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Cardiovascular Outcomes in Aortopathy: GenTAC Registry of Genetically Triggered Aortic Aneurysms and Related Conditions

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Abstract

Background: GenTAC Registry enrolled patients with genetic aortopathies between 2007–2016.

Objective: To compare age distribution and probability of elective surgery for proximal aortic aneurysm, any dissection surgery and cardiovascular mortality (CVM) among aortopathy etiologies.

Methods: Retrospective/Prospective design. Participants with bicuspid aortic valve with aneurysm (BAV, n=879), Marfan syndrome (MFS, n=861), non-syndromic Heritable Thoracic Aortic Disease (nsHTAD, n=378), Turner Syndrome (TS, n=298), Vascular Ehlers-Danlos syndrome (VEDS, n=149) and Loeys-Dietz syndrome (LDS, n=121) were analyzed.

Results: The 25% probability of elective proximal aortic aneurysm surgery was 30 years for LDS (95% CI: 18–37), followed by MFS (34 years, 95% CI: 32–36), nsHTAD (52 years, 95% CI: 48–56), and BAV (55 years, 95% CI: 53–58). Any dissection surgery 25% probability was highest in LDS (38 years, 95% CI: 33–53) followed by MFS (51 years, 95% CI: 46–57) and nsHTAD (54 years, 95% CI: 51–61). BAV experienced the largest relative frequency of elective surgery to any dissection surgery (254/33=7.7), compared to MFS (273/112=2.4), LDS (35/16=2.2), or nsHTAD (82/76=1.1). With MFS as the reference population, risk of any dissection surgery or CVM, was lowest in BAV patients (HR 0.13, 95% CI: 0.08–0.18; HR 0.13, 95%: CI 0.06–0.27). The greatest risk of mortality was seen in patients with vEDS.

Conclusions: Marfan and LDS cohorts demonstrate age and event profiles congruent with current understanding of syndromic aortopathies. BAV events weigh towards elective replacement with relatively few dissection surgeries. Non-syndromic HTAD patients experience near equal probability of dissection versus prophylactic surgery, possibly due to failure of early diagnosis.

Condensed Abstract:

The GenTAC Registry enrolled patients with genetic aortopathies over a period of 8 years. The current study’s objective is to compare probability and age distribution of elective surgery for proximal aortic aneurysm, emergent surgery for dissection, and cardiovascular death. Marfan

and LDS cohorts demonstrate age and event profiles congruent with current understanding of syndromic aortopathies. In contrast, BAV events weigh towards elective replacement. Non-syndromic HTAD is the least likely to undergo elective replacement. Genetic diagnosis with expanded aortopathy panels in the current era is crucial for management of these heritable diseases.

Keywords

aortic dissection; aortic aneurysm. Non-Syndromic Heritable Aortic Disease; Marfan; Loeys-Dietz; Bicuspid aortic valve; Turners; Vascular Ehlers-Danlos

INTRODUCTION

The GenTAC (Genetically Triggered Thoracic Aortic Aneurysm and Cardiovascular Conditions) Registry enrolled cohorts of patients with aortopathies due to multiple diagnoses over 8 years with the goal of evaluating cardiovascular and surgical outcomes(1,2). The purpose of the study design was to examine and compare diagnostic cohorts within a single repository of longitudinal data using biospecimen, imaging, and genetic data. Previous GenTAC studies have described the variability in surgical patterns and patterns of new dissections(3,4). In this study, we examine cardiovascular events between and within the largest diagnostic cohorts: Marfan Syndrome (MFS), Bicuspid aortic valve (BAV), Loeys-Dietz Syndrome (LDS), Turner syndrome (TS), Vascular Ehlers-Danlos (vEDS), and Non-syndromic Heritable Thoracic Aortic Disease (nsHTAD). We sought to determine the risk related to diagnosis, age of events, and timing of events based on age at diagnosis.

METHODS

Study population:

The rationale and design of the GenTAC Registry have been previously described(1). In brief, GenTAC was established as a longitudinal observational cohort study of individuals with heritable thoracic aortic aneurysms. Enrollment was initiated in 2007 with 6 clinical centers, with two additional centers added in 2011(2). Follow-up closed in 2016 at the conclusion of the study. While there were 11 diagnostic categories, the main diagnoses included: MFS, BAV, nsHTAD, vEDS, TS (XO or mosaic), and LDS (TGFBR1 or TGFBR2). Over 3700 participants were enrolled; each enrollment was reviewed for accuracy and confirmed by a study investigator.

Patients with Marfan syndrome were evaluated either by genetic testing or revised Ghent criteria (those entered prior to 2010 were re-evaluated and categorized accordingly). Non-syndromic HTAD required a first-degree family member with a proximal aortic dissection and absence significant syndromic features based on careful physical examination. A GenTAC Co-PI reviewed all enrollment diagnoses. Standardized data collection included clinical information related to physical phenotypic features, imaging studies, cardiovascular complications, genetic testing results, and surgical/endovascular interventions. Institutional Review Board approval was obtained for this study at each of the 8 participating GenTAC

clinical centers. Individual informed consent was obtained from each GenTAC Registry patient. We included the following diagnostic groups with a total of 2,686 participants: BAV (n = 879), MFS (n = 861), nsHTAD (n = 378), TS (n = 298), vEDS (n = 149) and LDS (n = 121).

Data Collection and demographics:

Data were collected from patient interviews and chart reviews at the primary center entered into the GenTAC database (RTI international) for coding and extracted for analysis in August of 2016. Demographic information included diagnosis, age at diagnosis, biological sex, race, and ethnicity. History of prior aortic interventions and dissection were extracted from medical charts while new dissections, surgical interventions, and death were identified during follow-up. Patients who withdrew from the study had data included up until their withdrawal date.

Genetic Testing:

Genetic testing forms were available for those who had documentation. This testing included commercial CLIA-approved labs and samples evaluated as a research protocol. At the time of the study (2007–2016), aortopathy gene panels were not available, and systematic genotyping was not performed due to funding limitations. As a result, some patients were tested as part of a research study, others were limited by insurance co-pay or in some cases, the patient may have refused testing. Turner syndrome, vEDS, nsHTAD, and Loey's-Dietz syndrome all required confirmation by a GenTAC co-investigator. Patients with Marfan syndrome were evaluated either by genetic diagnosis or revised Ghent criteria (those entered prior to 2010 were re-evaluated and categorized accordingly).

Cardiovascular Endpoints:

Proximal aortic aneurysm surgeries included valve-sparing and valve-replacement procedures. While most surgeries were confined to the aortic root, surgeries could extend into the aortic arch. Isolated aortic valve replacements were excluded. Aortic surgeries were classified as either elective proximal aortic aneurysm surgery, emergent proximal dissection surgery, or any aortic dissection surgery. Date of surgery for dissection was used as a surrogate endpoint for the date of aortic dissection due to ambiguities in the enrollment forms noted on review. Location and extent of the dissections were categorized based on the DeBakey Classification(5,6). Dissections managed without surgery were not included in surgical dissection analysis but were included in analysis related to CVM. In order to compare the percent elective ascending aortic replacements versus surgery for aortic dissection, we calculated an elective surgery to dissection surgery ratio for each diagnosis. Deaths were categorized as CVM or non-CVM related and reviewed for accuracy. Surgical outcomes for 30 mortality and surgical complications were reviewed.

Statistical Approach:

Descriptive methods were used to characterize the study population, dissection classifications, and the distribution of cardiovascular endpoints; mean and standard deviation for continuous variables as well as frequency and percentages for categorical variables

were calculated. To test for differences across diagnoses, we used ANOVA for continuous variables and chi-square tests for categorical variables. For illustrative purposes only, we calculated the relative frequency of elective proximal aortic aneurysm surgery to emergent proximal dissection surgery, and of elective proximal aortic aneurysm surgery any aortic dissection surgery for each diagnosis. Graphical methods were used to compare the age at which each cardiovascular outcome occurred across diagnoses. Preliminary evaluation of the time to each cardiovascular outcome included the creation of Kaplan-Meier plots using raw data. Median surgery-free time could not be calculated for most diagnoses, as less than half of most groups experienced a surgical event. Similarly, less than half of all diagnoses experienced a CVM, limiting our ability to calculate median survival time. As we aimed to describe when these events were occurred across diagnoses, we estimated the age at which risk was 25% for elective aortic aneurysm surgery and any aortic dissection surgery, and 5% for emergent proximal dissection surgery and CVM. In addition, we estimated the incidence of cardiovascular outcomes within the GenTAC registry using Poisson regression. To further assess the difference in risk of each cardiovascular surgery outcome, we created a Cox-proportional hazard (PH) model with MFS as the reference diagnosis group, gender as a co-variate, and chronical age as the timescale. Differences according to diagnosis in time to CVM-related mortality were modeled using a Fine-Gray model for competing risk of non-CVM related mortality. For all time-to-event models, assumptions were assessed, and no violations were identified. Time from age at diagnosis to age at each cardiovascular outcome was calculated. Descriptive statistics were used to assess these differences across diagnoses; t-tests or Mann-Whitney U tests were used to assess potential differences in this time span according to diagnosis. All analyses were performed in Stata/SE version 15.1.

RESULTS

Characteristics of the study cohort and cardiovascular endpoints:

Table 1 demonstrates the characteristics of the selected GenTAC diagnostic cohorts. Overall mean age at study entry was 36.9 years (SD 19.6 y). Distribution of sex was specific to each cohort diagnosis, with MFS, LDS, and vEDS more evenly distributed compared to nearly complete female assignment for TS. BAV and nsHTAD were predominantly male. Highlighted in Table 2 are the total and individual cardiovascular endpoints for each cohort. Elective proximal aortic aneurysm surgery (aortic root and/or ascending aorta) occurred either prior to or after study entry in 24.2 % of the total cohort, with the highest prevalence of elective aortic replacement occurring in MFS (31.7%) followed by BAV (28.9%). There were no reported elective aortic replacement operations in the vEDS cohort. Surgery for any aortic dissection was most common in the nsHTAD cohort (20.1%) compared to Marfan (13.0%) and LDS (13.2%). BAV experienced the largest relative frequency of elective proximal aortic surgeries for aneurysm to emergent proximal dissection surgeries (254/31=8.2), compared to MFS (273/54=5.1), LDS (35/11=3.2), or nsHTAD (82/51=1.6). When compared to any type of dissection surgery, BAV experienced the largest relative frequency of elective aortic surgeries to any aortic dissection surgeries (254/33=7.7), compared to MFS (273/112=2.4), LDS (35/16=2.2), or nsHTAD (82/76=1.1). In contrast CVM did not correspond to surgical frequency, where CVM was highest for vEDS (4.0%) followed by MFS (3.1%), nsHTAD (2.4%), LDS (1.7%), BAV (1.1%) and TS (0.7%).

Frequency and distribution of cardiovascular events across the lifespan:

We were interested in understanding the pattern of events by age and by diagnosis. The Central Illustration displays 6 panels of superimposed age distributions by diagnosis for the described endpoints: elective proximal aortic surgery, any surgery for aortic dissection, and cardiovascular mortality. Each diagnosis panel demonstrates a distinct distribution pattern. For MFS (top left), the histogram demonstrates elective proximal aortic aneurysm surgery occurred at a relatively high frequency early to mid-life compared to surgery for dissection or CVM, which occurred in mid to later life at relatively lower frequencies. For LDS (lower middle), elective proximal aortic aneurysm surgeries generally occurred at a much younger age than dissection surgeries. BAV (lower left) demonstrates a high frequency of elective proximal aortic aneurysm surgeries at all ages compared to any surgery for dissection. CVM in the BAV population occurred only at age 55 or older. Non-syndromic HTAD (upper middle) demonstrated the most heterogeneous age distributions where elective surgery for dissection and dissection surgery occurred across the age spectrum with the greatest frequencies for both types of surgeries during middle age. Histograms for TS (upper right) and vEDS (lower right) were challenging secondary to the small number of events; however, in both cases, CVM occurred at a relatively young age (40 years and under). As is often the case in vEDS, CVM occurs without precipitating surgical intervention.

Event free probability of cardiovascular endpoints:

Kaplan-Meier (KM) plots in Figure 1 display the event-free probability for proximal aortic aneurysm surgery (panel A), any aortic dissection surgery (panel B), emergent proximal dissection surgery (panel C), and CVM (panel D). In all panels, the risk of each event varied widely across diagnoses, and for some diagnoses, less than half of patients experienced an event. For this reason, we compare the age at which the risk of each surgical event was 25%, and the risk of CVM was 5%. Panel A displays that the probability of an elective proximal aortic aneurysm surgery was 25% for LDS at 30 years (95% confidence interval [CI]: 18–37), followed by MFS at 34 years (95% CI: 32–36), nsHTAD at 52 years (95% CI: 48–56), and BAV at 55 years (95% CI: 53–58). Elective Aortic replacement was rare in TS, and there were no patients with vEDS who underwent elective aortic repair. Panel B demonstrates that the risk of any aortic dissection surgery was highest in LDS (25% probability at 38 years, 95% CI: 33–53) followed by MFS (51 years, 95% CI: 46–57) and HTAD (54 years, 95% CI: 51–61). Any aortic dissection surgery in BAV was quite low, with an approximate 10% probability of dissection surgery at 80 years. Panel C displays the probability of emergent proximal dissection surgery was 5% at 31 years for LDS (95% CI: 15–36), 33 years for MFS (95% CI: 29–38), 35 years for nsHTAD (95% CI: 27–37), 45 years at TS (95% CI: 42-NA), and 59 years for BAV (95% CI: 53-NA). Shown in panel D, the risk of CVM was less than the risk of each surgical event. CVM occurred at older ages for nsHTAD and BAV patients (age of first case>45 years) compared to all other diagnosis groups (age of first case, range=19–28). The risk of CVM was 5% at 42 years for vEDS (95% CI: 24-NA), 53 years for MFS (95% CI: 50–57), 66 years for nsHTAD (95% CI: 53–79), and 75 years for BAV (95% CI: 67–80).

Incidence of cardiovascular outcomes:

The incidence of cardiovascular outcomes (Table 3) mirrors the Kaplan-Meyer plots. Per 10,000 patient-years, the incidence of any aortic dissection surgery is highest in LDS with 54.2 per 10,000 person-years (95% CI: 33.2–88.4), next in nsHTAD with 46.3 per 10,000 person-years (95% CI: 36.9–58.0), followed by MFS at 39.2 per 10,000 person-years (95% CI: 32.6 –47.2). Incidence of cardiovascular death was highest in vEDS at 11.9 per 10,000 person-years (95% CI: 5.3–26.6), followed by MFS at 9.2 per 10,000 person-years (95% CI: 6.2–13.3).

Risk of cardiovascular events by diagnosis and biological sex:

To understand the risk of adverse outcome events by diagnosis and sex, we generated a series of Cox proportional hazard models, using MFS as the reference population (Table 3). Compared to MFS, the risk of EPAS was substantially less in TS (Hazard Ratio [HR] 0.11, 95% CI: 0.05–0.23), BAV (HR 0.36, 95% CI: 0.30–0.43) and nsHTAD (HR 0.33, 95% CI: 0.25–0.42) and higher in the LDS cohort (HR 1.58, 95% CI: 1.07–2.34). Similar findings were demonstrated for any aortic dissection surgery and emergent proximal dissection surgery where vEDS and BAV were less likely to undergo dissection surgery compared to MFS, and LDS demonstrated a significantly higher HR (Table 3). No risk difference was seen in nsHTAD compared to MFS. We created a Fine and Gray competing risk model to examine the risk of CVM by diagnosis and sex. BAV and nsHTAD were at significantly lower risk for CVM compared to MFS. TS was also at lower risk, while vEDS and LDS were at higher risk, although none of these HRs reached statistical significance. Among all diagnoses, the female sex had a lower HR for elective surgery (HR 0.73, 95% CI: 0.61–0.88) and CVM (HR 0.49, 95% CI: 0.25–0.94). Supplemental Table 1 demonstrates surgical outcomes for elective and emergent procedures. In general, mortality for elective aortic replacement is very low; mortality from elective aortic aneurysm surgery was documented only in Marfan syndrome (n=2). Morbidity for elective aortic replacement for aneurysm was also low, with an overall 0.6% documenting a myocardial infarction and 1.2% stroke. The most common complication was prolonged intubation at 4.7%.

Age at diagnosis relative to age at cardiovascular event:

Cohorts with well-described phenotypic features (MFS, TS, LDS) were diagnosed at a younger age than those with BAV or nsHTAD, likely due to lack of syndromic features (table 5). Patients with TS were youngest at diagnosis (mean 6.1 y, SD 7.7 y), while those with BAV were the oldest (mean 37.0 y, SD 21.0 y). MFS and TS had the longest mean time in years prior to elective surgery or surgery for dissection (range 13–19 y for MFS and 21–30 y for TS). In contrast, BAV and nsHTAD had a much shorter time span between diagnosis and any aortic surgery event (1–6 y for both BAV and nsHTAD). In addition, the range of diagnosis to dissection for BAV was 0–4 years and nsHTAD 0–1 years. Age to event for Turner and vEDS were rare and difficult to demonstrate a trend. Of note, data for LDS is challenging to interpret as a number of patients, who were previously diagnosed with MFS, were reclassified by genetic testing. For patients with LDS, we compared patients with TGFBR1 to TGFBR2 and found no differences in age at cardiovascular events (table 6).

Genetic test results in nsHTAD:

Of the 378 patients with nsHTAD, 107 underwent limited genetic testing with 6 pathogenic variants identified. Of these 6 pathogenic variants, 5 patients experienced aortic events. Three patients with *ACTA2* or *TGFBR1* pathogenic variants were found to have undergone emergent surgery for aortic dissection. Two additional patients underwent elective proximal aortic surgery with subsequent testing revealing one with *SMAD3* and the other *TGFBR2* pathogenic variants. One patient tested positive with a pathogenic *MHY11.* The *MHY11* patient demonstrated aortic aneurysm with family history of dissection and experienced neither aortic dissection nor aortic replacement surgery during the time of the study.

DISCUSSION

The GenTAC Registry enabled comparisons between diagnosis cohorts predisposed to aortic aneurysm and dissection. While some cohorts, such as MFS, are extensively characterized, GenTAC has proved to be a rich source of clinical data for how diagnostic cohorts are affected by pregnancy, aortic dissection, surgery for aneurysms and imaging (3,7–10), as well as a resource for genetic discovery (11–14).

Acute aortic dissections cause substantial morbidity and mortality. In conditions such as MFS, early diagnosis and appropriate elective aortic root replacement has increased life expectancy (15), and the GenTAC data confirms this modified natural history. In addition, GenTAC results, along with other data, suggest that patients with LDS have a more severe disorder, with elective aortic replacement (generally recommended at a lower threshold) and dissection surgery at an earlier age and size (16). LDS patients characterized by a pathogenic variant in *TGFBR1* or *TGFBR2*, the Montalcino Aortic Consortium found that the relative risk of dissection is associated with female biological sex, aortic size, and LDS systemic features (17). These genetic predispositions are critical when deciding the timing of surgical intervention. It is interesting to note that 18.8% of GenTAC patients with LDS underwent surgery for dissection prior to their diagnosis (data not shown) as some patients with LDS had an initial clinical diagnosis of MFS that subsequently was modified by increased genetic testing over the course of the study.

Cardiovascular outcome and surgical management of BAV is distinct from other cohorts within this study. Historically, patients with BAV were reported to have an increased risk of ascending aortic dissection compared to patients with trileaflet aortic valves (18). However, multiple population studies have suggested increased morbidity but close to normal life expectancy (19). The GenTAC cohort of BAV patients demonstrates a greater relative frequency of elective aortic replacement to dissection aortic replacement compared to MFS, LDS, or nsHTAD. While many of these elective replacements may be at the same time as an aortic valve replacement, Nissen et al. (20) demonstrated in the combined BAV Consortium (BAVCon) and GenTAC registries that more than one-third of patients with a bicuspid aortic valve undergo ascending aortic replacement at diameters less than 45 mm. While the diameter of 45 may currently be considered small, the 2010 ACC/AHA guidelines (in effect during latter part of GenTAC enrollment and all of the follow-up period) recommended elective aortic replacement surgery at relatively smaller diameters (4.0–5.0 cm) for patients with vEDS, TS and BAV(21). Given the low incidence of the BAV

cohort undergoing surgery for dissection (3.8% compared to Marfan at 9% in GenTAC), a pressing question is whether the elective ascending aortic replacement is too aggressive for the BAV population or if these replacements, even at a smaller dimension, are a sign of a long-term successful preventive strategy for acute ascending aortic dissection (22). Conversely, Melvinsdottir et al. demonstrated that in a detailed population of Iceland, patients with BAV were twice as likely to present to the hospital with dissection over their known connective tissue counterparts(23), suggesting that subsets of patients with BAV are at higher risk. Current guidelines more specific to BAV and aortopathy have increased the size cut-off for surgery, but it is too early to assess the effect of this change(24). In addition, the ratio in our registry of 7.7 elective surgeries to dissection surgeries may appear to point to aggressive management; however, the low morbidity of the elective replacement and the lack of dissection events may demonstrate that this strategy has proven effective in reducing overall mortality in the BAV population.

In GenTAC, patients with nsHTAD have a shorter time interval between diagnosis and proximal aortic events, and these events occur at all ages (Central Figure). While those with unknown diagnoses in the GenTAC cohort did not undergo systematic genetic testing, we discovered that subsequent clinical or research genetic testing demonstrated pathogenic variants in six nsHTAD patients, including *ACTA2 and MYH11, TGFBR1, TGFBR2,* and *SMAD3*. In non-syndromic heritable thoracic aortic disease, there have been exciting recent discoveries related to familial genes associated with non-syndromic aneurysm and dissection(25) (26), including *TGFBR1* and *TGFBR2*(27). With further confirmatory research, these genes can be added to aortopathy panels (if not already added), which will assist in identifying at-risk family members. These genetic panels are particularly important as this heterogeneous group, along with BAV, generally do not have an obvious physical phenotype unless associated with a specific syndrome for BAV such as TS or LDS. If the remaining nsHTAD are tested with the larger 40 gene panels available today, more of these patients might have undergone elective proximal aortic aneurysn surgery rather than surgery for an acute ascending dissection.

Specific trends were more difficult to detect in the smaller cohorts in the GenTAC registry, i.e., vEDS and TS. Patients with TS were generally diagnosed early in life and had overall few cardiovascular events related to aortic dissection. Those with vEDS had the highest frequency of CVM; however, aortic dissection was rare, and replacement was not reported. Details regarding specific cardiovascular events were somewhat limited in GenTAC, and the remarkably low 2.1% CVM mortality is likely related to survivor bias in the registry as well as relatively short follow-up time. The GenTAC cohort is subject to referral bias, and findings may not reflect surgical management in a non-tertiary care center. It is important to note that although the investigators and NHLBI made attempts to enroll patients of various ethnic and racial backgrounds a priority, the registry reflects the demographic of the referral institutions. We assume significant under-reporting of non-white racial groups. Other limitations include the retrospective and prospective nature of the GenTAC dataset, which can pose a problem related to exact dates of dissection as well as change in clinical management. In particular, dissection rates may be influenced by whether the individual was the proband or identified by cascade screening, with the latter category presumably less likely to dissect given identification of the underlying diagnosis followed by appropriate

medical management, surveillance imaging, timely surgical intervention, and a clinically less evident disorder.

Conclusions:

The objective of the current GenTAC study is to compare frequency and age distribution of elective proximal aortic aneurysm surgery, emergent aortic dissection surgery, and cardiovascular death. Marfan and LDS, while maintaining a significant disease burden, demonstrate profiles congruent with current surgical recommendations, whereas aortic replacement in BAV remains controversial. In addition, heterogeneity of dissection surgery versus elective replacement in nsHTAD suggests risk alleles awaiting additional discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations List:

BAV	Bicuspid aortic valve
CVM	Cardiovascular mortality
GenTAC	Genetically Triggered Thoracic Aortic Aneurysm and Cardiovascular Conditions
LDS	Loeys-Dietz Syndrome
MFS	Marfan Syndrome
nsHTAD	Non-syndromic Heritable Thoracic Aortic Disease
TS	Turner syndrome
vEDS	Vascular Ehlers-Danlos

References

1. Eagle KA. Rationale and design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). Am Heart J 2009;157:319–26. [PubMed: 19185640]
2. Kroner BL, Tolunay HE, Basson CT et al. The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC): results from phase I and scientific opportunities in phase II. Am Heart J 2011;162:627–632.e1. [PubMed: 21982653]
3. Weinsaft JW, Devereux RB, Preiss LR et al. Aortic Dissection in Patients With Genetically Mediated Aneurysms: Incidence and Predictors in the GenTAC Registry. J Am Coll Cardiol 2016;67:2744–54. [PubMed: 27282895]

4. Song HK, Bavaria JE, Kindem MW et al. Surgical treatment of patients enrolled in the national registry of genetically triggered thoracic aortic conditions. Ann Thorac Surg 2009;88:781–7; discussion 787–8. [PubMed: 19699898]
5. LeMaire SA, Russell L. Epidemiology of thoracic aortic dissection. Nat Rev Cardiol 2011;8:103–13. [PubMed: 21173794]
6. DeBakey ME, Beall AC Jr., Cooley DA et al. Dissecting aneurysms of the aorta. Surg Clin North Am 1966;46:1045–55. [PubMed: 6003090]
7. Shalhub S, Roman MJ, Eagle KA et al. Type B Aortic Dissection in Young Individuals With Confirmed and Presumed Heritable Thoracic Aortic Disease. Ann Thorac Surg 2020;109:534–540. [PubMed: 31376376]
8. Frankel WC, Song HK, Milewski RK et al. Open Thoracoabdominal Aortic Repair in Patients With Heritable Aortic Disease in the GenTAC Registry. Ann Thorac Surg 2020;109:1378–1384. [PubMed: 31568749]
9. Asch FM, Yuriditsky E, Prakash SK et al. The Need for Standardized Methods for Measuring the Aorta: Multimodality Core Lab Experience From the GenTAC Registry. JACC Cardiovasc Imaging 2016;9:219–26. [PubMed: 26897684]
10. Holmes KW, Maslen CL, Kindem M et al. GenTAC registry report: gender differences among individuals with genetically triggered thoracic aortic aneurysm and dissection. Am J Med Genet A 2013;161a:779–86. [PubMed: 23444191]
11. Corbitt H, Gutierrez J, Silberbach M, Maslen CL. The genetic basis of Turner syndrome aortopathy. Am J Med Genet C Semin Med Genet 2019;181:117–125. [PubMed: 30770620]
12. Corbitt H, Morris SA, Gravholt CH et al. TIMP3 and TIMP1 are risk genes for bicuspid aortic valve and aortopathy in Turner syndrome. PLoS Genet 2018;14:e1007692. [PubMed: 30281655]
13. Fujita D, Preiss L, Aizawa K et al. Circulating interleukin-6 (IL-6) levels are associated with aortic dimensions in genetic aortic conditions. PloS one 2019;14:e0214084. [PubMed: 30883599]
14. Prakash S, Kuang SQ, Regalado E, Guo D, Milewicz D. Recurrent Rare Genomic Copy Number Variants and Bicuspid Aortic Valve Are Enriched in Early Onset Thoracic Aortic Aneurysms and Dissections. PloS one 2016;11:e0153543. [PubMed: 27092555]
15. Pyeritz RE. Marfan syndrome: improved clinical history results in expanded natural history. Genet Med 2019;21:1683–1690. [PubMed: 30573797]
16. Loeys BL, Schwarze U, Holm T et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788–98. [PubMed: 16928994]
17. Jondeau G, Ropers J, Regalado E et al. International Registry of Patients Carrying TGFBR1 or TGFBR2 Mutations: Results of the MAC (Montalcino Aortic Consortium). Circ Cardiovasc Genet 2016;9:548–558. [PubMed: 27879313]
18. Roberts WC, Vowels TJ, Ko JM. Natural history of adults with congenitally malformed aortic valves (unicuspid or bicuspid). Medicine (Baltimore) 2012;91:287–308. [PubMed: 23117850]
19. Siu SC, Silversides CK. Bicuspid aortic valve disease. Journal of the American College of Cardiology 2010;55:2789–800. [PubMed: 20579534]
20. Nissen AP, Truong VTT, Alhafez BA et al. Surgical repair of bicuspid aortopathy at small diameters: Clinical and institutional factors. JTCVS 2020;159:2216–2226 e2.
21. Hiratzka LF, Bakris GL, Beckman JA et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol 2010 Apr 6;55(14):e27–e129. [PubMed: 20359588]
22. Roman MJ, De Backer J. Hereditary thoracic aortic disease: How to save lives. JTCVS 2021.
23. Melvinsdottir IH, Lund SH, Agnarsson BA, Sigvaldason K, Gudbjartsson T, Geirsson A. The incidence and mortality of acute thoracic aortic dissection: results from a whole nation study. Eur J Cardiothorac Surg 2016;50:1111–1117. [PubMed: 27334108]

24. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021 Feb 2;77(4):450–500. [PubMed: 33342587]

25. Renard M, Francis C, Ghosh R et al. Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysm and Dissection. Journal of the American College of Cardiology 2018;72:605–615. [PubMed: 30071989]

26. Elbitar S, Renard M, Arnaud P et al. Pathogenic variants in THSD4, encoding the ADAMTS-like 6 protein, predispose to inherited thoracic aortic aneurysm. Genet Med 2021;23:111–122. [PubMed: 32855533]

27. Tran-Fadulu V, Pannu H, Kim DH et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. J Med Genet 2009;46:607–13. [PubMed: 19542084]

Perspectives

Competency in Patient Care and Procedural Skills:

Genetic screening for familial aortopathy may lead to reclassification of variants of unknown significance as pathogenic, especially in families with mild phenotypes.

Translational Outlook:

Additional research is needed to identify patients with genetically triggered aortopathy at risk of dissection at relatively small aortic diameters to refine recommendations on the timing of surgical intervention.

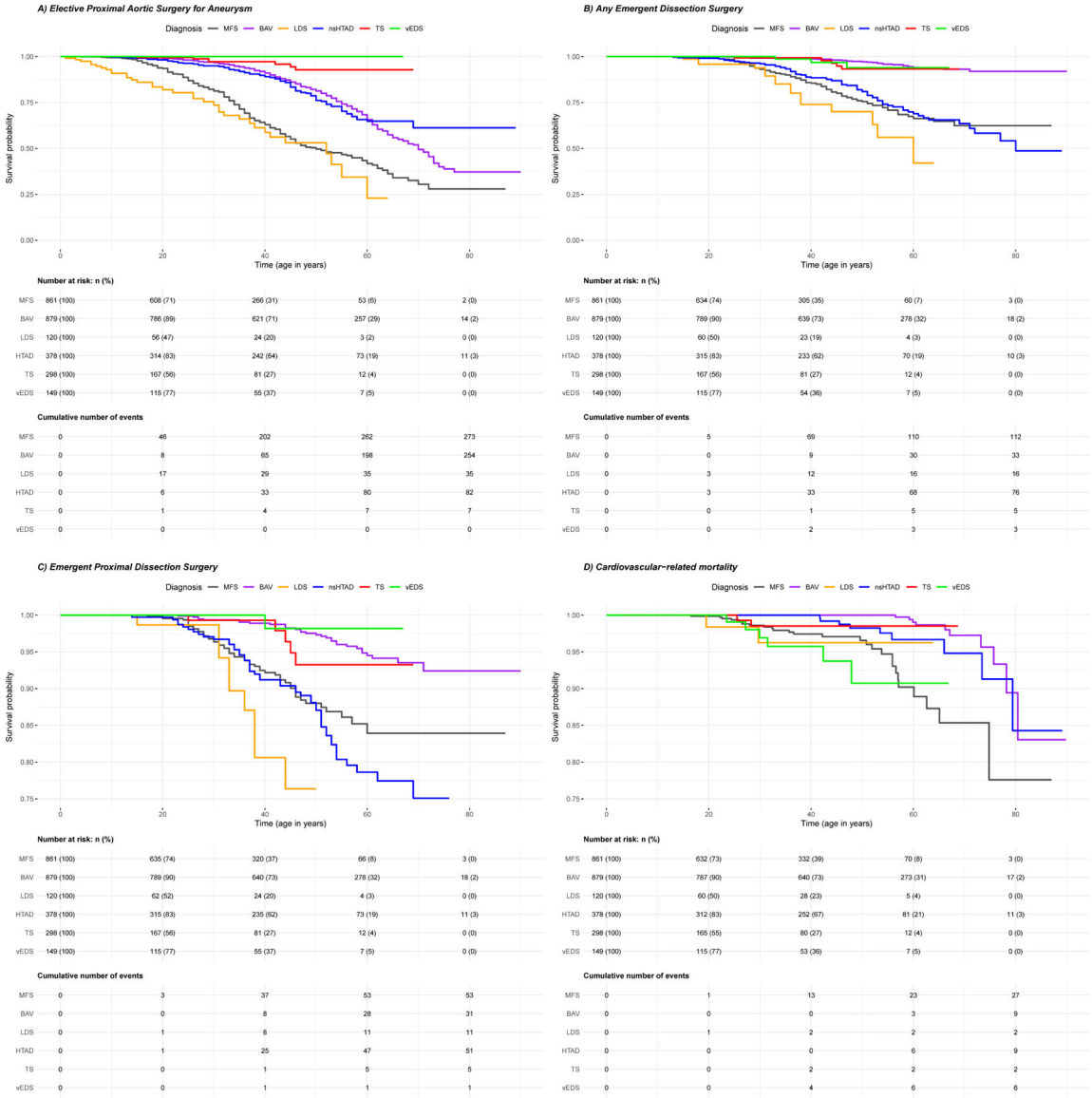
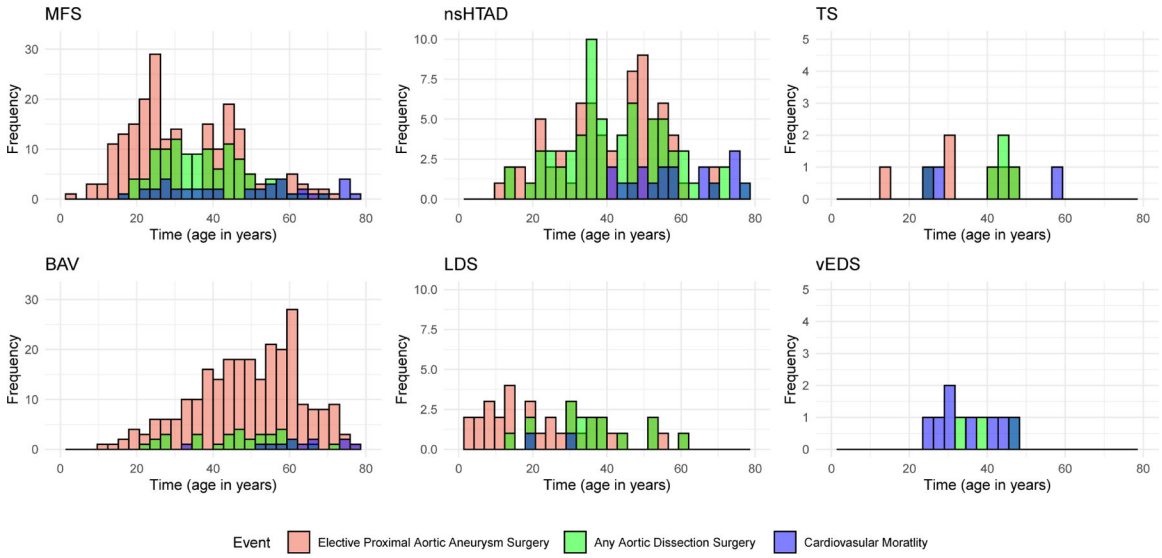


Figure 1. Event-free probability for aortic events among diagnosis group

Kaplan-Meier plots display the probability and time to cardiovascular events, since birth, for the GenTAC cohort; each color represents a separate diagnosis. Panel A demonstrates the probability of an elective proximal aortic aneurysm surgery. Panel B demonstrates probability of any aortic dissection surgery. Panel C displays the probability of emergent proximal dissection surgery and panel D demonstrates probability of CVM. Marfan and LDS cohorts demonstrate age and event probabilities congruent with current understanding of syndromic aortopathies. BAV events weigh towards elective replacement with relatively few dissection surgeries. CVM is greatest in vEDS cohort.



Central Illustration. Distribution of Cardiovascular Events by Age in the GenTAC Registry

Each panel displays histograms for each cardiovascular endpoint by diagnosis: 1) elective proximal aortic aneurysm surgery (pink), 2) any aortic dissection surgery (green), and 3) cardiovascular mortality (blue). Blended colors represent more than one endpoint with identical frequency at a given age. MFS (top left), LDS (bottom middle) demonstrate event patterns consistent with current understanding of these diseases. BAV (lower left), demonstrates high frequency of elective proximal aortic aneurysm surgery relative to dissection surgery. Non-syndromic HTAD (upper middle) demonstrates marked heterogeneity among endpoints with considerable overlap. Vascular EDS presents with sudden CVM at a young age.

Table 1.

Characteristics of the GenTAC study cohort

Characteristic		Total N=2,686	MFS N=861	BAV N=879	LDS N=121	nsHTAD N=378	TS N=298	vEDS N=149	p-value[a]
Enrollment age mean (SD)		36.9 (19.6)	31.3 (17.5)	46.1 (18.2)	23.44 (16.7)	43.0 (19.29)	26.0 (17.0)	32.5 (15.7)	<0.01
Sex, n (%)	Male	1,526 (56.8)	466 (54.1)	690 (78.5)	56 (46.3)	259 (68.5)	1 (0.3)	54 (36.2)	<0.01
	Female	1,160 (43.2)	395 (45.9)	189 (21.5)	65 (53.7)	119 (31.5)	297 (99.7)	95 (63.8)	
Race, n (%)	White	2,402 (90.0)	756 (88.6)	797 (91.2)	106 (88.3)	333 (88.6)	268 (90.2)	142 (95.3)	<0.01
	Black/African American	90 (3.4)	48 (5.6)	14 (1.6)	6 (5.0)	11 (2.9)	8 (2.7)	3 (2.0)	
	Asian	81 (3.0)	27 (3.2)	35 (4.0)	1 (0.8)	12 (3.2)	5 (1.7)	1 (0.7)	
	American Indian/Alaska Native	15 (0.6)	5 (0.6)	1 (0.1)	0 (0.0)	6 (1.6)	3 (1.0)	0 (0.0)	
	Native Hawaiian/Pacific Islander	43 (1.6)	6 (0.7)	19 (2.2)	4 (3.3)	9 (2.4)	3 (1.0)	2 (1.3)	
	Unknown/No answer	38 (1.4)	11 (1.3)	8 (0.9)	3 (2.5)	5 (1.3)	10 (3.4)	1 (0.7)	
Hispanic/Latino origin, n (%)	No	2,265 (84.3)	738 (85.7)	697 (79.3)	113 (93.4)	316 (83.6)	264 (88.6)	137 (91.9)	<0.01
	Yes	169 (6.3)	71 (8.2)	33 (3.8)	8 (6.6)	21 (5.6)	25 (8.4)	11 (7.4)	
	Unknown/No answer	252 (9.4)	52 (6.0)	149 (17.0)	0 (0.0)	41 (10.8)	9 (3.0)	1 (0.7)	

Diagnosis abbreviations: MFS, Marfan syndrome; BAV, Bicuspid aortic valve with enlargement; LDS, Loeys Dietz syndrome; nsHTAD, Non-synromic Heritable thoracic aortic disease; TS, Turner syndrome; vEDS, vascular Ehlers Danlos syndrome

Abbreviations: SD, standard deviation

[a]p-values from ANOVA for continuous variables and chi-square for categorical variables

Table 2:

Cumulative Number of Cardiovascular Outcomes in the GenTAC Cohort

Outcome		Total N=2,686	MFS N=861	BAV N=879	LDS N=121	nsHTAD N=378	TS N=298	vEDS N=149	p-value [a]
Elective proximal aortic aneurysm surgery, ever had, n (%)	No	2,035 (75.8)	588 (68.3)	625 (71.1)	86 (71.1)	296 (78.3)	291 (97.7)	149 (100.0)	<0.01
	Yes	651 (24.2)	273 (31.7)	254 (28.9)	35 (28.9)	82 (21.7)	7 (2.3)	0 (0.0)	
Any aortic dissection surgery, ever had, n (%)	No	2,441 (90.9)	749 (87.0)	846 (96.2)	105 (86.8)	302 (79.9)	293 (98.3)	146 (98.0)	<0.01
	Yes	245 (9.1)	112 (13.0)	33 (3.8)	16 (13.2)	76 (20.1)	5 (1.7)	3 (2.0)	
DeBakey dissection type, n (%)[n]	Type I	88 (36.4)	36 (32.7)	12 (36.4)	8 (50.0)	30 (40.0)	1 (20.0)	1 (33.3)	<0.01
	Type II	65 (26.4)	18 (15.5)	19 (57.6)	3 (18.8)	21 (28.0)	4 (80.0)	0 (0.0)	
	Type IIIa	33 (13.2)	21 (18.2)	1 (3.0)	2 (12.5)	9 (12.0)	0 (0.0)	0 (0.0)	
	Type IIIb	56 (22.7)	34 (30.9)	1 (3.0)	3 (18.8)	16 (20.0)	0 (0.0)	2 (66.7)	
Mortality, n (%)	CVM	56 (2.1)	27 (3.1)	10 (1.1)	2 (1.7)	9 (2.4)	2 (0.7)	6 (4.0)	<0.01
	Other causes	33 (1.2)	14 (1.6)	4 (0.5)	0 (0.0)	12 (3.2)	1 (0.3)	2 (1.3)	

Diagnosis abbreviations: MFS, Marfan syndrome; BAV, Bicuspid aortic valve with enlargement; LDS, Loeys Dietz syndrome; nsHTAD, Non-syndromic Heritable thoracic aortic disease; TS, Turner syndrome; vEDS, vascular Ehlers Danlos syndrome

Abbreviations: CVM, cardiovascular mortality; SD, standard deviation

[a] p-values from chi-square tests

[b] n=3 dissections could not be classified

Table 3:

Incidence of Cardiovascular Outcomes in the GenTAC Cohort

	Incidence Rate per 10,000 p-y (95% CI)							
	Total	**MFS**	**BAV**	**LDS**	**nsHTAD**	**TS**	**vEDS**	**p-value** [a]
Elective proximal aortic surgery	64.0 (59.3, 69.1)	100.4 (89.2, 113.1)	60.7 (53.6, 68.6)	124.3 (89.3, 173.2)	49.5 (39.9, 61.5)	8.4 (4.0, 17.7)	0 (0, 0)	<0.01
Any aortic dissection surgery	23.5 (20.7, 26.7)	39.2 (32.6, 47.2)	7.7 (5.4, 10.8)	54.2 (33.2, 88.4)	46.3 (36.9, 58.0)	6.0 (2.5, 14.5)	6.0 (1.9, 18.6)	<0.01
Emergent proximal dissection surgery	14.5 (12.3, 17.0)	18.3 (13.9, 23.9)	7.2 (5.0, 10.2)	36.9 (20.4, 66.6)	30.8 (23.4, 40.6)	6.0 (2.5, 14.5)	2.0 (2.8, 14.2)	<0.01
CVM	5.2 (4.0, 6.8)	9.1 (6.2, 13.3)	2.3 (1.2, 4.3)	6.5 (1.6, 26.2)	5.2 (2.7, 10.1)	2.4 (0.6, 9.6)	11.9 (5.3, 26.6)	<0.01

Diagnosis abbreviations: MFS, Marfan syndrome; BAV, Bicuspid aortic valve with enlargement; LDS, Loeys Dietz syndrome; nsHTAD, Non-syndromic Heritable thoracic aortic disease; TS, Turner syndrome; vEDS, vascular Ehlers Danlos syndrome

Abbreviations: CI, confidence interval; CVM, cardiovascular-related mortality; IR, incidence rate; py, patients-years; SD, standard deviation

[a]Incidence rates estimated from Poisson regression; p-value from likelihood ratio chi-square test

Table 4.

Cox proportional hazard model: Risk of surgery for aneurysm, dissection or cardiovascular death

	Hazard Ratio (95% CI)[a]							
Diagnosis	**Elective proximal aortic aneurysm surgery** [b]	**p-value** [b]	**Any aortic dissection surgery** [b]	**p-value** [b]	**Emergent proximal aortic dissection surgery** [b]	**p-value** [b]	**Cardiovascular-related mortality** [c]	**p-value** [c]
MFS	ref	<0.01	ref	<0.01	ref	<0.01	ref	<0.01
BAV	**0.36 (0.30–0.43)**	-	**0.12 (0.08–0.19)**	-	**0.26 (0.17–0.41)**	-	**0.13 (0.06–0.27)**	-
LDS	**1.58 (1.07, 2.34)**	-	**1.81 (1.07–3.05)**	-	**2.67 (1.40–5.06)**	-	1.24 (0.28–5.49)	-
nsHTAD	**0.33 (0.25–0.42)**	-	0.84 (0.63–1.13)	-	1.23 (0.83–1.81)	-	**0.32 (0.15–0.69)**	-
TS	**0.11 (0.05–0.23)**	-	**0.18 (0.07–0.45)**	-	0.41 (0.16–1.06)	-	0.60 (0.13–2.74)	-
vEDS[d]	-	-	**0.16 (0.05–0.51)**	-	**0.12 (0.02–0.86)**	-	2.11 (0.83–5.37)	-
Sex, female	**0.73 (0.61–0.88)**	<0.01	0.89 (0.68–1.17)	0.41	0.83 (0.58–1.19)	0.32	**0.49 (0.25–0.94)**	0.03

Diagnosis abbreviations: MFS, Marfan syndrome; BAV, Bicuspid aortic valve with enlargement; LDS, Loeys Dietz syndrome; nsHTAD, Non-syndromic Heritable thoracic aortic disease; TS, Turner syndrome; vEDS, vascular Ehlers Danlos syndrome

Abbreviations: CI, confidence interval; ref, reference group

[a] Hazard ratios that are statistically significant (p-value<0.05) are indicated in bold font

[b] Hazard ratios are from Cox proportional hazard model in which age is the time scale; p-values from chi-square tests for overall effect of each variable.

[c] Hazard ratios are from Fine and Gray competing risk model in which age is the time scale; competing risk = mortality from all other causes. p-values from chi-square tests for overall effect of each variable.

[d] Ehlers Danlos Vascular was excluded from the elective surgery for proximal aortic aneurysm as this group did not have this event

Table 5.

Age at diagnosis relative to age at cardiovascular event

	MFS	BAV	LDS	nsHTAD	TS	vEDS	p-value [a]
Mean age at diagnosis, mean (SD)	15.7 (14.8)	37.0 (21.0)	18.7 (15.9)	35.8 (18.9)	6.1 (7.7)	25.7 (15.7)	<0.001
Difference between age in years at diagnosis and age at elective proximal aortic aneurysm surgery, median (IQR) [b]	12.0 (2.0–20.0)	1.0 (1.0–6.0)	1.0 (−0.5–1.0)	1.0 (1.0–6.0)	21.5 (14.5–28.5)	-	<0.001
Difference between age in years at diagnosis and age at any aortic dissection surgery, median (IQR) [b]	13.0 (1.0–23.0)	1.0 (0.0–4.0)	1.0 (0.0–2.5)	0.0 (0.0–1.0)	30.0 (-)	1.0 (−1.0–2.0)	<0.001
Difference between age in years at diagnosis and age at emergent proximal dissection surgery, median (IQR) [b]	2.0 (0.0–18.0)	1.0 (0.0–1.0)	1.0 (−3.0–1.0)	0.0 (0.0–1.0)	30.0 (-)	-1.0 (-)	<0.001
Difference in age in years between diagnosis and CVM, median (IQR) [b]	14.5 (10.0–22.0)	4.5 (2.0–11.0)	22.0 (-)	14.0 (8.5–17.5)	28.0 (-)	5.5 (3.0–7.0)	0.037

Diagnosis abbreviations: MFS, Marfan syndrome; BAV, Bicuspid aortic valve with enlargement; LDS, Loeys Dietz syndrome; nsHTAD, Non-syndromic HTAD, Heritable thoracic aortic disease; TS, Turner syndrome; vEDS, vascular Ehlers Danlos syndrome

Abbreviations: CVM, cardiovascular-related mortality; IQR, interquartile range; SD, standard deviation

[a] p-values from t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed data

[b] Positive differences indicate a diagnosis occurred prior to an event and negative differences indicate a diagnosis occurred after an event

Table 6.

Age at outcomes for those with Loeys Dietz syndrome

	TGFBR1	TGFBR2	p-value[a]
Age at elective proximal aortic aneurysm surgery, median (IQR)	18 (13–38)	19 (8.5–33.5)	0.8686
Age at any aortic dissection surgery, median (IQR)	44 (33–52)	33 (29–38)	0.1940
Age at emergent proximal aortic dissection surgery, median (IQR)	38.5 (33–44)	35.5 (31–38)	0.6128
Age at CVM, median (IQR)	-	24.6 (19.5–29.7)	-

[a] p-values from Mann-Whitney U tests