2 When Should Surgery Be Performed in Marfan Syndrome and Other Connective Tissue Disorders to Protect Against Type A Dissection?

Yskert von Kodolitsch, Peter N. Robinson, and Jürgen Berger

Abstract

In western countries, thoracic aortic aneurysms and dissections (TAAD) are a common cause of death. Among patients with TAAD, 9 % have Marfan syndrome, and another 19 % exhibit a family history of TAAD which is unrelated to Marfan syndrome. Patients with heritable TAAD usually develop aortic rupture or dissection at an age under 40 years. Before the evolution of open-heart surgery, affected persons died from aortic dissection or rupture at young age. Currently, Marfan patients and most other individuals with heritable TAAD face a close to normal life-expectancy because elective replacement of the proximal aorta (type A dissection) is performed before aortic dissection or rupture develop.

We discuss all major medical rationales for performing surgery in Marfan syndrome and other connective tissue disorders to protect against type A dissection. These rationales comprise consideration of guidelines (1), of aortic biomechanics (2), of expected normal aortic diameters (3), of the speed of aortic growth (4), of aortic geometry and shape (5), and of etiology of aortic disease (6). The discussion of each of these six approaches follows the same pattern, which is first, explanation of the basic rationale of each approach with presentation of supporting data, second discussion of the limits and presentation of conflicting data, and third a final conclusion with statement of our personal view on the respective issue. Finally, we introduce the concept of our so-called "strategic decision making paradigm" that introduces the patient as a person into the surgical decision making process.

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Background

In the United States aortic aneurysms account for up to 47,000 deaths annually [1] and they rank as the 19th most common cause of death in the US population irrespective of age, sex, or race [2]. Based on ICD-9 codes, thoracic aortic aneurysms and dissections (TAAD) are identified as the cause for ≥26 % of ≥135,000 hospitalizations for aortic aneurysms in a 5-year period from 2002 to 2007 [3]. Among 520 TAAD patients registered in the Yale aneurysm databank, the cause of TAAD was Marfan syndrome in 50 individuals (9 %), whereas another 101 patients (19 %) exhibited a family history of TAAD which was unrelated to Marfan syndrome [4]. In contrast to idiopathic or degenerative TAAD patients with heritable TAAD usually develop aortic rupture or dissection at an age <40 years [5]. Currently the spectrum of diseases that cause heritable TAAD is now known to be much broader than formerly recognized [6–10]. In addition, whereas mutations in the *FBN1* gene in Marfan patients were the only known major causes for heritable TAAD [11], numerous new causative genes for TAAD phenotypes have now been discovered [12–19]. Until today, Marfan syndrome remains the single most frequent cause of heritable TAAD, and the one that has been best investigated. Thus, the syndrome remains the disease model for heritable TAAD.

Marfan syndrome is a disorder of the connective tissue with an estimated prevalence of 1 in 3,000–5,000 individuals and no predilection for either sex. [20] The syndrome is inherited as an autosomal dominant trait with complete penetrance but with highly variable phenotypic expression. Complications comprise severe scoliosis, pectus excavatum, spontaneous pneumothorax, retinal detachment and glaucoma resulting from dislocated lenses, but these rarely develop before adulthood. Before the development of open-heart surgical procedures for prophylactic replacement of the aortic root, Marfan patients usually died from aortic dissection or rupture of the proximal aorta at a mean age of 32 years [21, 22]. Currently, Marfan patients and most other individuals with heritable TAAD may enjoy a nearly normal life-expectancy because elective replacement of the proximal aorta (type A dissection) is performed before aortic dissection or rupture develop [23].

Method

We discuss the question when to perform aortic surgery in adults with Marfan syndrome and other connective tissue disorders to protect against type A dissection. We do not consider special issues such as timing of surgery in children, in adolescents or during pregnancy. From an exclusively medical perspective the basic question is how to identify the time where the risk of dissection is higher than the risk of surgery in terms of life-expectancy [24]. Instead of providing a straightforward answer, we elucidate major approaches to decision making with respect to the elective timing of surgery. These major approaches comprise consideration of guidelines (1), of aortic biomechanics (2), of expected normal aortic diameters (3), of the speed of aortic growth (4), of aortic geometry and shape (5), and of etiology of aortic pathology including a family history of aortic dissection (6). The discussion of each of these six approaches follows the same pattern, comprising first, an explanation of the basic rationale of each approach with presentation of supporting data, second a discussion of the limits and

Table 2.1 Guideline recommendations for elective replacement of the proximal aorta in adults with heritable aortic disease

	CSANZ [25]	Canadian [26]	ACCF/AHA [3]	ESC/EACTS [27]
All adults with MFS	SOV >5.0 cm	SOV or TAA >5.0 cm (Class I, level B)	SOV or TAA ≥5.0 cm (Class I, level C)	SOV ≥5.0 cm; irrespective of AVR (Class I, level C)
Lower intervention thresholds	SOV >4.5 cm with FH of AOD, or aortic growth >5–10 mm/year, or significant AVR	SOV or TAA >4.5–5.0 cm with FH of AOD at <5.0 cm, or aortic growth >5 mm/year, or progressive AVR[b], or severe MVR that requires surgery (Class I, level B)	External AOR or TAA <5.0 cm with FH of AOD at <5.0 cm, or aortic growth >5 mm/year, or significant AVR	SOV ≥4.5 cm with FH of AOD, or aortic growth >2 mm/year, or severe AVR, or severe MVR (Class IIa, level C)
Women planning pregnancy	SOV >4.7 cm[a]	Maximal SOV or TAA >4.4 cm (Class I, level B)	SOV or TAA >4.0 cm (Class IIa, level C)	SOV or TAA >4.5 cm, or AVR > mild degree (Class IIa, level C)[c]
All adults with LDS or with TGFBR1/2 mutation			Internal aortic diameter ≥4.2 cm on TEE, or external aortic diameter ≥4.4–4.6 cm on CT/MRI (Class IIa, level C)	
Patients with MFS, or other genetic diseases or with BAV			Maximal SOV or TAA cross-sectional area (πr^2; cm^2) divided by patient's height (m) >10, or patients undergoing aortic valve repair with SOV or TAA >4.5 cm (Class IIa, level C)	
Patients with BAV			AOR or TAA >5.0 cm, or aortic growth ≥5 mm/year [28] (Class I, level C)	SOV or TAA ≥5.0 cm with CoA, or systemic hypertension, or FH of AOD, or aortic growth >2 mm/year (Class IIa, level C)

The abbreviations are explained in Box 1. In parenthesis we provide the class of recommendation and the level of evidence as classified in the guideline

[a]The risk is lower for pregnancy following elective aortic root replacement for aortic diameters of ≥4.7 cm

[b]Especially if the surgeon believes the aortic valve can be spared and an aortic valve-sparing procedure is planned

[c]The same recommendations are classified Class I, Level C in the ESC guidelines for the management of grown-up congenital heart disease [29]

presentation of conflicting data, and third, a final conclusion with statement of our personal view on the respective issue. Moreover, in Tables 2.1, 2.2, 2.3, 2.4, 2.5, and 2.6 we provide results from the literature which offers support for decision making on the timing of surgery. We do not comment on each study listed in these tables. Rather, the Tables are designed to encourage the readers to assess the quality of data themselves and to draw their own conclusions. Finally, we introduce the concept of our so-called "strategic decision making paradigm" that introduces the patient as a person into the surgical decision making process.

Table 2.2 Expert recommendations for elective replacement of the proximal aorta in adults with heritable aortic disease

	Purpose/rationale	Method	Recommendation for elective surgery
Ergin et al. [30]	The data emerging on MFS patients point out the fallacy of applying an absolute size criterion to all patients. One should be thinking more in terms of ratios or aortic indices rather than absolute sizes	Aortic ratio for SOV [cm][a] is defined according to Roman et al. [31] $Age_{18–40\ ys} = (SOV/(0.97 + 1.12*BSA)$ $Age \geq_{40\ ys} = (SOV/(1.92 + 0.74*BSA)$	Recommendations for elective surgery of the aortic root MFS with FH of AOD: aortic ratio ≥1.3 Chronic AOD: aortic ratio ≥1.3 DTAA without AVR: aortic ratio ≥1.5 DTAA with relevant AVR: aortic ratio ≥1.5 BAV with dysfunction: aortic ratio ≥1.4 Other cardiac surgery: aortic ratio ≥1.5 Surgeons' experience: aortic ratio + 0.15
Svensson and Khitin [32]	15 % of MFS patients have AOD at <5.0 cm. Because stature influences aortic diameter, the usefulness of aortic cross-sectional area indexed to height was evaluated for timing of surgery	Analysis of aortic diameters in 23 MFS patients with surgery for aortic dissection	Perform elective operation of the aorta in MFS with Aortic cross-sectional area to body height ratio $R = \pi r^2[cm^2]/height[m] > 10$
Svensson et al. [33]	35 % of patients with BAV have AOD at ≤5.5 cm	CT, MRI, and TTE performed before aortic replacement were reviewed in 40 BAV patients with AOD (36 men, 4 women; mean age 50 years)	Elective operation of the aorta in BAV disease with TAA >4.5 cm or with AXR to body height ratio $R = \pi r^2[cm^2]/height[m] > 10$
Codecasa et al. [34]	Purpose: to calculate the right time for elective surgery, when the operative risk is lower than the risk of dilation related complications	Predictions are based on 2-dimensional TTE measurements of aortic ridge according to Roman et al. [31]	Potential indication for surgery with R (risk for AOD or AOR) >2.7, where R is calculated as $R = e^{C*[MD–PD]/MD}$ Surgery should not be delayed if aortic size is higher than the critical aortic size, calculated as Critical aortic size = PD × K Where MD is the measured SOV [cm], PD the predicted SOV according to Roman et al. [cm] [31], and C the coefficient defined as 4.3 for MFS, 3.5 for BAV, and 3.0 for other conditions. K is defined as 1.45 for MFS, 1.55 for BAV, and 1.65 for other conditions
Sievers [35]	Author suggests a liberalized, but aggressive approach to tailoring surgical threshold values to the individual's characteristics	Assessment of the upper limits (>2 SD) of the normal diameter of SAR [31] and definition of an entity factor as 1.10 for MFS, 1.20 for BAV requiring surgery, and for DTAA with AVR, 1.25 for BAV not requiring valve surgery, and 1.30 for DTAA without valve pathology	Calculate the smallest acceptable measured diameter of SAR requiring no surgical intervention as $Age_{18–40\ ys} = (1.48 + 0.82*BSA)*entity\ factor$ $Age \geq_{40\ ys} = (2.35 + 0.62*BSA)*entity\ factor$ Definition of upper acceptable absolute threshold diameter SAR for elective surgery as 4.0 cm for MFS, 4.3 cm for BAV and for DTAA with concomitant valve replacement, and 5.0 cm for DTAA without valve surgery

Table 2.2 (continued)

	Purpose/rationale	Method	Recommendation for elective surgery
Davies et al. [36]	Propose ASI for appropriate surgical decision-making. ASI (defined as aortic diameter [cm]/BSA [m^2]) rather than absolute aortic size predicts AOD, AOR, or both	Serial imaging using MRI, CT, TTE, TEE, and angiography. Aneurysm of TAE defined as maximum aortic diameter ≥3.5 cm, age >6 years at presentation, absence of congenital aortic malformations, and ≥1 size measurement before operative repair. Exclusion of patients with chronic AOD at presentation	ASI allows for the stratification of patients into 3 levels of risk for surgical decision making ASI <2.75 cm/m^2 (low risk; ~4 % per year), ASI = 2.75–4.24 cm/m^2 (moderate risk; ~8 % per year), ASI ≥4.25 cm/m^2 (high risk; ~20 % per year)

The abbreviations are explained in Box 1
[a]BSA was calculated as an index of obesity according to Stavig et al. [37]

Guidelines

Rationale and Supporting Data

Since guidelines are available, timing of elective surgery may simply be about following these guidelines. Indeed, the European Society of Cardiology states that their "guidelines summarize and evaluate all evidence available [. . .] with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition [. . .]" [89]. Within the last 5 years, the Australian CSANZ Cardiovascular Genetics Working Group [25], the Canadian Cardiovascular Society [26], the American Heart Association [3], and the European Society of Cardiology [89] have proposed guidelines for elective replacement of the aortic root in Marfan patients. As listed in Table 2.1, these guidelines uniformly recommend elective replacement of the aortic root in Marfan patients at diameters >5.0 cm with lower thresholds when risk factors are present such as a family history of aortic dissection, rapid aortic growth, or severe aortic or mitral valve regurgitation with indication for surgery. In women with Marfan syndrome who plan pregnancy, the recommendations for elective aortic root replacement vary between diameters >4.0 cm and >4.7 cm. Whereas the AHA recommends elective aortic surgery in patients with bicuspid aortic valve disease at diameters >5.0 cm, or with aortic growths >5 mm/year, the ESC is more conservative by recommending surgery at diameters >5.0 cm only with additional risk factors. The AHA guideline also provides recommendations for elective aortic root replacement in Loeys-Dietz patients (Table 2.1) [3].

Limits and Conflicting Data

The Canadian recommendations for elective aortic root surgery in Marfan patients and those released by the AHA and ESC are all based on the same available evidence. Interestingly, however, the Canadian Cardiovascular Society assigns this evidence to level "B", which means that data are derived from a single randomized clinical trial or from large non-randomized studies, whereas the AHA and the ESC assign the evidence to level "C", meaning that recommendations are based only on consensus of opinion of experts and/or small studies, retrospective studies, and/or registries (Table 2.1) [89]. Evidence is pivotal for proper interpretation of recommendations [90] and discrepancies in assessing the quality of evidence points out to variance of expert judgements. Moreover, many experts suggest operating earlier and some recommend intervention already at diameters ≥4.0 cm (Table 2.2) [30, 32–36]. Finally, extensive aortic growth is considered a

Table 2.3 Normative values of proximal aortic diameters in adults

	Study population	Method of measurement	Equations
Henry et al. [38]	92 younger normal subjects (age 1 month–23 years) and 136 older normal subjects (age 20–97 years)	TTE. SOV measured using exclusively M-mode at end-diastole at the onset of the QRS complex, using leading edge–to–leading edge technique [39]	Prediction of mean SOV [mm] for both age groups[a] $SOV_{mean} = 24.0^{*}(BSA)^{1/3} + 0.1^{*}(AGE) - 4.3$ Prediction of 95 percentile of SOV [mm] for both age groups $SOV_{95percentile} = SOV + 0.18^{*}SOV$
Roman et al. [31]	135 adults (age 20–74 years, mean 54 years) derived from the healthy, employed population, and unaffected relatives and spouses of patients evaluated in family studies of mitral prolapse and MFS	TTE. ANU, SOV, SAR and TAA measured in parasternal long-axis using 2-dimensional measurements at end-diastole using leading edge technique	Z-score for SOV [cm][b] $Z_{age<40\ ys} = (SOV - (0.97 + 1.12^{*}BSA))/0.24$ $Z_{age\geq 40\ ys} = (SOV - (1.92 + 0.74^{*}BSA))/0.37$ Z-score for SAR $Z_{age<40\ ys} = (SAR - (1.48 + 0.82^{*}BSA))/0.21$ $Z_{age\geq 40\ ys} = (SAR - (2.35 + 0.62^{*}BSA))/0.33$
Reed et al. [40]	182 persons (age 17–26, mean 21 years) recruited from local colleges and universities with a body height >95th percentile (≥189 cm in men; ≥175 cm in women) with exclusion of heart disease, hypertension, or phenotypic features of MFS	TTE. SOV measured in the parasternal long-axis using 2-dimensional guided M-mode at end-diastole using leading edge–to–leading edge technique [39]	Expected mean SOV [cm] $SOV = -1.915 + 3.826^{*}BSA - 0.704^{*}BSA^{2}$ 95 percentiles can be obtained from a nomogram but they can not be calculated
Hager et al. [41]	70 consecutive adults (17–89, mean 50 years) with CT for various non-cardiovascular indications, with exclusion of cardiovascular disease	Contrast enhanced helical CT with measurements of the internal aortic diameter at SOV, and TAA at their maximum size. Calculation of ratios of diameters as SOV/TADd and as TAA/TADd	Expected mean aortic diameter [cm] $SOV = 0.0124^{*}age[ys] + 2.36$ $TAA = 0.0153^{*}age[ys] + 2.32$ 97.5 percentile of ratios of aortic diameters SOV/TADd = 1.7 TAA/TADd = 1.6 Z-scores or 95 percentiles can be obtained from a nomogram but they can not be calculated
Hannuksela et al. [42]	77 consecutive adults (age 18–82, mean 54 years) with exclusion of acute aortic dissection	Spiral CCT with TAA measured 20 mm and 40 mm above the aortic valve	Upper normal limit of TAA [mm][c] Extreme body size = $21 + 0.14^{*}age + 0.41^{*}BMI$ Normal body size = $31 + 0.16^{*}age$
Wolak et al. [43]	4,039 adults (age 26–75 years) undergoing coronary artery calcium scanning	NCCT. TAA measurements of the outer aortic wall perpendicular to the axis of rotation of the aorta in the axial plane at the lower level of the pulmonary artery bifurcation	Expected mean TAA[d] Male = $13.01 + 0.17^{*}age[ys] + 5.80^{*}BSA$ Female = $14.10 + 0.13^{*}age[ys] + 5.80^{*}BSA$ 97.5 percentile of expected TAA

Table 2.3 (continued)

	Study population	Method of measurement	Equations
Biaggi et al. [44]	1,799 adults (age 20–80 years) with normal cardiac findings, exclusion of non-tricuspid aortic valves, and proven or suspected connective tissue disease such as MFS or EDS	TTE. SOV and TAA measured in the in parasternal long-axis using 2-dimensional guided M-mode at end-systole using leading edge–to–leading edge technique	95th percentile [cm][e] $SOV_{(men)} = 2.250 + 0.023^{*}age - 0.00014^{*}age^2 + 0.486^{*}BSA$ $TAA_{(men)} = 1.691 + 0.028^{*}age - 0.00009^{*}age^2 + 0.505^{*}BSA$ $SOV_{(women)} = 2.145 + 0.021^{*}age - 0.00014^{*}age^2 + 0.448^{*}BSA$ $TAA_{(women)} = 1.614 + 0.028^{*}age - 0.00012^{*}age^2 + 0.525^{*}BSA$
Shiran et al. [45]	150 adults (age 22–90 years, mean 49 years) with normal TTE findings or with severe heart failure, with severe valvular disease (excluding those with AVR), or with other cardiac conditions which were all expected not to affect diameters at LVOT and SOV	TTE. SOV and LVOT measured in the parasternal long-axis using 2-dimensional measurements at maximum dimension, typically at end-systole, using leading edge–to–leading edge technique	Expected mean SOV [cm] $SOV = 0.99 + 1.06^{*}LVOT[cm]$

The abbreviations are explained in Box 1
[a]Method for calculation of BSA is not reported
[b]BSA was calculated as an index of obesity according to Stavig et al. [46]
[c]TAA20/40 is a compound measure for the TAA measured at 20 or 40 mm above the aortic valve
[d]BSA was calculated according to the formula of Mosteller [47]
[e]Equations for 5th percentiles are also available

Table 2.4 Predicted mean sov in 14 adult putative patients

Patient				Method of prediction of normal SOV (cm)				
ID	Age (ys)	Sex	BSA (m^2)	Henry [38]	Roman [31]	Reed [40]	Hager [41]	Wolak [43]
1	20	M	1.7	2.6	2.9	2.6	2.6	2.6
2	20	F	1.8	2.7	3.0	2.7	2.6	2.7
3	35	M	1.9	2.9	3.1	2.8	2.8	3.0
4	35	F	2.0	2.9	3.2	2.9	2.8	3.0
5	40	M	2.1	3.0	3.5	3.0	2.9	3.2
6	40	F	2.2	3.1	3.5	3.1	2.9	3.2
7	45	M	2.3	3.2	3.6	3.2	2.9	3.4
8	45	F	2.4	3.2	3.7	3.2	2.9	3.4
9	50	M	2.5	3.3	3.8	3.3	3.0	3.6
10	50	F	2.6	3.4	3.8	3.3	3.0	3.6
11	55	M	2.7	3.5	3.9	3.3	3.0	3.8
12	55	F	2.8	3.5	4.0	3.3	3.0	3.7
13	60	M	2.9	3.6	4.1	3.3	3.1	4.0
14	60	F	3.0	3.6	4.1	3.2	3.1	3.9

F identifies female persons, *M* male persons; other abbreviations are explained in Box 1

Table 2.5 Growth rates of the proximal aorta in adults with thoracic aortic aneurysm

	Study population	Method of measurement	Annual growth rate
Legget et al. [48]	62 patients (age 1–54, mean 21 years) with MFS and serial echocardiography, of whom 56 patients had no events, and 6 patients developed events defined as death or surgery for AOD-A or aneurysm	Serial TTE of SOV measured in parasternal long-axis using 2-dimensional measurements at end-diastole using leading edge–to–leading edge technique with calculation of aortic ratios according to Roman et al. [31]	Rate of annual change of SOV diameter [mm/year] Patients without aortic events = 0.7 Patients with aortic events = 5 Rate of annual change of SOV ratios [ratio/year] Patients without aortic events = 0.00 Patients with aortic events = 0.15
Coady et al. [49]	79 patients (mean age 59 years) with thoracic aortic aneurysm defined as maximum diameter ≥3.5 cm (16 with chronic AoD, 15 with MFS) with serial imaging over mean of 26 months (see also [50])	Serial imaging using MRI (22 %), CT (34 %), and TTE (44 %)	Annual growth rate [mm/year] of aneurysm TAE = 1.2; TAA = 1.0; TAD = 2.9 Growth rate [mm/year] prediction equations; time [months] and diameters [mm] $TAE_{final} = TAE^{*}_{baseline} e^{(0.001395^{*}time)}$ $TAA_{final} = TAA^{*}_{baseline} e^{(0.001571^{*}time)}$ $TAD_{final} = TAD^{*}_{baseline} e^{(0.004598^{*}time)}$
Shimada et al. [51]	88 patients (52 men, 36 women) with TAA defined as maximum aortic diameter ≥3.5 cm (52 with non-dissecting TAA, 30 with chronic AoD, and 6 with mixed pathology) with serial imaging over ≥6 months	Serial MRI or CT. Aortic outer diameter was measured using a calliper method, calculating diameter from the reference within the image.	Mean linear expansion rate at any thoracic aortic site = 2.6 mm/year Growth rate [mm/year] prediction equation at any thoracic aortic site (TAE); time [months] and diameters [mm] $TAE_{final} = TAE^{*}_{baseline} e^{(0.00367^{*}time)}$
Meijboom et al. [52]	113 men (age 18–65, median 25 years) and 108 women (age 18–68, median 27 years) with MFS studied separately. AOR at baseline in men median 4.2 cm (2.8–6.2 cm), in women median 3.7 cm (2.5–6.0 cm). Serial imaging over 4.2 years (men) and 4.4 years (women)	Serial TTE of the native SOV measured in the parasternal long-axis using 2-dimensional guided M-mode at end-diastole using leading edge–to–leading edge technique	Average annual aortic growth rate [mm/year] in men All men $SOV_{men} = 0.42$ Fast growing SOV_{men}(15%of men) = 1.5 Slow growing SOV_{men}(85%of men) = 0.36 Average annual aortic growth rate [mm/year] in women All women $SOV_{women} = 0.38$ Fast growing SOV_{women}(11%of women) = 1.8 Slow growing SOV_{women}(89%of women) = 0.27

Lazarevic et al. [53]	43 patients (mean age 22 ± 14 years; range 1–59 years, 23 males) with MFS, TTE follow-up ≥ 1 year, and no proximal aortic surgery before baseline TTE with the mean follow-up period of 5.2 ± 3.2 years (range 1–10 years)	Serial TTE of ANU, SOV, SAR, and TAA measured in the parasternal long-axis using 2-dimensional guided M-mode at end-diastole using leading edge–to–leading edge technique	Average annual aortic growth rate [mm/year] in all patients ANU = 0.4; SOV = 1.5; SAR = 0.7; TAA = 0.4
Donnelly et al. [54]	32 women with MFS and 52 pregnancies without previous aortic surgery, followed prospectively throughout pregnancy with a minimum of 3 pre-pregnancy TTE, 3 intra-partum TTE, and 3 post-partum TTE	TTE of SOV measured in parasternal long-axis using 2-dimensional measurements at end-systole using leading edge technique	Growth of SOV during pregnancy = 3 mm

The abbreviations are explained in Box 1

Table 2.6 Therapeutic recommendations according to etiology

Etiology of aortic disease[a]	Aortic and cardiovascular phenotype characteristics	Recommendations for surgical management
Marfan syndrome (MFS); Gene with causative mutations: *FBN1*	Mean age at death is 32.0 ± 16.4 years without treatment as compared to >60 years with optimal treatment. >80 % of all deaths in untreated patients are caused by AOD or AOR. Cardiovascular co-manifestations: MVP (~58 % of adults), BAV (5 %), CoA (2 %), ASD (2 %), PDA (1 %), VSD (0.7 %), sporadic reports on aneurysms of iliacal or subclavian artery	(1) SOV >50 mm or >45 mm in patients with FH of AOD, or with rapid aortic growth (>5–10 mm/year), or with significant AVR. (2) Prophylactic surgery with AHR (πr^2; cm^2) of TAA >10. (3) Annual imaging is recommended if stability of SOV/TASS is documented. If the maximal aortic diameter is ≥4.5 cm, or if the aortic diameter shows significant growth from baseline, more frequent imaging should be considered
Loeys-Dietz syndrome type 1 (LDS1); Genes with causative mutations: *TGFBR1* and *TGFBR2*	Mean age at first major event: 24.5 years. Mean age at death 22.6 (0.5–45 years). Location of aortic aneurysms in 64 patients: TAA (84 %), AA (8 %), TAD (6 %), TAT (5 %). Cardiovascular co-manifestations: aneurysms in arterial branches in 64 patients: thoracic (27 %), head or neck (11 %), abdominal (3 %). Other features in 40 patients: Arterial tortuosity (84 %), PDA (35 %), ASD (22 %)	Young children: surgery with TAA >99th percentile and ANU >1.8 cm. Adolescents and adults: surgical repair with TAA ≥4.0 cm. Patients should have yearly MRI from the cerebrovascular circulation to the pelvis. Surgical procedures are not complicated by tissue fragility. Surgical repair of the aorta is reasonable in all adults with LDS or a confirmed TGFBR1 or TGFBR2 mutation and an aortic diameter ≥4.2 cm by TEE (internal diameter) or 4.4 to ≥4.6 cm CT and/or MRI (external diameter)
Loeys-Dietz syndrome type 2 (LDS2); Genes with causative mutations: *TGFBR1* and *TGFBR2*	Mean age at first major event: 29.8 years. Mean age at death 31.8 (18–47 years). Location of aneurysms in 26 patients: TAA (85 %), TAT (23 %), TAD (19 %), AA (15 %). Location of aneurysms in arterial branches: abdominal (15 %), thoracic (8 %), head or neck (8 %). Arterial tortuosity (67 %)	Similar surgical thresholds like in type 1 phenotype; peri-operative mortality: 4.8 %
Familial aneurysm, TAAD2 locus (TGFBR2-TAAD); Gene with causative mutations: *TGFBR2*	Analysis of 40 patients in 3 families: AOD-A (50 %), TAA aneurysm (43 %), distal aortic aneurysm or AOD-B (15 %). AOD-A prior to reaching a diameter of 50 mm (some with 42 mm). Aneurysms of the cerebral, carotid, and popliteal arteries	Patient with the TGFBR2 mutation R460 should be operated upon at TAA 4.0–4.2 cm
TGFB2-associated TAAD; Gene with causative mutations: TGFB2	The median age at presentation of aortic disease was 35 years, Location of aneurysm at SOV (14/19 individuals), AOD in 3/23 individuals (all ≥31 years of age). Cerebrovascular disease in 3/10, arterial tortuosity in 3/5, MVP in 3/19 individuals	No recommendations published. Aortic disease location and prognosis seems similar to MFS

Table 2.6 (continued)

Etiology of aortic disease[a]	Aortic and cardiovascular phenotype characteristics	Recommendations for surgical management
Aneurysms-osteoarthritis syndrome (AOS); Gene with causative mutations: *SMAD3*	OMS patients died suddenly at an age of 34–69 years (most patients died because of AOD). All AOD at adulthood; youngest patient with AOD was 34 years of age. Thoracic aortic aneurysm was present in 28/39, abdominal aortic aneurysm in 4/33, aortic dissection/rupture in13/39, aneurysm(s) of thoracic/abdominal arteries in 9/25, aneurysm(s) of cerebral arteries in 6/16, aortic tortuosity in 10/26, arterial tortuosity of thoracic/abdominal arteries in 8/21, arterial tortuosity of cerebral arteries in 8/16, ventricular hypertrophy in 6/33, atrial fibrillation in 8/33, mitral valve anomalies in 18/36, and congenital heart malformation (including ASD, PDA, pulmonary valve stenosis and BAV) in 3/33 individuals	Van der Linde et al. present detailed recommendations for cardiovascular management of OMS: (1) Pregnancy should be considered high risk in AOS patients with aneurysms, as in those with MFS and LDS. (2) Medical treatment with losartan, beta-blockade, or both may be beneficial. Stringent control of hypertension to limit aortic wall stress is recommended. (3) We suggest applying the surgical recommendations for LDS. Valve-sparing aortic root replacement using the reimplantation technique is the intervention of choice. (4) For peripheral aneurysms, individual size or rate of growth and location must determine the treatment strategy. (5) Life expectancy and size, location, and rate of growth of the aneurysm are the most important determinants to decide whether intervention is needed. (6) For postoperative surveillance, we recommend TTE at 6 months postoperatively and annually thereafter to monitor aortic root diameter and valve competence
Ehlers-Danlos syndrome, vascular type (vEDS); Gene with causative mutations: COL3A1	Mean age at first major event: 24.6 years; median survival: 48 years. First arterial dissection or rupture at mean age 24.7 years. Location of aortic complications in 24 patients with 132 arterial complications: TAT (4.5 %), TAD (7.6 %), AA (5.3 %). Fatal complications during or immediately after vascular surgery occur in 45 %. Dissection and rupture of medium-sized arteries	A higher threshold for operating on non-ruptured AOD is recommended, particularly for elective operations that carry excessive risk of complications, and in patients with sporadic disease and mild phenotype
Turner syndrome (TS) 45,X karyotype (women with complete or partial monosomy for the X chromosome)	Mortality of TS is increased with a standardized mortality ratio (SMR) of 2.86 (95 % confidence interval, 2.18–3.55). 50 % of females with 45, X die before age of ~62 years. The estimated incidence of AOD is 36 per 100,000 Turner's syndrome years, compared with an incidence of 6 per 100,000 in the general population. The incidence of AOD is also reported as ~618 cases per 100,000 TS-years (almost 100-fold higher than for women in general. Onset of AOD between age 20–40 years. Two-thirds AOD-A; on-third AOD-B. Cardiovascular co-manifestations: BAV (~30 %), CoA (~12 %), septal defects (≤2 %); MVP (≤2 %)	TS patients with aortic anomalies, dilation, or both need close follow-up, control of blood pressure. TS patients with significant aortic valve disease and aortic dilation, replacement of TAA should be considered at aortic valve replacement. Individuals with ASI >2.0 cm/m^2 require close cardiovascular surveillance. Those with ASI ≥2.5 cm/m^2 are at highest risk for AOD. Patients should undergo imaging of the heart and aorta for evidence of BAV, CoA, or dilatation of TAA. If initial imaging is normal and there are no risk factors for AOD, repeat imaging should be performed every 5–10 years or if otherwise clinically indicated. If abnormalities exist, annual imaging or follow-up imaging should be done

(continued)

Table 2.6 (continued)

Etiology of aortic disease[a]	Aortic and cardiovascular phenotype characteristics	Recommendations for surgical management
Osteogenesis imperfecta (*OI*); Genes with causative mutations: *COL1A1*, *COL1A2*	Dilatation of the SOV (12 % of 66 patients at age 5–64 years), 3 case reports on AOD-A and 1 report with AOD-B. Cardiovascular co-manifestations: MVP in 7 % of 29 OI patients aged ≥16 years	Special efforts are required because of the fragility of tissues and propensity for bleeding. Reinforcement of any vascular suture line should be considered to reduce failure and bleeding
Familial aneurysm, (TAAD with PDA at 16p locus); Gene with causative mutations: *MYH11*	Aneurysm of TAA sparing SOV, AOD-A and AOD-B; 1 woman with AOD-A at 48 years with aortic root diameter of 4.4 cm. PDA, intracranial carotid dissection, association with stroke and coronary artery disease is discussed but not proven	No specific treatment recommendations published
Familial aneurysm, TAAD4 locus (TAAD4); Gene with causative mutations: *ACTA2*	67 % of deaths caused by AOD-A, 15 % at diameters <50 mm. AOD often < age 20 years. Cardiovascular co-manifestations: PDA, BAV	No specific treatment recommendations published
Bicuspid aortic valve disease (BAV); Gene with causative mutations in some families: *NOTCH1*	A study of 13 families (unknown NOTCH1 mutation status) with at least one individual with aortic aneurysm: 35 % (39/110) of family members had BAV/TAA or TAA, and 11 of 13 families had maximal dilatation above SAR. Vascular dissection or rupture occurred in 7 of 13 families and in individuals with structurally normal aortic valves	In patients with non-syndromic BAV ESC guidelines recommend operation at diameters >5.0 cm (irrespective of specific gene or mutation involved). All first-degree relatives should receive echocardiographic follow-up at regular intervals regardless of the presence or absence of BAV. Aggressive treatment with replacement of both the SOV and the TAA is recommended

Literature used for MFS [3,11, 21, 33, 55], LDS1 and LDS2 [13,37, 56–58], *TGFBR2*-TAAD [12, 15, 59, 60], *TGFB2-associated* TAAD [18, 19], AOS, vEDS [61–67], TS [68–74], OI [75–77], TAAD with PDA at 16p locus [12, 16, 78–81], TAAD4 [17, 82–87], and BAV

"Recommendation for Patients with Loeys-Dietz syndrome or a confirmed genetic mutation known to predispose to aortic aneurysms and aortic dissections (TGFBR1, TGFBR2, FBN1, ACTA2, or MYH11) should undergo complete aortic imaging at initial diagnosis and 6 months thereafter to establish if enlargement is occurring"

"Patients with Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes and other patients with dilatation of the aortic root and sinuses of Valsalva should undergo excision of the sinuses in combination with a modified David reimplantation operation if technically feasible or, if not, root replacement with valved graft conduit"

[a]Inheritance other than autosomal-dominant is indicated

risk factor for early onset of aortic dissection or rupture. Hence, all guidelines recommend using this criterion. However, recommended thresholds for aortic growth vary between >2 mm/year [88] and >5–10 mm/year [25]. This translates into a maximum of 500 % difference in the recommended thresholds of annual millimeters of aortic growth, which appears unacceptably large variance of expert recommendations.

Comment

The guidelines provide highly useful orientation to guide complex decisions for elective surgery of the aortic root. It must be kept in mind, however, that these recommendations are mainly derived from expert opinions that are based on scarce and conflicting data. The rate of early and late postoperative complications has decreased continuously

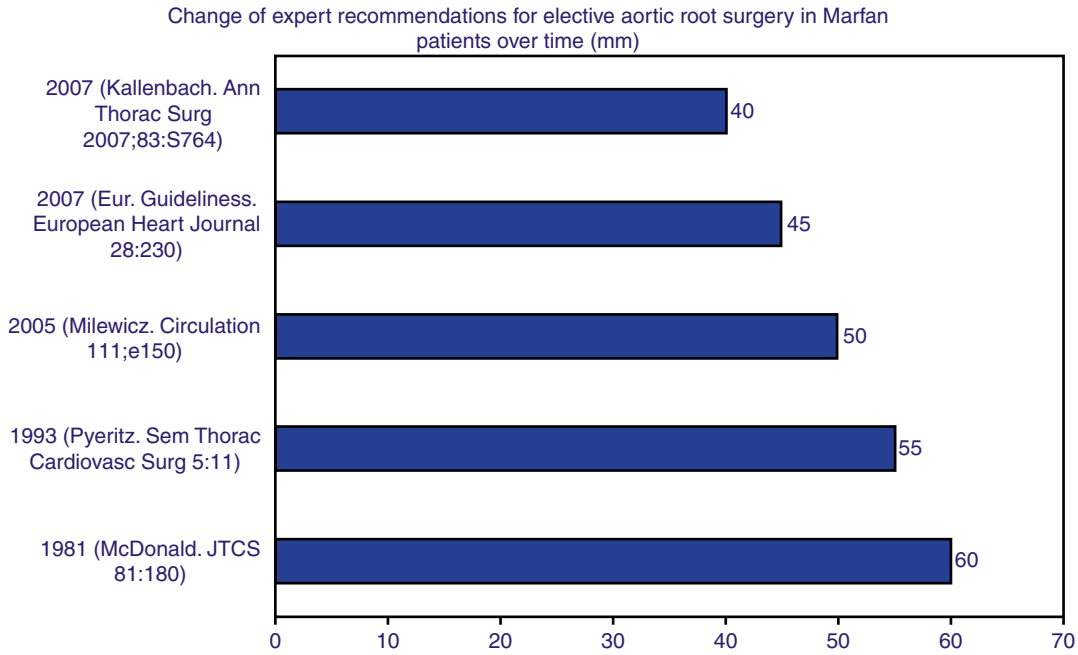

Fig. 2.1 Expert recommendations from different eras of aortic surgery: the thresholds for elective intervention dropped with increasing experience and improved surgical results. The recommendation of Kallenbach et al. refers to Marfan patients with additional risk factors [90]

over time and recommended thresholds for elective intervention have correspondingly dropped with these advances (Fig. 2.1). Most importantly, with the rise of reconstructive surgical techniques such as the David procedure, the postoperative course of patients has improved significantly because patients usually escape the need for lifelong anticoagulation [90, 91]. Thus, surgeons with outstanding surgical results tend to be more aggressive than a presumed average surgeon, who forms the basis for guideline recommendations [30, 35, 90].

Aortic Biomechanics

Rationale and Supporting Data

The law of Laplace and its modifications provide the basic biomechanical paradigm for the prediction of aortic rupture and dissection [92–94]. This law describes circumferential wall stress of a cylinder as the product of the pressure gradient and the radius of the cylinder divided by the thickness of the cylinder wall (Fig. 2.2) [92, 93, 95]. Some surgeons express the law of Laplace as the simple clinical rule that "gradual, continuous dilatation is the sine qua non of aortic dissection" [92], or even simpler, "that a balloon blown up to its limit of elasticity would pop" [1]. Indeed, many studies were performed to establish a "size-rupture correlation" [49, 96–100]. Finally, based on their analysis of 54 patients with ascending aortic aneurysms, Coady et al. concluded that when the diameter of the ascending aorta reached a "hinge point" of 6 cm, the probability of dissection or rupture increases dramatically by 32.1 percentage points [49]. Until today, the recommendation to perform prophylactic surgery at 5.5 cm of the ascending aorta in idiopathic aneurysm is based on this "hinge- point" finding in 54 TAAD patients [101]. However, more recently, a French cohort study of 732 Marfan patients with follow-up over a mean of 6.6 years documented a risk for aortic dissection or sudden death of 0.09 % per year with aortic root diameters <40 cm and of

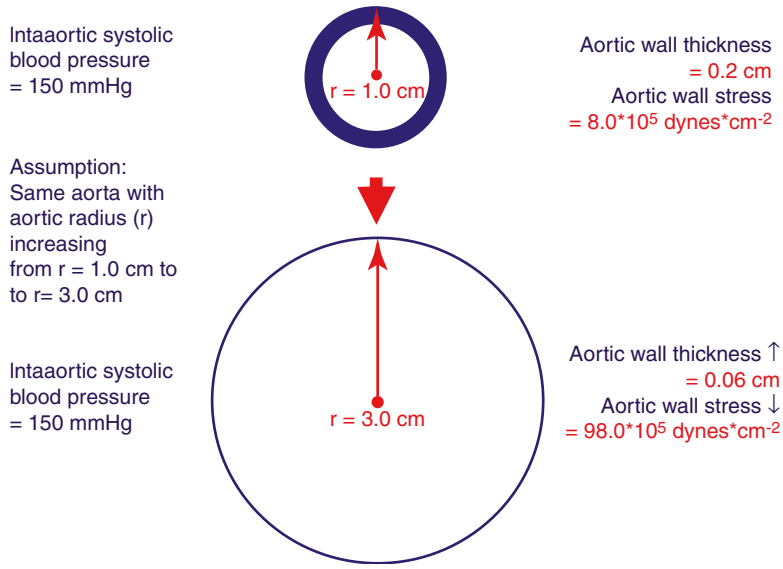

Fig. 2.2 The law of Laplace as explained by Robicsek [93]: the aortic wall with an external radius of 1.0 cm, an inside radius of 0.8 cm and a blood pressure of 150 mmHg would be exposed to a circumferential stress of $8.0*10^5$ $dyn*cm^{-2}$. If the aorta is dilated to an external radius of 3.0 cm and an internal radius of 2.94 cm, the wall thickness deceases from 0.2 cm to 0.06 cm and the wall tension increases to $98.0*10^5$ $dyn*cm^{-2}$

0.3 % per year with diameters of 45–49 mm. The "hinge point" with a four times increase of risk in these Marfan patients was identified at aortic root diameters ≥5.0 cm [102].

More sophisticated consideration of the law of Laplace suggests two major types of mechanisms to account for an increase of aortic wall tension. First, the hypertensive type, where an increase in blood pressure causes a linear increase in the wall stress, and second, the Marfan type where an increase in the aortic radius is associated with a decreased aortic wall thickness, which jointly cause the wall stress to increase as a square of the radius [92]. The recognition of blood pressure as a driving force of aneurysmal growth has led to the treatment of aneurysm with blood pressure lowering agents, especially beta-adrenergic blockers [103] with demonstration of retarded aneurysmal growth in Marfan patients [104, 105]. Until today, beta-adrenergic blockers are the standard therapy of medical treatment for patients with thoracic aneurysm, although many other agents are currently tested for superiority of treatment efficacy in this setting [106]. Some researchers focussed on the exploration of biomechanical triggers of aneurysmal rupture to enhance our knowledge for predicting the exact day and hour of aneurysmal rupture [101]. Some patterns of aneurysmal rupture have been identified [107] including preponderance of aortic events in winter [108–111], of the early morning hours [111–114], and an increased risk during instances of extreme exertion or emotion [115–117]. Although the exact biomechanical mechanisms remain to be identified, authors agree that these peaks of aortic events relate to the well-known peaks of blood pressure. Thus these findings underpin the importance of classical recommendations to control blood pressure and to avoid activities such as weight lifting, that are associated with predictably unacceptable increases of blood pressure [118].

Another important approach to make use of insights form vascular biomechanics is to measure aortic wall properties. Especially in Marfan patients it is well documented that aortic wall thickness and elasticity are reduced [92].

These insights are founded in classical histologic studies which document aortic wall degeneration in aortic aneurysm and Marfan patients [119–122], biomechanical studies on the function of elastic fibers such as collagen and elastin [92, 123–125], and in sophisticated studies of the functional effects of *FBN1* gene mutations of the biochemical aortic tissue wall function (see Robinson for review [126]). Numerous studies have applied non-invasive imaging modalities to assess elastic wall properties in Marfan patients [127–146]. A major insight from these studies is that aortic elasticity is reduced in Marfan patients as compared to normal subjects. Moreover, aortic stiffness parameters were found to predict aortic disease progression both, in Marfan patients [147] and in patients with Marfan-like syndromes [148], independently of aortic root diameters. Thus, this line of research may yield important additional diagnostic tests of biomechanical parameters to be used for aortic risk stratification and surgical decision making [149, 150].

Limits and Conflicting Data

In Marfan patients, the hinge point for significant increase of risk corresponds to an aortic root diameter of 5.0 cm [102, 151]. However, up to 15 % of Marfan patients may develop dissections at diameters <50 mm [32, 105, 152] including some patients with dissections at normal aortic diameters [32, 153]. The absolute size criterion has also been found to fail also in patients with aortic dissection unrelated to Marfan syndrome [154, 155]. Indeed, the "maximum diameter criterion" following a "one size fits for all" philosophy has been challenged not only by empirical data but also from a biomechanical point of view. The law of Laplace which is valid for a simple cylinder or sphere with a single radius of curvature needs to be adjusted for the complex wall geometry, hemodynamics, and elastic wall properties of the aortic root [156]. However, despite impressive computational and modelling advances [94], prediction of rupture in complex hemodynamic, geometric and biologic wall conditions of individual patients is not possible today.

Comment

Absolute aortic diameter size is the most powerful aid for aortic risk assessment in Marfan patients. However, since some patients are at risk for rupture or dissection in spite of aortic diameters below the usual hinge points of significantly increased risk, other possibilities of risk stratification should be considered in patients with below-hinge-point diameters. Non-invasive measurements of aortic stiffness parameters appear extremely promising to enhance risk stratification in Marfan patients especially when the aortic root is below usual surgical thresholds for elective surgery.

Use of Expected Normal Aortic Diameters

Rationale and Supporting Data

Identification of enlarged aortic root diameters often cannot be done on the basis of absolute aortic size alone. Accordingly, the AHA defines aneurysm as a permanent localized dilatation with ≥50 % increase in diameter compared with the expected normal aortic diameter, and aortic ectasia dilatation <150 % of normal diameter [3, 157]. Similarly, the current Ghent nosology for diagnosing Marfan syndrome defines aortic root dilatation as an diameter ≥2 Z-scores of normal values. [158] Unfortunately, what can be considered a "normal aortic diameter" has been found to depend on age, sex and body height. For instance, adult women with Marfan syndrome exhibit on average a 5-mm smaller aortic root diameter adjusted for age than men [52]. Similarly, women with Turner syndrome have small statures and, hence, application of common absolute aortic size criteria has been recognized to underestimate the risk of aortic dissection [68]. Normative data with consideration of age, sex, body height, and body surface area are available for M-mode echocardiography [38, 44], 2-dimensional echocardiography [31, 40], and computed tomography [41–43] (Table 2.3). Alternatively, investigators apply allometric scaling methods where they use

internal references to establish normative aortic root dimensions. Using this approach in children, aortic dilatation was identified as the ratio of aortic diameters to the aortic annulus >95 % confidence limits of mean of normal [159, 160], or as the ratio of the aortic root to descending aortic diameter ≥2 [161]. In adults, the left ventricular outflow tract was used to predict the normal aortic root size [45] (Table 2.3).

Limits and Conflicting Data

Usage of normative size criteria is not a common practice, although evidence appears compelling that absolute aortic size criteria are often not adequate for timing elective surgery. Many experts point out to "the fallacy of applying an absolute size criterion to all patients" especially in women and other patients with small stature [30]. However, only the AHA guideline recommends aortic cross-sectional area to body height ratio >10 as a criterion for surgical intervention (see Table 2.2 for formula) [3]. One major limitation for widespread use of normative data might be that studies proposing such data are based on small populations (70–182 persons [40, 41]) which may not be representative enough of the general adult population [162]. Only one echocardiographic study [44] and one other study using non-contrast computed tomography [43] are based on data from large populations. However, in the echocardiographic study measurements were obtained by M-mode at end-systole, instead at end-diastole as recommended [39]. Similarly, non-contrast computed tomography is not in use for serial aortic imaging in Marfan patients. Thus, concerns about the use of the available normative data seems justified, especially in Marfan patients, who have taller statures than those in most normative populations [31, 162]. However, despite these concerns, our comparison of predictions of normal mean aortic root diameters in 14 putative patients including some with large body surface area yielded similar results between different prediction models. Of note, the most popular prediction model of Roman et al. [31] yielded the most outlying predictions (Table 2.4). Other reasons that may account for the limited use of size prediction models are that investigators often lack information on body height and body weight [45, 159–161], and that the information required calculating the predicted mean normal aortic diameters is often not provided in the original publication [42, 44]. Moreover, unlike aortic ratios, the frequently used 95th percentiles and Z-scores allow only for quantifying a deviation for diameters from normal but not for quantifying the degree of deviation needed to distinguish dilatation from aneurysm. Finally, it often turns out to be another fallacy to believe that what is predicted as a normal diameter of a healthy aorta is also a normal diameter in a diseased aorta. It does not therefore come as a surprise that some Marfan aortas dissect at diameters that are within predicted normal ranges of healthy aortas [154, 155].

Comment

Normative data instead of absolute aortic size criteria help to avoid an underestimation of aortic pathology in adults. Thus we recommend using relative size criteria at least in adults with borderline size aortic diameters.

Aortic Growth

Rationale and Supporting Data

There are two different approaches for using aortic expansion rates for surgical decision making. The first approach attempts to predict the time at which aortic diameters reach a critical size threshold [49, 51]. To this end, investigators measured expansion rates in patients with dilated aortas and modelled exponential equations that allow for prediction of future aortic diameters based on current diameter measurements. For instance, Coady et al. found an annual growth rate of the ascending aorta of 1.2 mm/year in patients with aortic dilatation. Using their formula, a patient with an ascending aortic diameter of 40 mm at baseline it would take the aorta

229 months to reach a diameter of ≥55 mm (=40 mm*$e^{0.001395*229}$; Table 2.5) [49]. Thus, the doctor might recommend a patient with a 40 mm aortic diameter at baseline to make an appointment for surgery in 19 years.

The second approach suggests identifying an unusually rapid aortic expansion rate of the dilated aorta, which is thought to indicate an increased risk of dissection or rupture. For instance, Legget et al. compared six Marfan patients with aortic events with 56 Marfan patients without such events during echocardiographic follow-up. They found an annual change of both aortic root diameters of 5 mm/year in the event group compared to 0.7 mm/year in the no-event group, and of aortic root rations of 0.15 per year, corresponding to a 15 % increase of diameter compared to 0, respectively [48]. Similarly, Meijboom et al. distinguished two normally distributed subgroups of adult Marfan patients, which they called slow and fast aortic growers. They identified 15 % of men with a growth of 1.5 mm/year, and 11 % of women with a growth of 1.8 mm/year as fast growers who experienced significantly more aortic events than slow growers comprising aortic dissection and elective surgery [52]. The recommendation is to operate electively with lower thresholds in patients with unusually high aortic expansion rates.

Limits and Conflicting Data

Apparently, surgeons do not use aortic growth formulas for timing of elective surgery. One major reason might be that such predictions may not be reliable enough. Indeed, if the 40-mm-aorta of the above mentioned patient grows according to the formula suggested by Shimada et al. [51], after 19 years the aortic diameter would reach 72 mm instead of 55 mm as predicted by the formula of Coady et al.. [49] Conversely, it is more popular to measure aortic growth during follow-up to identify "rapid growers". The ESC guideline [88] cites as evidence for their >2 mm/year criterion a review by Judge and Dietz [163], who actually recommend earlier timing of surgery at aortic growth exceeding 1 cm/year. Similarly, both the AHA and the Australian guideline with their growth criteria >5 mm/year and >5–10 mm/year, respectively, do not reference original studies for their recommendations (Table 2.1) [3, 25]. Thus, there is a large diversity of growth criteria suggested in the literature and original data are too sparse to provide hard evidence. There are only two studies to provide data on criteria for rapid aortic growth in Marfan patients. The first study identifies rapid growth in only six patients with aortic events [48]. The other study identifies fast growing aortic root dimensions in 15 % of 113 Marfan men as 1.5 mm/year, and as 1.8 mm/year in 11 % of 108 Marfan women [52]. These growth rates are currently the best evidence available to identify fast growing aortas in Marfan patients. However, a similarly well-designed historic study by Roman et al. found, that in 113 Marfan patients followed by echocardiography over 49 ± 24 months aortic growth rates were quite variable with −0.1 to 0.3 cm/year in patients with complications and 0.0–0.3 cm/year in patients without complications [164].

Comment

Increased speed of aortic growth is a highly important harbinger of aortic events, and serial imaging should aim at identifying patients with rapid growth. However, a stringent definition of what is "rapid" does not exist. Moreover, the changes of diameter over time are within 1 mm/year and only minor changes in the method of measurement can lead to wrong conclusions about growth dynamics. Here, we agree with Elefteriades who points out that reports of rapid growth of the thoracic aorta are usually reflective of measurement error. Thus, in our experience it is pivotal that doctors who make the decision on surgery evaluate serial imaging material personally together with a radiologist, and that these doctors are well aware of the many methodological pitfalls of each imaging technique. Finally, Elefteriades recommendation in serial imaging not to compare current diameters with the most

previous images but with baseline images, appears wise and may help to avoid missing the relevance of gradual minor changes [101].

Aortic Geometry

Rationale and Supporting Data

The risk of chronic aortic root disease may not exclusively be identified by enlarged or rapidly growing diameters but also by its geometric features [166]. In a clinical setting, especially on angiography where normalized aortic diameters are not available, aortic dilatation or aneurysm is diagnosed when one aortic segment appears disproportionally larger than its adjacent segment. Accordingly, the AHA guideline suggests considering the ascending aorta to be enlarged if the diameter of the ascending aorta exceeds the diameter of the aorta at the level of the sinuses Valsalva, even if both are within normal range [3]. There is evidence that proximal aortic geometric features are of both diagnostic and prognostic relevance. Most conspicuously, in Marfan patients the aortic event rate is much higher when dilatation extends from the aortic sinuses to beyond the aortic ridge with involvement of the proximal ascending aorta [164]. Similarly, when dilatation of the sinuses involves the supra-aortic junction, aortic regurgitation ensues by outward deviation of the commissures of the aortic valve leaflets [166]. Regurgitation is rare with diameters <4.0 cm and it is obligatory at diameters >6.0 cm [167]. Receiver operating characteristic analysis of published aortic root diameters in 152 adults with Marfan syndrome revealed that 5.4 cm of maximum root diameter was a threshold for aortic valve regurgitation with a sensitivity of 91.3 % and a specificity of 88.9 % [55]. In Fig. 2.3 we summarize the little information that is available on various types of aneurysms and the associations with etiology and prognosis. Robicsek pointed out that especially in asymmetric ascending aortic aneurysms with change of geometry from cylindrical to ellipsoidal to spherical, the circumferential wall stress increases less rapidly than the longitudinal wall stress [92]. Medial degeneration [175] and longitudinal stress are largest in the outer curvature of the aorta and this may explain why dissections typically occur at this site of the aorta and why intimal tears are usually transverse [94, 176, 177].

Limits and Conflicting Data

Aortic root geometry apparently is important to judge the risk of an aortic pathology. Current data however are limited in some ways. First, there is overlap of aortic phenotypes and there is also a Babylonian confusion on terminology in the description of phenotypes. [178] Second, proximal aortic geometry should be considered in conjunction with aortic arch pathology [179, 180]. Third, longitudinal data are needed to establish the power of different pathological aortic root shapes to predict aortic events.

Comment

Abnormal shapes of the aortic root and ascending aorta should be considered for diagnosing aortic pathology even with presence of "normal" absolute and normalized aortic diameters, and echocardiographic follow-up appears justified in patients with such abnormalities. In Marfan patients the risk for aortic events increases when dilatation progresses beyond the sinutubular junction and earlier timing of elective surgery might be considered in these patients.

Etiology of Aortic Pathology

Rationale and Supporting Data

The basic idea of using etiology to assess the risk of aortic rupture or dissection is that the natural history of aneurysms depends on their underlying disease. As a rule of thumb, idiopathic thoracic aortic aneurysms or those aneurysms where chronic arterial hypertension is identified as their exclusive

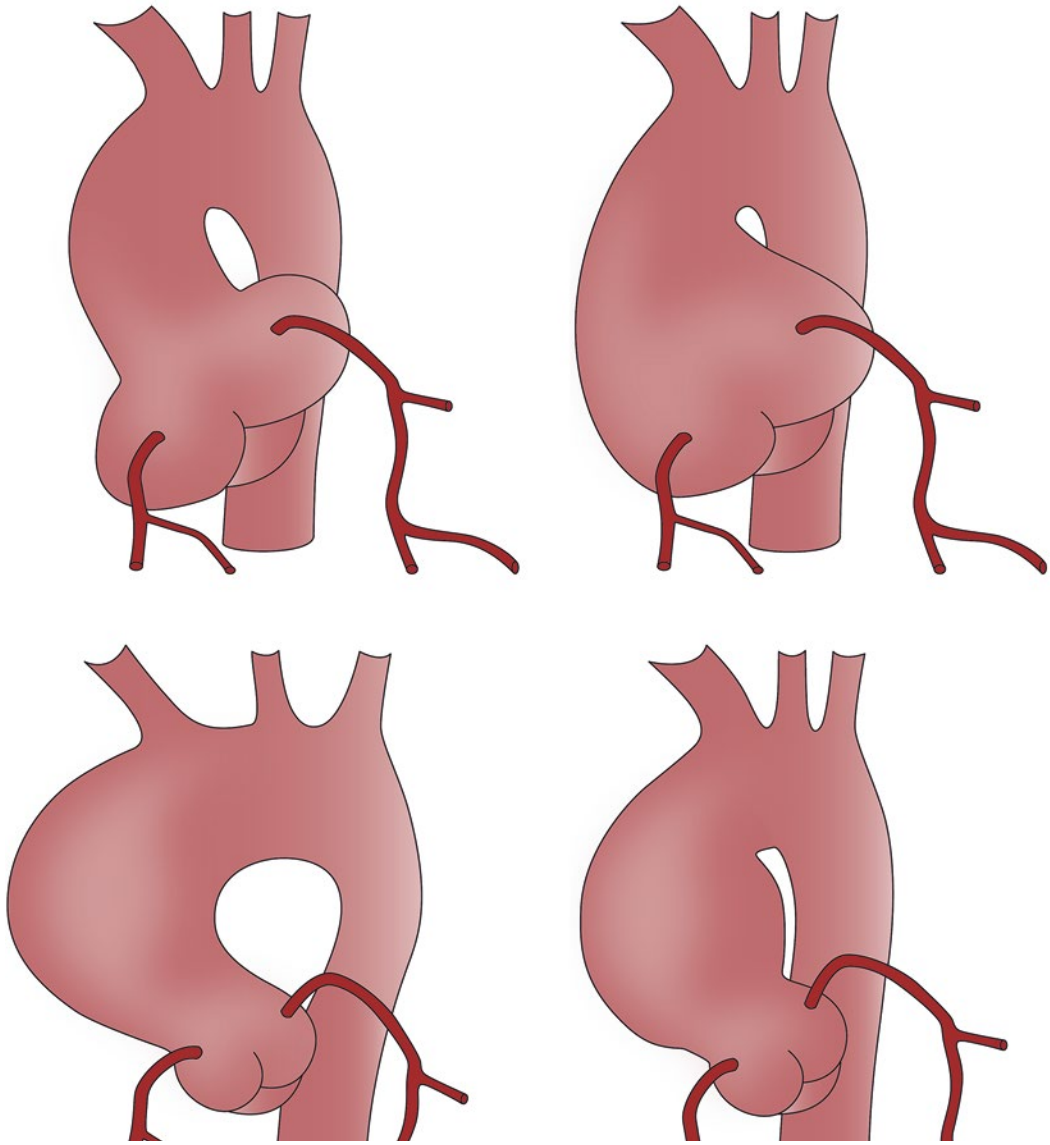

Fig. 2.3 Different shapes of aortic root pathology may relate to both underlying mechanisms of aneurysmal formation and prognosis of the natural cause of the disease. *Left upper* panel: *Localized annulo-aortic ectasia* with restriction to the sinutubular junction [164]. This pathology is defined by dilatation of all three sinuses of Valsalva, and it is typical in adults with Marfan syndrome [168], but it may also be encountered in some patients with bicuspid aortic valve disease [169, 170]. *Right upper* panel: *Generalized annulo-aortic ectasia* with extension beyond the sinutubular junction [164]. This pathology is defined by dilatation of all three sinuses of Valsalva with symmetric dilatation of the sinutubular junction and the proximal ascending aorta. The pathology is frequently associated with some degree of aortic valve regurgitation and indicates presence of an increased risk for rupture and dissection in Marfan patients [164]. *Left lower* panel: *Asymmetric ascending aortic aneurysm* with extensive enlargement of the outer curve of the ascending aorta but with maintained shape of the inner curve of the ascending aorta, both with normal diameters of the sinuses and the sinutubular junction [171], and, especially in patients with aortic valve dysfunction with dilatation at these levels [172–174]. This type of aneurysm is usually associated with elongation of the ascending aorta, and it is a typical finding in patients both with bicuspid aortic valve disease and with hypertensive aortic aneurysms. [101, 171] Degeneration of the aortic media was found to be more pronounced in the convexity than in the concavity of the ascending aorta of patients with bicuspid aortic valve disease [175]. *Right lower* panel: *Symmetric ascending aortic aneurysm (fusiform aneurysm)* with similar bulging of the outer and the inner aortic curvature but with normal diameters of the aortic sinuses [171]. This type is described in the so-called post-stenotic dilatation in patients with aortic valve stenosis which is unrelated to bicuspid aortic valve disease [174]

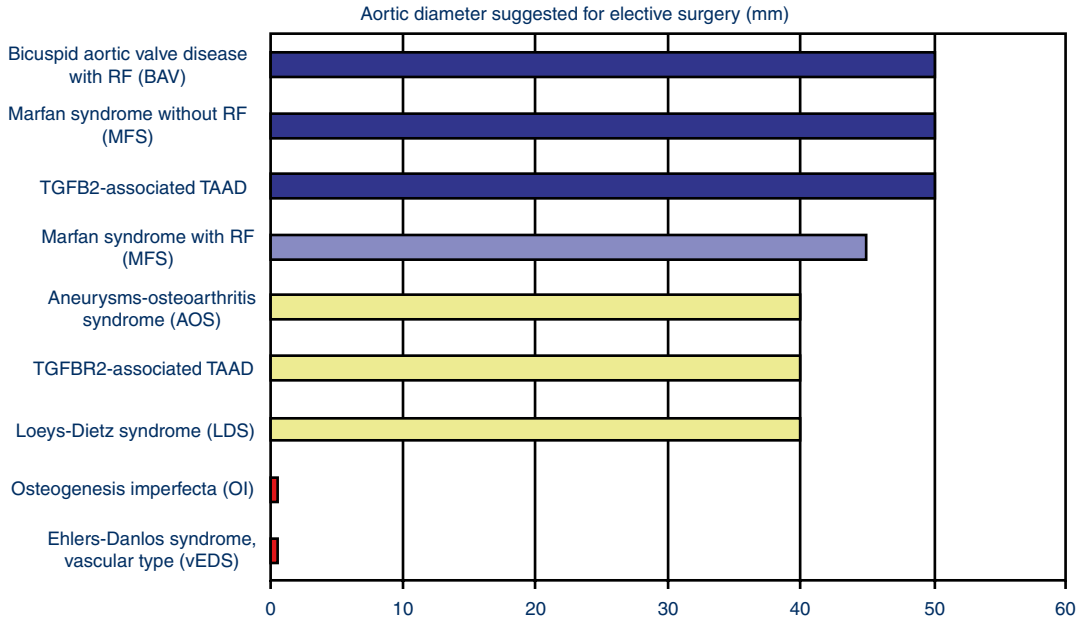

Fig. 2.4 Recommendations for elective surgery of the aortic root according to aortic diameters in aortic disease etiologies related to specific gene defects. RF identifies risk factors which comprise rapid growth of aneurysm diameter, extension of aneurysm beyond the sinutubular junction, a family history of aortic rupture at diameters <5.0 cm, or significant degree of aortic valve regurgitation

cause are the most benign pathologies with highest thresholds for elective surgical intervention. In contrast, aneurysms that result from an inherent weakness of the aortic wall are observed to dissect or to rupture earlier in life and at smaller diameters. Therefore recommended thresholds for elective intervention are generally lower in these patients (Table 2.1).

As mentioned above, the Marfan syndrome is the primary model for heritable thoracic aortic aneurysmal disease. Recently, however, other hereditary syndromes have been discovered that also account for premature aortic dissection or rupture (Table 2.6). These syndromes are reviewed elsewhere in detail [12, 126, 181]; for surgical decision making there are, beside the Marfan syndrome, three other disease entities that may be considered as paradigmatic diseases (Fig. 2.4):

First, there is the vascular type of the Ehlers-Danlos syndrome. The Ehlers-Danlos syndromes are associated with marfanoid habitus, joint hypermobility and kyphoscoliosis [182]. However, only the vascular type of Ehlers-Danlos syndrome and the Ehlers-Danlos syndrome with peri-ventricular heterotopia [183, 184] are associated with aortic aneurysm, rupture, and dissection that may also are localized in the smaller arteries outside the aortic vessel [61–67]. This type of aortic disease is paradigmatic for aortic disease with a vascular tissue that is very fragile and thus carries a high risk for intra- and perioperative complications. Consequently, most surgeons avoid elective surgery.

Second, the Loeys-Dietz syndromes are paradigmatic for connective tissue disorders that carry a risk for aortic dissection and rupture that is even higher than in Marfan syndrome. Thus, with 4.0 cm of aortic root diameter, the lowest recommended thresholds for elective surgery in entire surgical literature are provided for this syndrome. The syndrome is related to mutations in the *TGFBR1* and *TGFBR2* genes

cause both, Loeys-Dietz syndrome type I (LDS), and Loeys-Dietz syndrome type II, but also non-syndromic familial TAAD. Loeys-Dietz syndrome type I exhibits some systemic manifestations of Marfan syndrome but also some additional features including cleft palate, bifid uvula, blue sclerae, translucent skin, easy bruising, craniosynostosis, cleft palate, Chiari-type I malformation of the brain, learning disability, patent ductus arteriosus, atrial septal defect, bicuspid aortic valve, and club-foot deformity. Loeys-Dietz syndrome Type II exhibits similar clinical features as vascular type of the Ehlers-Danlos syndrome but it is not known to have fragile vascular tissue during surgery. In both syndromes, aneurysms and dissections tend to be diffuse, and they can occur at almost normal vascular diameters with lethal outcome even in young childhood [181]. Non-syndromic TAAD related to *TFGBR1/2* mutations and the *SMAD3*-related aneurysms-osteoarthritis syndrome are currently considered as aortic disease entities that resemble the Loeys-Dietz type of aortic pathology and thus they are recommended to be handled in a similar way as Loeys-Dietz syndrome.

Third, aortic aneurysms related to bicuspid aortic valve disease. Many patients with bicuspid aortic valve have been shown to exhibit a family history of valve disease, and in some cases an autosomal dominant mode of inheritance [185], with causative *NOTCH1* mutations [186], or linkage to other genetic loci at 18q, 5q and 13q [187]. Reports have been made of family members of patients with a bicuspid aortic valve who have thoracic aortic aneurysm despite the absence of a bicuspid aortic valve [188]. Patients with a bicuspid aortic valve can display marked degeneration of the aortic media [119, 189], develop aortic dilatation and dissection at young age [121, 172, 190–193], and even in normally functioning bicuspid aortic valves [169, 194], may exhibit progression of aortic dilatation or dissection after replacement of the bicuspid aortic valve [195–199], and can have increased stiffness of the aortic wall [200–205]. While these data have convinced some researchers that bicuspid aortic valve disease is also a systemic disease affecting the aortic wall [169, 206], others emphasize hemodynamic factors associated with the aortic valve malformation as the relevant cause of aneurysm formation [207, 208]. Thus, bicuspid aortic valve disease is a paradigm for thoracic aortic aneurysms that relate to a very complex etiology of genetic and hemodynamic factors where consensus on elective surgery is difficult to establish (see the specific chapter in this book). Aortic pathology in Turner syndrome and in Noonan syndrome seems similar to the bicuspid aortic valve disease paradigm.

Limits and Conflicting Data

The etiologic perspective tends to look at diseases in terms of defined entities with well-described natural histories. However, even the natural course of Marfan syndrome as the best defined syndrome among genetic aortic diseases is strikingly variable. For instance, Rand-Hendriksen et al. found that their 87 Norwegian patients with Marfan syndrome exhibited 56 different combinations of clinical features of the syndrome [209]. Similarly, the prognosis of Marfan patients varies widely with, on the one hand, severe aortic media degeneration already in utero [210], or with heart failure in Marfan neonates [211, 212], or with aortic dissection or rupture in juvenile Marfan patients [213–215], whereas on the other hand Marfan patients may still be free from any dilatation of their aortic root at an age >50 years [216]. Pyeritz at al. found that a family history of aortic dissection at an age <40 years predicted aortic dissection in Marfan families [151]. However, usage of this criterion of aortic risk is limited for some reasons. First, there is considerable intra-familial variability of the severity of cardiovascular phenotype [216, 217], and thus a mild course in one family member cannot safely be extrapolated to other family members. Second, a family history of Marfan

syndrome is present in only 45–65 % of patients with classical Marfan syndrome [7, 209], and thus in many patients with a sporadic *FBN1* gene mutation, the family history is not informative. Third, premature onset of aortic complications is part of heritable TAAD syndromes and thus usage of this criterion may be tautology. Fourth, current guidelines try to escape this tautology by defining the risk criterion as a family history of aortic dissection at aortic diameters <5.0 cm [3]. However, guidelines cite no original studies to support this suggestion, and more seriously, in clinical practice it is almost impossible to obtain information on pre-dissection aortic diameters [155], especially in family members of a patient.

Another limiting issue when considering aortic disease etiology is related to the current discoveries of novel causative genes and syndromes. First, we need to keep in mind that recommendations are based on cohorts that comprise less than 50 patients who were sampled from all over the world (Table 2.6). Second, new syndromes usually are described in patients with severe phenotypes, and thus early descriptions of syndromes tend to pick up the severer end of a disease spectrum. Accordingly, it is likely that in the future some patients may be identified with less aggressive aortic disease despite evidence for a Loeys-Dietz syndrome or an aneurysms-osteoarthritis syndrome.

Comment

Despite some limits it is essential to consider etiology of aortic disease for proper timing of surgery. According to our experience, the diagnosis of the genetic disease underlying aortic pathology should not rely on clinical phenotype alone. The reason is that phenotypic overlap between syndromes such as Marfan and Loeys-Dietz can be substantial [6, 7]. Failing to distinguish between these syndromes, however, may cost human lives when, consequently, surgery is planned too late and at thresholds that are too conservative. In contrast, we believe that molecular testing with sequencing at least of the genes *FBN1*, *TGFBR1*, and *TGFBR2* is prerogative for proper surgical decision making [22, 181, 218].

The Strategic Decision Making Paradigm

In summary, there is overwhelming evidence that a "one-size-fits-for-all" approach to decisions on elective surgery is not reasonable. The work of surgeons and scientists has brought forth an impressing thesaurus of medical knowledge that is helpful to assist decision making [219]. However, there is no consistent data and no single recommendation for all clinical settings related to elective surgery on TAAD. Moreover, medical and surgical therapy is unlike industrialized production but it is to a vast extent a process based on interaction of persons. Clearly, surgical success requires more than ordinary skills and virtues of both, the surgeon and the patient [220]. Thus, whenever a medical rationale argues for considering an elective operation, the surgeon turns from a scientist into a strategist who performs a careful analysis of specific strengths and weaknesses of his patient to weigh these against the opportunities and risks of various therapeutic options (Fig. 2.5). There is a mastery of strategic action and reflection that has in depth been elaborated by the Prussian general Carl von Clausewitz [222] whose thoughts have been found highly productive also in management philosophy [223] and, most recently, in medical decision making [219]. Strategic clinical decision making is needed to make medical knowledge really helpful and supportive for patients in their real lives.

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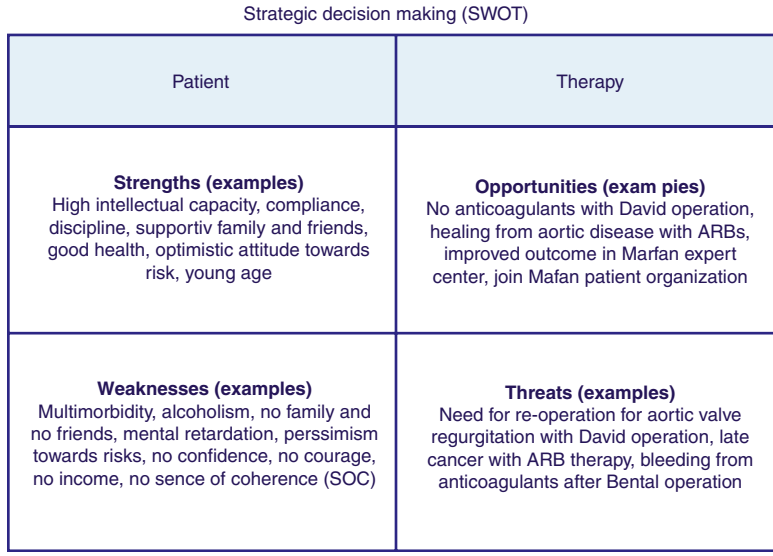

Fig. 2.5 Strategic medical decision making starts with considering specific strengths and weaknesses of the patient and the opportunities and risks of various therapeutic options. In management theory, this operation is well known as the SWOT analysis [221]

Abbreviation

*	Multiplied by
AA	Abdominal segment of the aorta
AHR	*A*ortic cross-sectional area (π r^2) [cm^2] to *h*eight [m] *r*atio [32, 33]
ANU	Diameter of the aortic annulus
AOD	Aortic dissection
AOD-A	Aortic dissection Stanford type A
AOD-B	Aortic dissection Stanford type B
AOR	Aortic rupture
ASD	Atrial septal defect
ASI	Aortic size index defined aortic diameter [cm]/BSA [m^2] [36]
AVR	Aortic valve regurgitation
AXR	Aortic cross-sectional area
BAV	Congenitally bicuspid aortic valve
BSA	Body surface area [m^2] assessed by the method of Du Bois [224] if not otherwise indicated
CCT	Contrast enhanced computed tomography
CoA	Coarctation of the aorta
DTAA	Degenerative thoracic aortic aneurysm
EDS	Ehlers-Danlos syndrome
FH	Family history
LDS	Loeys-Dietz syndrome
Ln	Natural logarithm
LVOT	Left ventricular outflow tract
MFS	Marfan syndrome
MRI	Magnetic resonance imaging
MVP	Mitral valve prolapse
MVR	Mitral valve regurgitation
NCCT	Non-contrast enhanced computed tomography
PDA	Patent ductus arteriosus
SAR	Supra-aortic ridge or sinutubular junction
SD	Standard deviation
SOV	SOV diameter of the sinus of Valsalva corresponding to the diameter of the aortic root

SQRT	SQRT square root
TAA	(Diameter of the) thoracic aorta ascending segment
TAAD	Thoracic aortic aneurysms and dissections
TAD	(Diameter of the) thoracic aorta descending segment
TADd	(Diameter of the) thoracic aorta descending segment at the level of the diaphragm
TAE	(Diameter of the) thoracic aorta entire vessel
TAT	(Diameter of the) thoracic aorta transverse arch
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VSD	Ventricular septal defect
ys	Years

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