality and morbidity once complications occur. The decision to intervene prophylactically, however, is complicated by the significant mortality and morbidity associated with surgical intervention for these conditions. Current practice guidelines call for surgical repair of asymptomatic thoracic aortic aneurysms with diameters of 55mm or larger as a Class I recommendation.\(^1\) Extensive TAA aneurysms are given a higher threshold of 60mm.\(^1\)

Recent observations have shown that adverse aortic events may occur at smaller diameters.\(^2,3\) For instance, reports from the International Registry of Acute Aortic Dissection showed that 40% of patients with acute type A AD may have aortic diameter of 50mm or less, and among those with type B AD as many as 80% had aortic diameters less than 55mm.\(^3,4\) These observations have encouraged re-examination of the current practice guidelines. Furthermore, progression of endovascular technology enables treatment of the aortic diseases less invasively, potentially reducing treatment-related mortality or serious morbidity.\(^5-9\)

Convergence of these forces suggest that earlier prophylactic interventions for descending thoracic aortic aneurysms may be appropriate, and emphasize the need for a deeper understanding of the predictors of these aortic complications. Finally, several aortic measures indexed to body size have been proposed recently as alternatives to simple diameter for predicting complications,\(^10,11\) however there have been few studies examining the predictive value of these metrics.

Unfortunately, there are a number of significant challenges in determining the natural course of unrepaired thoracic aortic aneurysms including the relatively uncommon population...
frequency of the condition, the incomplete nature of most data sets, and the problem of
ascertaining causes of sudden death not to mention the impact of censoring of data at the time of
surgical intervention.\textsuperscript{12} Much of our current understanding of the disease is based on the
pioneering studies conducted by the group at Yale University which is almost unique in the
evaluation of the natural prognosis of unrepaired thoracic aortic aneurysms, and stand as the only
data of its kind cited in the current guidelines for indication of prophylactic aortic aneurysm
repairs.\textsuperscript{10,13,14} Despite their widespread use, these data have significant limitations, however. For
instance, patients with and without connective tissue disease were included in the data set, and
ascending versus descending thoracic aneurysms were not anatomically differentiated. A very
sophisticated study was performed by Juvonen et al to derive an equation to estimate rupture rate
based on 114 patients with descending thoracic aorta (DTA)/TAAA.\textsuperscript{15} However, the study was
limited by a relatively small sample size and lack of consideration of the time effect in the
statistical model.

We therefore sought to evaluate the outcomes of unrepaired descending thoracic and
TAA aneurysms as captured in our institution’s Thoracic Aortic Center database in the interest of
contributing to a greater understanding of the optimal triggers for surgical intervention by
determining independent predictors of adverse events.

\textbf{Methods}

\textbf{Study Subjects}

Patients with diverse aortic diseases referred to the Massachusetts General Hospital Thoracic
Aortic Center are prospectively registered into an institutional database recording baseline
patient characteristics, detailed information on aortic interventions, and follow-up outcomes.
This Database was queried for “thoracic aortic aneurysm” from July 1992 through August 2013 which yielded 3,247 adult patients (age ≥ 17 years). A retrospective review was then undertaken for these patients including systematic reviews of computed tomography (CT) or magnetic resonance imaging (MRI) of the whole aorta performed at baseline. Aortic diameters were measured systematically at the levels of ascending, arch, descending thoracic and thoracoabdominal segments. Patients with maximal aortic diameter of 35mm or greater were included in this study. In the interest of forming a more homogenous study population with primary degenerative descending thoracic aortic aneurysms, those with known connective tissue disorders (Marfan, Loeys-Dietz and Ehlers-Danlos syndromes), inflammatory/neoplastic aortic diseases, aortic dissection, isolated ascending aortic aneurysm, history of prior thoracic aortic surgery, or congenital anomaly of the aorta (i.e. coarctation of aorta and Kommerell’s diverticulum) were excluded. Patients scheduled to receive elective aortic interventions at the time of entry to the database were excluded (n=564: open surgery in 286, thoracic endovascular repair [TEVAR] in 278) since the course of dilated native aorta could not be evaluated. There was, however, one patient scheduled for elective surgery who had aortic rupture 19 days after initial presentation while awaiting operation; this patient was included in this study.

Most patients with aortic diameters of 55mm or greater, those demonstrating rapid expansion (>5mm/yr) or symptomatic aneurysms, underwent timely surgery during the study period; however, some of these patients refused surgery or were counseled against the same related to comorbidities. Ultimately, 257 patients formed the study population as shown in a flow chart for enrollment in Figure 1. When these patients were compared with 564 patients who were excluded because they underwent prompt surgery, the study group was significantly older (74.6±8.9 yrs vs. 70.1±9.9 yrs, P=0.001) and more frequently had chronic obstructive pulmonary
disease (50.5% [52/103] vs. 20.0% [113/564], P<0.001).

Among the study patients, baseline CT or MRI images were reviewed for findings of atherosclerosis, mural calcification and ulcer-like projection. The largest external diameter of the aorta was measured perpendicular to the axis of blood flow based on baseline CT or MRI images.\[1]\ In cases where the aorta had elliptical cross-sectional shape, the smallest diameter was taken for the measurement as previously reported.\[16,17] Patients were designated as having aortic atherosclerosis if calcifications or luminal irregularity was identified in the aortic wall on these studies.

To evaluate the indexed aortic sizes relative to the body size, body surface area (BSA) was calculated based on the Du Bois formula (BSA=0.007148 x Weight\[0.425\] x Height\[0.725\]), and several indexes were calculated as follows:
- **Yale index\[10\]** = Maximal aortic diameter (cm)/BSA (m\(^2\))
- **Svensson index\[11\]** = Maximal aortic cross sectional area (cm\(^2\)) / Height (m)
- **Indexed area** = Maximal aortic cross sectional area (cm\(^2\))/ BSA (m\(^2\))

The study protocol was approved by the institutional review board, and the requirement for informed consent from individual patients was waved as a minimal risk study due to the retrospective nature of the study design.

**Definitions and Statistical Analysis**

The primary endpoint was defined as a composite of adverse aortic events that include acute AD, aortic rupture and sudden death not explained by causes other than aortic diseases. In order to establish unbiased definitions of the aortic events, we estimated aortic event rates as ‘definite’ and ‘possible’ events as suggested by Lederle and his colleagues.\[19\] Definite events were aortic rupture or dissection as confirmed by adequate imaging studies (MRI, CT) or surgical findings.
Possible events included, in addition to definite events, cases in which patients had sudden unexplained or unwitnessed deaths. True event rate was assumed to lie somewhere between the definite event rate and the possible event rate.

Since the primary aim of this study is to evaluate the natural course of unrepaired aortic aneurysm, patients who underwent elective aortic surgery before the aortic events or who died of other causes than aortic disease were regarded as censored at the time of such events.

Information on clinical endpoints of individual patient was obtained through August 2014 by a review of longitudinal data from Partners Health Care system. This is the largest health care system in Massachusetts, which maintains a centralized clinical data registry of all patient encounters within the system.20 Data on vital status and dates of death were further validated by the Social Security Death Index if necessary. Patients who were lost to follow-up were regarded as censored at the latest visit date if they had not have any adverse events up to that point.

SPSS software version 14.0 (SPSS Inc, an IBM Company, Chicago, IL) and R statistical software, version 3.1.2. were used for statistical analyses. Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as mean±SD or median with range (or Quartile 1-3). Kaplan–Meier curves were plotted to display conditional probability of adverse aortic events and Log-rank tests were used to compare between-group differences in the rates. For multivariable analyses, the Cox-proportional hazards models were used to determine independent risk factors of adverse aortic events. Variables with a $P$ value of 0.20 or less in univariable analyses were candidates for the multivariable Cox models. Multivariable analyses involved a stepwise backward elimination technique and only variables with a $p$ value of less than 0.10 were used in the final model. In order to test the proportional hazards assumption in the Cox models, Log ($-\log[\text{survival}]$) curves were inspected, which
confirmed no violation in the models.

Receiver Operating Characteristic (ROC) curve method was used to assess the predictability of baseline maximal aortic sizes for adverse aortic event within one year. This test was done for either absolute or relative aortic diameters indexed by body sizes. The results are presented by area under curve (AUC) with 95% CI, and were compared between absolute and each of indexed aortic diameters using the method suggested by DeLong et al.21 Risks of aortic events within 1-year based on initial aortic diameter were estimated using the logistic regression models.

All reported $P$ values were 2-sided, and a value of $P<0.05$ was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

For the baseline imaging of the aorta, CT was used in 237 patients whereas 20 patients were evaluated with MRI. Table 1 summarizes baseline profiles of subject patients. As might be anticipated, most patients (> 80%) had hypertension. A similar percentage had evidence of atherosclerosis in the aneurysmal aorta. Concomitant ascending aortic dilatation was observed in approximately 60% of patients, most of which were less than 5.5cm. About 60% of patients presented with aneurysms of the TAA which was followed by DTA and arch in the descending frequencies. Distributions of maximal aortic diameter are illustrated in Figure 1, which shows differences in the distributions according to the location of the main aneurysmal lesions. At
baseline, 103 patients (40.1%) demonstrated a diameter of 55mm or greater, with 62 patients (24.1%) having an aortic diameter of 60mm or greater. Data on height and weight were available for 196 (76.3%) to allow the calculation of indexed aortic sizes.

Clinical outcomes

Follow-up was complete in 88.7% (n=228) with a median duration of 25.1 months (quartile 1-3, 8.3-56.4 months; 791.5 patient-years). Figure 2 illustrates the outcomes summary of patients. At baseline, 103 patients (40.1%) met conventional surgical indications based on aortic diameter (55mm or greater), however, they refused surgery or delayed the decision to undergo surgery. In this patient group, 24 (23.3%) had aortic events during follow-up, of which 12 occurred within one year of initial presentation. Of these 24 patients, 10 patients underwent emergent operation (conventional open surgery in 4 and TEVAR in 6). Fatal outcome occurred in 15 out of the 24 patients with aortic events (62.5%) including one who received emergent TEVAR. Another 63 of these patients (61.2%) underwent delayed elective aortic repair at a median of 7.1 months (range, 1.8 to 120 months) without experiencing interim aortic events. The final 16 patients with aortic diameter ≥5mm at entry (15.5%) had been followed up for a median of 13.6 months (range, 2.7-71.6 months) free of adverse aortic events even without aortic intervention. Among these, two patients died of causes other than aortic disease at 26.9 and 58.0 months, respectively, after the diagnosis of aortic aneurysm.

Among patients for whom surgery was not indicated at the initial presentation (n=154, 59.9%), 68 (44.1%) subsequently underwent elective aortic repair at a median of 34.8 months (range 3.4-155.7 months) most often due to progressive aortic dilatation (Figure 2). Another seven patients (4.5%) in this group experienced adverse aortic events (rupture in 2, sudden death in 3 and AD in 2) at 3.2-141.2 months, of whom four had the events within 1 year of diagnosis.
The remaining, 79 patients remained alive (n=74) or died of other causes (n=5: cancer in 2, respiratory failure in 2 and multiple comorbidity in 1) without aortic intervention or aortic event up to a median of 36.3 months (Quartile 1-3, 15.1-76.1 months).

Overall, 131 patients (60.0%) underwent elective aortic interventions (conventional open surgery in 74 and TEVAR in 57) at a median of 17.1 months (IQR, 5.9-38.4 months) with an operative mortality rate of 4.6% (n=6; TEVAR, 5.2% [3/57]; open surgery, 4.1% [3/74]) while the operative mortality rate among the 10 emergent cases was 10% (1/10), a TEVAR case).

**Summary of Adverse Aortic Events**

There were 19 definite and 31 possible adverse aortic events occurring at a median of 8.7 months (Quartile 1-3, 3.2-16.8 months) (*Table 2*). Of these, 10 definite and 16 possible events occurred within one year after diagnosis of aortic aneurysm. There were numbers of adverse events in detail as follows: 4 cases of AD’s, 15 of aortic rupture and 12 sudden deaths. Locations of the 19 definite aortic events in patients who had rupture or dissection were as follows: arch in 1 (rupture), DTA in 7 (rupture in 6 and dissection in 1) and TAA in 11 (rupture in 8 and dissection in 3). The lesion locations were unidentified in 12 patients who died suddenly in whom the aneurysm had been located at the arch in 3 and TAA in 9.

Emergent aortic interventions were conducted for 10 patients with definite aortic events including conventional open surgical TAA repair in 4 and TEVAR in 6. Fatal outcomes occurred in 9 (47.4%) of the 19 patients with definite aortic events that included one case who underwent emergent TEVAR (mortality rate of emergent surgery, 10.0%).

Out of 31 patients who had possible aortic events, 14 patients had interim CT assessments between the time of initial presentation and the time of aortic events (*Supplemental Table 1*). Mean aortic expansion rate was 3.9mm/yr in these patients and 3 patients showed rapid...
expansion of the aorta (>5mm/yr). In four patients whose aneurysms were <55mm, follow-up CT scans showed aortic diameter of greater than 55mm in all patients.

For the study group as a whole, regardless of aortic diameter, cumulative incidence rates at 1, 3 and 5 years were 4.3±1.3%, 6.9±1.9% and 9.7±2.6%, respectively, for definite aortic events and 6.6±1.6%, 12.1±2.4% and 16.5±3.1%, respectively, for possible events (Figure 3-A). Both the definite and possible event rates were significantly different according to the baseline maximal aortic sizes. Figure 3-B and C illustrate cumulative incidence rates of aortic events according to the maximal baseline aortic diameters indicating significantly higher risks of adverse aortic events in larger aorta.

The probability of adverse aortic events within 1 year according to the baseline aortic diameters is illustrated in Figure 4. Patients with aortic diameter <50mm experienced an event rate less than 1%, however, the definite/possible event rates rose to 2.7/8.1% at aortic diameter between 50mm and 60mm, and sharply increased thereafter at a rate of 37.5-62.5% at >70mm.

Predictors of Adverse Aortic Events

Table 3 summarizes the univariable and multivariable risk factor analyses of the adverse aortic events. On multivariable analyses, maximal aortic diameter (HR 1.10; 95% CI 1.06-1.15; P<0.001) and presence of chronic obstructive pulmonary disease (HR, 2.76; 95% CI, 1.04-7.32; P=0.042) emerged as significant independent predictors of the definite aortic events. When extended to the possible aortic events, baseline maximal aortic diameter was the only significant and independent risk factor (HR, 1.12; 95% CI, 1.08-1.15; P<0.001).

Receiver Operating Characteristic (ROC) curve method was used to assess the predictability of baseline maximal aortic sizes for adverse aortic event within one year (Table 4). The ROC curve yielded an area under curve (AUC) of 0.852 (95% CI, 0.759-0.945; P<0.001) for
the possible event and 0.805 (95% CI, 0.604-1.006; \( P = 0.012 \)) for the definite event. All of the relative aortic size indexes presented by the Yale index, the Svensson index and the Indexed area showed greater AUC and accuracy for both the possible and definite aortic events compared to the absolute aortic diameter (Table 4), however, these differences were not statistically significant (\( P \) values of 0.14-0.31 for definite events and 0.15-0.39 for possible events).

**Estimation of Adverse Aortic Events within 1 Year**

Risks of aortic events within 1-year based on initial aortic diameter were estimated using the logistic regression models described in Figure 5 (upper part). The Figure also illustrates the estimated risk for varying initial aortic diameter. For these models, 200 patients who were followed for over 1 year from baseline or had aortic events (10 definite and 16 possible events) within 1 year were included. Maximal aortic diameter was the only independent factor of both definite and possible events; therefore we included only the aortic diameter as an independent variable in the model. The estimated risks of definite aortic events were 5.5%, 7.2%, 9.3% and 15.4% at aortic diameters of 50mm, 55mm, 60mm and 70mm, respectively. The estimated risks of possible aortic events were 8.0%, 11.2%, 15.6% and 28.1% at aortic diameters of 50mm, 55mm, 60mm and 70mm, respectively. Similarly, the risks of aortic events based on indexed aortic dimensions were shown in Figure 5 (lower part). At indexed aortic dimension of 20.0, definite and possible aortic events are estimated as 12.1% and 18.1%, respectively.

**Discussion**

The current practice guidelines from American College of Cardiology/American Heart Association recommend surgical or interventional aortic repair for symptomatic thoracic aortic aneurysm regardless of the aneurysm size, and prophylactic intervention for asymptomatic
aneurysm when the aortic diameter reaches 55-60mm or demonstrates rapid expansion (>5mm/yr). The size criterion of 55mm in the Guidelines is derived principally from a series of pioneering studies conducted by a single research group. In their 1997 study, Coady et al evaluated 230 patients with thoracic aortic aneurysm defined by the maximal aortic diameter of 35mm or greater. The authors found that AD or rupture occurred in 32 patients during follow-up, mostly occurring in ascending aorta or arch (n=23). Logistic regression analyses revealed that baseline aortic diameter was the only significant risk factor for adverse aortic events with a hinge point of aortic diameter of 60mm. From this result, the authors suggested prophylactic surgical aortic repair if the aortic diameter is 55mm or larger in non-Marfan patients. In this study, however, the aneurysm locations were heterogeneous (ascending aorta in 111 and its distal in 63) and the study population was mixed including 25 Marfan patients as well as patients with chronic dissection. Indeed fewer than 50 non-Marfan patients with degenerative DTA or TAA aneurysm were evaluated in the cited study with resultant less than 8 aortic events within this group. Two following studies from this research group were extensions of the original cohort, and showed similar findings.

Juvonen et al conducted a prospective study to determine the prognosis of thoracic aortic aneurysm. The study involved 114 patients with DTA/TAAA, for whom aortic sizes were measured systematically at the levels of DTA and abdominal aorta. During follow-up, 26 patients died of aortic rupture. On multivariable analyses, age, symptoms, COPD, and the diameters of DTA and abdominal aorta emerged as independent risk factors for rupture. From these results, the authors suggested a piecewise exponential equation to estimate rupture rate incorporating all the significant risk factors in the model. For instance, risks of aortic rupture in 65-year old patients at a given aortic diameter are estimated as 5% at 5cm, 9% at 6cm and 16%
at 7 cm. From the study results, the authors concluded that balancing of risk of operation and the risk of rupture can be much more precise with the aid of an equation for the probability of rupture.

Despite the pioneering aspect of this study, a major assumption of the work was that the risk of rupture is constant and is not influenced by either the time after diagnosis or by the length of time under surveillance. The lack of consideration of time under observation remains as a significant limitation of the analyses. In the present study, a predicted aortic events rate within 1 year can similarly be achieved by the logistic regression models as shown in Figure 5. At a given baseline aortic diameter, the estimated risks of aortic events seem to be greater than those drawn by the formula suggested by Juvonen et al; however, the discrepancies may be attributable to the differences in the study endpoints ("death due to rupture" vs. "composite of AD and rupture") as well as in the statistical methodologies.

The limitations of these pioneering studies led us to perform analyses on a larger, more homogeneous population of DTA/TAAA patients to seek more optimal and anatomically specific information from which to develop surgical recommendations. In the present study, aortic rupture was the most frequent mode of definite adverse aortic events (15/19) in patients with DTA and TAAA, and the diameter of aorta was the only identifiable predictive factor. Furthermore, we observed a significant incidence of rupture of aneurysms below the conventional criteria, with over 10% of patients with initial descending aortic diameter > 52mm experiencing aortic events within one year.

As is the case in any natural history study, some patients died of unknown cause. In this study we have made an effort to account for the possibility that some aortic events may be missed among those suffering sudden unexplained or unwitnessed death, by considering clinical
events in ‘definite’ or ‘possible’ categories. This approach was used in a previous prospective multicenter study on the incidence rupture in large abdominal aortic aneurysm among 198 patients with abdominal aortic aneurysm of 5.5cm or greater for whom elective AAA repair was not planned because of medical contraindication or patient refusal. In this study, AAA rupture was categorized as ‘definite, ‘probable’ or ‘possible’ based on ascertainment. The definite ruptures were those confirmed at surgery or autopsy or by CT. Probable ruptures included cases in which patients died with symptoms consistent with rupture but without objective confirmation of rupture, possible ruptures included cases in which patients had sudden unexplained or unwitnessed deaths. Using this methodology the authors assumed a true rupture rate to be somewhere in this range between definite and the possible rupture rates. By similar logic in the present study, the aortic event rates calculated ranged from 5.5% to 8.0% at 5cm, and from 9.3% to 15.6% at 6cm baseline aortic diameter. In our study, as in the aforementioned from Yale, Juvonen, and the multicenter AAA study, patients followed were declined or chose not to have surgery and were, accordingly, a selected subpopulation many of whom likely had greater baseline comorbidities compared to those undergoing elective repair. Accordingly, some of the sudden unexplained deaths may likely be attributable to other reasons related to those comorbidities, and therefore “possible event” may overestimate the true risk of aortic events than expected. In this respect, the estimated risk for possible event should be interpreted with caution.

The aim of prophylactic surgery is to improve survival; however, one certainly trades short-term risk of the procedure for relief from later risk of rupture. The most meaningful outcome then is a comparison of overall survival between operated and non-operated patients. We therefore evaluated overall survival outcomes in patients with aortic diameter of 50mm or greater between the operated (564 patients who were excluded) and the non-operated patients (subject patients). As
might be anticipated, the survival rates in operated patients (564 patients who were excluded) did not differ according to the aortic sizes, however, survival rates were significantly different in non-operated patients (Supplemental Figure 1). Compared to operated patients, survival rates of non-operated patients were similar at 50-55mm (P=0.74), but they were significantly poorer at 55-60mm (P=0.035) and at >60mm (P<0.001). Although there is clearly significant selection bias inherent in our data set in the decision to undertake surgery, these figures may offer a crude idea regarding operative thresholds. In addition, when the cumulative incidences of aortic events are assessed by several groups divided by 5mm in aortic diameters, there were tendencies of diverging prognosis at a 55mm-cutoff especially beyond 2-3 years period for both definite and possible events (Supplemental Figure 2), which may correlate better with the surgical threshold recommended by current practice guidelines. In these regards, there may be value in looking at a group of patients with aortic diameter of 50-55mm in further studies.

With the recognition that aortic size differs between individuals depending on body size, age, and gender and an appreciation for the limitations of simple aortic diameter, there has been interest of late from a number of investigators in the use of indexed aortic size. Of these factors, body size is the most dominant determinant. To account for these differences, Davis et al introduced the “aortic size index”, which is the aortic diameter indexed by BSA and now commonly known as the “Yale index”. In their evaluation of 410 patients with thoracic aortic aneurysm, the authors found that the Yale index better predicted the occurrence of rupture and death before operative repair than absolute diameter. Based on these observations, the authors recommended elective operative repair before the patient enters the zone of moderate risk (aortic size index greater than 2.75 cm/m²). Similarly, Svensson et al introduced a different aortic size index, calculated by dividing the maximal aortic cross sectional area by patient height, known as
the “Svensson index”, to guide concomitant aortic repair during bicuspid aortic valve surgery.\textsuperscript{11} We used our data to test these indexed size parameters, and while we found the Yale index, Svensson index and indexed cross-sectional area to have somewhat higher predictive values of ensuing aortic events than the absolute aortic diameter, however, this was not statistically significant.

Finally, the decision to proceed with surgery depends on the balance of the risks of surgery versus the risk of observation. A previous meta-analysis of the operative risks of conventional open TAA repairs in the current era involving 27 studies and 7,833 surgical patients undergoing open TAA repairs revealed a median early mortality rate of 5.06\% (range, 1.29-10.34) and rates of permanent neurologic damage less than 5\% under elective circumstances.\textsuperscript{24} We therefore compared these surgical risks with aortic event rates within 1-year in Figure 6, suggesting that the risks of adverse aortic events exceed the average surgical mortality rate in the meta-analysis even at the aortic diameter of 50mm. This comparison is imperfect given the fundamental differences in populations, that of the non-operative group being largely “inoperable” while the operated group was clearly selected. Nonetheless the figure graphically demonstrates that elective surgical indications should be determined not only by aortic size but also based on baseline patient risk profiles, the extent of aortic disease, and the institutional experience of DTA/TAAA repairs. The expected reduction in operative mortality and morbidity associated with TEVAR may further impact this balance.

In this study, for example, there were 46 patients with aortic diameter of 50-54mm. During the study period, 667 patients showed aortic diameters of 55mm or greater, who were regarded as surgical candidates (boxes entitled “Prompt Surgery” [N=564] and “Refuse/Delay Surgery” [N=103] in Figure 2). If we project the impact of lowering the surgical threshold to
50mm, the number of surgical candidates would increase by 6.7% (46/667). Lowering the threshold for elective repair of thoracic aortic aneurysms would, therefore impact quite a large population with significant economic impact. Therefore, a recommendation to extend the surgical criteria should have a robust foundation, perhaps based on a prospective randomized trial, to test whether such extension gives more benefits to these patients as has been conducted in the setting of infra-renal abdominal aortic aneurysm for abdominal aortic aneurysms that were 4.0 to 5.5 cm in diameter to receive surgery or close observation. Interestingly, this study failed to show overall benefits of surgery in these patients indicating that aneurysms should not be prophylactically repaired unless they are at least 5.5 cm in most circumstances.25,26

Limitations

This study has significant limitations, as do the similar prior studies on this subject. The data set represents the experience of a single tertiary academic referral center over two decades and, as such, is subject to referral (entry) bias from the community. This is even true within our institution, as given its large size and scope, thoracic aortic aneurismal disease is managed by members of several divisions and departments and not all are entered into this specific Thoracic Aortic Center database. Furthermore, it is difficult to adequately account for the impact of surgical intervention, which clearly interrupts the natural history of the condition as it is intended, but is also impacted by clinical judgments and secular trends beyond the actual behavior of the aorta. Indeed in the current era a true “natural history” study is not possible. Equally problematic, the study population includes many patients who did not undergo elective aortic repair because of serious comorbidities which may in themselves impact rupture rate as suggested by Juvonen and colleagues15. These unoperated patients therefore, may not be truly representative of usual patients with DTA/TAAA. The potential bias introduced by selection of
better risk patients for surgery may have impacted the results with the non-operated group faring worse than might be expected absent by surgical selection. Again this shortcoming is one also shared by the aforementioned studies upon which current recommendations are based.\textsuperscript{10, 13-15, 19} Nevertheless, these patients serve as the only windows available that allow us to estimate the prognosis of unrepaired aortic aneurysm. Finally the main analyses of the study were based on 19 definite and 31 possible aortic events, which may be regarded as small numbers to generalize the study results. Therefore, studies on larger cohorts are needed to further verify the main findings of the present study.

**Conclusions**

Aortic diameter remains a predictor of aortic events in unrepaired DTA or TAA aneurysm. Importantly, even among patients having aortic diameter of 50mm, 5.5\% had definite and 8.0\% had possible aortic events within one year. Consideration might therefore be given to lowering the threshold for intervention, particularly if less invasive endovascular approaches are feasible. Furthermore, these data suggest that relative aortic size may have an advantage in the prediction of adverse aortic events than absolute diameter alone.

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**References:**


Table 1. Patient Characteristics at Time of Presentation (N=257).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>72.4±10.5</td>
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<td>Female gender, n (%)</td>
<td>143 (55.6)</td>
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<tr>
<td>Body mass index, kg/m²*</td>
<td>27.4±4.9</td>
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<td>Body surface area, m²*</td>
<td>1.85±0.25</td>
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<td>Diabetes mellitus, n (%)</td>
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<td>Insulin therapy</td>
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<td>No insulin therapy</td>
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<td>Hypertension, n (%)</td>
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<td>Chronic obstructive pulmonary disease, n (%)</td>
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<td>Smoking history, n (%)</td>
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<tr>
<td>Medications, n (%)</td>
<td>Beta blockade 161 (62.6), Calcium channel blockade 76 (29.6), ACE inhibitor 84 (32.7), Angiotensin receptor blocker 31 (12.1), Diuretics 81 (31.5)</td>
</tr>
<tr>
<td>History of AAA surgery, n (%)</td>
<td>23 (8.9)</td>
</tr>
<tr>
<td>Main lesion location, n (%)</td>
<td>Arch 23 (8.9), Descending thoracic aorta 79 (30.7), Thoracoabdominal aorta 155 (60.3)</td>
</tr>
<tr>
<td>Imaging findings</td>
<td>Maximal aortic diameter, mm 52.4±10.8, Yale index* 2.90±0.72, Svensson index* 13.2±5.8, Indexed area*† 12.3±5.5, Ulcer-like projection, n (%) 20 (7.8), Atherosclerosis, n (%) 210 (81.7), Calcification, n (%) 188 (73.2), Concomitant ascending aorta dilatation ≥35mm, n (%) 154 (59.9), ≥ 35mm, &lt; 40mm 41 (16.0), ≥ 40mm, &lt; 50mm 80 (31.1), ≥ 50mm 33 (12.8)</td>
</tr>
</tbody>
</table>

* Data available in 196 patients (76.3%). †Indexed area= Maximal aortic cross sectional area (cm²)/ body surface area (m²). Abbreviations: ACE, angiotensin converting enzyme; AAA, infra-renal abdominal aortic aneurysm.
Table 2. Outcomes of patients.

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Total N=257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite adverse aortic event, n (%)*</td>
<td>19 (7.4)</td>
</tr>
<tr>
<td>Possible adverse aortic event, n (%)*</td>
<td>31 (12.1)</td>
</tr>
<tr>
<td>Rupture</td>
<td>15 (5.8)</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>Emergent surgery</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Open TAA surgery</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>TEVAR</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Fatal outcome by aortic events</td>
<td>19 (7.4)</td>
</tr>
<tr>
<td>Definite event within 1 year of diagnosis, n (%)*</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Possible event within 1 year of diagnosis, n (%)*</td>
<td>16 (6.2)</td>
</tr>
<tr>
<td>Elective operation during follow-up, n (%)</td>
<td>141 (54.9)</td>
</tr>
<tr>
<td>Open TAA surgery</td>
<td>69 (26.8)</td>
</tr>
<tr>
<td>TEVAR</td>
<td>57 (22.2)</td>
</tr>
<tr>
<td>Arch repair</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Death of other causes†, n (%)</td>
<td>13 (5.1)</td>
</tr>
</tbody>
</table>

*Definite aortic events include aortic dissection and rupture; possible aortic events include sudden death in addition to definite aortic events. † Cancer in 2, respiratory causes in 2, operative mortality after elective aortic repair in 6 and multiple comorbidity in 3. Abbreviation: TAA, thoracoabdominal aorta; TEVAR, thoracic endovascular aortic repair.
### Table 3. Univariable and Multivariable Analyses for Adverse Aortic Events.

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<thead>
<tr>
<th>Risk factors</th>
<th>Univariable</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
<td></td>
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<tr>
<td><strong>Definite event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age <em>by 1 yr increment</em></td>
<td>1.06</td>
<td>1.00-1.12</td>
<td>0.048</td>
<td>2.76</td>
<td>1.04-1.32</td>
<td>0.042</td>
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</tr>
<tr>
<td>Female gender (vs. male)</td>
<td>0.73</td>
<td>0.29-1.85</td>
<td>0.51</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>1.65</td>
<td>0.48-5.72</td>
<td>0.43</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>4.12</td>
<td>0.55-30.92</td>
<td>0.17</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Current smoking</td>
<td>1.48</td>
<td>0.32-6.74</td>
<td>0.61</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>COPD</td>
<td>3.52</td>
<td>1.33-9.23</td>
<td>0.011</td>
<td>1.04</td>
<td>0.99-2.99</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Hypertension medications</td>
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<td>-</td>
<td>0.24-0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal aortic diameter <em>by 1 mm increment</em></td>
<td>1.11</td>
<td>1.06-1.15</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>1.06-1.15</td>
<td>&lt;0.001</td>
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<tr>
<td>Ulcer-like projection</td>
<td>0.05</td>
<td>0.01-385.34</td>
<td>0.50</td>
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<tr>
<td>Atherosclerosis</td>
<td>6.93</td>
<td>0.91-53.00</td>
<td>0.062</td>
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<tr>
<td>Calcification</td>
<td>1.72</td>
<td>0.60-4.94</td>
<td>0.32</td>
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<td></td>
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<tr>
<td>Ascending aortic diameter</td>
<td>0.97</td>
<td>0.91-1.04</td>
<td>0.35</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Possible event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age <em>by 1 yr increment</em></td>
<td>1.07</td>
<td>1.02-1.12</td>
<td>0.004</td>
<td>1.04</td>
<td>0.99-1.09</td>
<td>0.12</td>
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</tr>
<tr>
<td>Female gender (vs. male)</td>
<td>1.04</td>
<td>0.51-2.13</td>
<td>0.91</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.59</td>
<td>0.35-19.3</td>
<td>0.35</td>
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<td>Hypertension</td>
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<td>0.23</td>
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<tr>
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<tr>
<td>COPD</td>
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<td>0.84-3.43</td>
<td>0.14</td>
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<td></td>
</tr>
<tr>
<td>Hypertension medications</td>
<td>-</td>
<td>-</td>
<td>0.11-0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal aortic diameter <em>by 1 mm increment</em></td>
<td>1.12</td>
<td>1.09-1.16</td>
<td>&lt;0.001</td>
<td>1.12</td>
<td>1.08-1.15</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ulcer-like projection</td>
<td>0.60</td>
<td>0.08-4.43</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>5.12</td>
<td>1.21-21.74</td>
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<tr>
<td>Calcification</td>
<td>2.00</td>
<td>0.84-4.72</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending aortic diameter</td>
<td>0.95</td>
<td>0.90-1.01</td>
<td>0.086</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval. COPD, chronic obstructive pulmonary disease.
Table 4. Receiver Operating Characteristic curve methods for baseline size indexes of the aorta to predict adverse aortic events within one year.

<table>
<thead>
<tr>
<th></th>
<th>Definite aortic events</th>
<th>Possible aortic events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC 95% CI P value</td>
<td>AUC 95% CI P value</td>
</tr>
<tr>
<td>Diameter</td>
<td>0.805 0.604-1.006 0.012</td>
<td>0.852 0.759-0.945 &lt;0.001</td>
</tr>
<tr>
<td>Yale index</td>
<td>0.889 0.788-0.991 0.001</td>
<td>0.908 0.830-0.986 &lt;0.001</td>
</tr>
<tr>
<td>Svensson index</td>
<td>0.832 0.654-1.010 0.006</td>
<td>0.874 0.734-1.014 &lt;0.001</td>
</tr>
<tr>
<td>Indexed area*</td>
<td>0.874 0.743-1.006 0.002</td>
<td>0.905 0.803-1.008 &lt;0.001</td>
</tr>
</tbody>
</table>

* Indexed area= Maximal aortic cross sectional area (cm²)/ BSA (m²). Abbreviation: AUC, area under curve; CI, confidence interval. The P-values are computed to test the null hypothesis that the AUC is from random prediction.

Figure Legends:

Figure 1. Distributions of maximal aortic diameters at baseline.

Figure 2. Flow chart for study enrollment and patients’ outcomes.

Figure 3. Cumulative risk of adverse aortic events in overall (A), and possible (B) and definite (C) events stratified by initial maximal aortic diameter.

Figure 4. Observed proportions of definite and possible adverse aortic events within 1 year based on baseline maximal aortic diameter.

Figure 5. Predicted probability of aortic event within 1 year based on baseline aortic diameter (upper 2 figures) and aortic cross sectional area indexed by body surface area (lower 2 figures) illustrated by logistic regression models. The dotted lines are 95% confidence bounds.
Figure 6. Risks of aortic events within 1 year based on initial aortic diameter versus early surgical mortality of elective thoracoabdominal aortic surgery are illustrated. Elective surgical mortality in current era ranges from 1.29% to 10.34% (gray zone) with the median rate of 5.06% (dotted line) according to recent meta-analysis by Piazza et al.24
Figure 1
Thoracic Aortic Aneurysm: N=3247

Inclusion
Maximal aortic diameter ≥ 35mm

Exclusion
Marfan syndrome
Aortic dissection
Inflammatory/neoplastic diseases
Isolated ascending aneurysm, etc.

N=821

Surgical indication at baseline?

Yes

Prompt Surgery
N=564

Refuse/Delay Surgery
N=103

Surgical indication (-)
N=154

No

Study Subjects

Follow-up Results

Aortic Event
N=24 (23.3%)

Elective Surgery
N=63 (61.2%)

No Surgery
N=16 (15.5%)

Aortic Event
N=7 (4.5%)

Elective Surgery
N=68 (44.2%)

No Surgery
N=79 (51.3%)

Figure 2
Figure 3

(A) Probability of aortic events over years after diagnosis for all patients, separated by possibility of event:
- Possible
- Definite

(B) Probability of aortic events for possible events, categorized by aortic size:
- Aorta ≥ 60 mm
- Aorta ≥ 50 mm, <60 mm
- Aorta < 50 mm

(C) Probability of aortic events for definite events, categorized by aortic size:
- Aorta ≥ 60 mm
- Aorta ≥ 50 mm, <60 mm
- Aorta < 50 mm

Number at risk:

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Aorta &lt; 50 mm</th>
<th>Aorta 50-60mm</th>
<th>Aorta ≥ 60mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>109</td>
<td>84</td>
<td>64</td>
</tr>
<tr>
<td>1</td>
<td>101</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Though the text is not visible in the image, it appears to discuss the probability of aortic events over years after diagnosis, categorized by possibility and aortic size, with corresponding number at risk for each category.
Figure 4

Probability of aortic events in 1 yr

Maximal aortic diameter, mm
Figure 5

**Definite event**
- Probability of event within 1 year vs. Maximal aortic diameter (mm)
- Probability of event within 1 year vs. Indexed aortic area

**Possible event**
- Probability of event within 1 year vs. Maximal aortic diameter (mm)
- Probability of event within 1 year vs. Indexed aortic area

**Absolute aortic diameter**

\[
\text{Probability of aortic event} = \frac{e^{(\beta_0 + \beta \times \text{Aorta})}}{1 + e^{(\beta_0 + \beta \times \text{Aorta})}}
\]

For definite event, \(\beta_0 = -5.697\) and \(\beta = 0.057\)
For possible event, \(\beta_0 = -6.191\) and \(\beta = 0.075\)

**Indexed aortic area**

\[
\text{Probability of aortic event} = \frac{e^{(\beta_0 + \beta \times \text{Aorta})}}{1 + e^{(\beta_0 + \beta \times \text{Aorta})}}
\]

For definite event, \(\beta_0 = -4.176\) and \(\beta = 0.110\)
For possible event, \(\beta_0 = -4.447\) and \(\beta = 0.147\)
Figure 6

The graph shows the probability of aortic event within 1 year as a function of maximal aortic diameter in millimeters. The x-axis represents the maximal aortic diameter, ranging from 40 to 80 mm, while the y-axis shows the probability of an event, ranging from 0 to 0.25. Two curves are depicted:

- **Possible event**
- **Definite event**

The area below the definite event curve represents the early surgical mortality, indicated with a shaded region.

American Heart Association.
Supplemental Table. Interim computed tomographic finding between baseline and aortic events in 14 patients who had adverse aortic events

<table>
<thead>
<tr>
<th>Case#</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Aorta diameter, mm</th>
<th>2\textsuperscript{nd} CT timing, mon*</th>
<th>Aortic expansion rate, mm/yr</th>
<th>Event type</th>
<th>Event timing, mon*</th>
<th>Surgery</th>
<th>Fatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>82</td>
<td>F</td>
<td>60</td>
<td>68</td>
<td>5.4</td>
<td>17.89</td>
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</tr>
<tr>
<td>2</td>
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<td>F</td>
<td>54</td>
<td>59</td>
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<td>3</td>
<td>70</td>
<td>F</td>
<td>49</td>
<td>58</td>
<td>12.0</td>
<td>9.03</td>
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<td>-2.38</td>
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</table>

Mean±SD: 75.6±7.1, 57.1±5.9, 62.4±7.9, 22.6±18.9, 3.9±6.1, 39.9±36.2

* From the time of diagnosis. Abbreviation: CT, computed tomography; TEVAR, thoracic endovascular aortic repair.
Supplemental Figure 1. Survival rates between the subject patients group and those who underwent surgical aortic replacement at the initial presentation (Surgery group, blue line). Subject patients were further classified based on their baseline aortic diameters: 50-55mm (orange), 55-60mm (red) and 60mm or greater (dark red).
Supplemental Figure 2. Kaplan-Meir plots for definite (A) and possible event rates (B) based on baseline aortic diameters.