4 Size Matters: Intervention Thresholds for Dissection Prophylaxis in the Ascending Aorta

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Abstract

This chapter provides an extensive review of the normal size of the ascending aorta, for different body surface areas including tall people. The different imaging techniques, by means of echocardiography, magnetic resonance and computed tomography, are extensively discussed, as well as pitfalls in size measurements. The size of the ascending aorta may increase due to aging or pathologic conditions. The authors consider an aortic root or ascending aorta diameter above 4.0 cm as abnormal. From a diameter of >4.0 cm begins a monitor-zone for extended diagnostic evaluation, treatment advices and pre-pregnancy counselling. From a diameter >4.5 cm, operative treatment of the ascending aorta is advised in patients with connective tissue disorders who have risk factors. From a diameter of >5.0 cm, operative treatment is advised in other cases of connective tissue disorders and in cases of bicuspid aortic valve with risk factors. From a diameter of >5.5 cm, operative treatment is advised in bicuspid aortic valve without risk factors and in all other cases.

Keywords/Phrases

Dilatation of the Ascending Aorta • Normal Aortic Diameter • Aortic size and aging • Aortic growth and pathologic conditions • Imaging techniques • Thoracic Aorta Aneurysm • Aortic dissection • Intervention thresholds

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Introduction

Acute dissection or rupture of the ascending aorta is often lethal. Even when emergency surgery can be performed, associated morbidity and mortality are high. Dissection and rupture are mainly related to aneurysm size, aortic diameter and expansion rate. Aneurysms remain silent as long as there are no complications. To prevent dissection or rupture of the ascending aorta, prophylactic operation of a, most often, asymptomatic

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patient with a known dilatation of the ascending aorta is advised, along with other supportive measures [1–3]. It is crucial to monitor patients with a dilated ascending aorta from an early stage, to choose the right moment for surgical repair.

Normal Diameters of the Ascending Aorta

Standard levels and methods for the echocardiographic measurement of ascending aortic have been described (Fig. 4.1) [4]. Aneurysm formation can occur at the level of the sinus of Valsalva (e.g. Marfan syndrome {MFS}) as well as superior of the supravalvular aortic ridge, in the tubular part of the ascending aorta (e.g. Familial Thoracic Aortic Aneurysm and Dissection {TAAD}). The prerequisite for diagnosis and monitoring are reference values. In the past, several studies have tried to establish upper limit of normal (ULN) values, using transthoracic echocardiography (TTE) [4, 5], transesophageal echocardiography (TEE) [6, 7], magnetic resonance imaging (MRI) [8] and computed tomography (CT) [9]. However "normal" dimensions of the ascending aorta are still not well defined.

Aortic Growth and Aging

During life the size of the aorta increases. In childhood and young adulthood this is caused by an increase of the luminal diameter. In adulthood, the aortic size is related to exercise and workload. Whereas the elastin content in the ascending aorta is high, aging of the aorta is accompanied by a loss of compliance and an increase in wall stiffness. The media displays loss of smooth muscle cells and fragmentation of elastic fibres with the appearance of cystic spaces, filled with mucoid material. This process, called cystic media degeneration, 'normally' occurs with aging. A growth of 1 mm per 10 years is regarded as a normal aortic growth rate [5, 10]. Recent longitudinal data from the Framingham Heart Study in 4,542 individuals indicated that the aortic root gradually increases by 0.89 mm in men and 0.68 mm in woman for each decade of life, assuming a normal BMi and adjusting for blood pressure. The presence of hypertension or obesity was associated with greater mean aortic root size over time [11] (Figs. 4.2 and 4.3).

At younger ages, cystic media necrosis is associated with various connective tissue diseases, such as MFS, Loeys Dietz syndrome

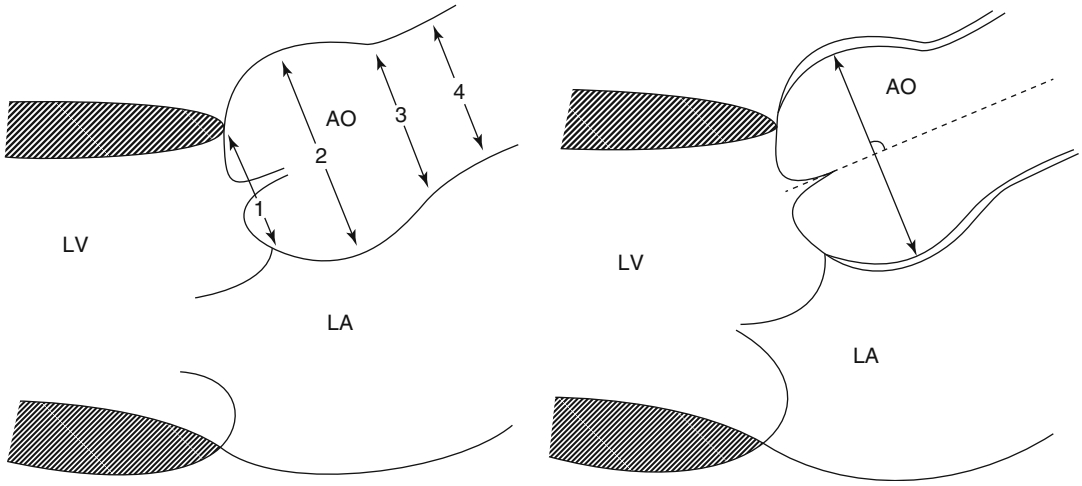

Fig. 4.1 Standard levels and methods for the echocardiographic measurement of ascending aortic (From Roman et al [4]). *Left*: Schematic illustration of the aortic root in the 2-dimensional parasternal long-axis view. Measurements were obtained at four levels, including the annulus, sinuses of Valsalva, supraaortic ridge, proximal ascending aorta. *Right*: measurement were made perpendicular to the long axis of the aorta, using the leading edge technique

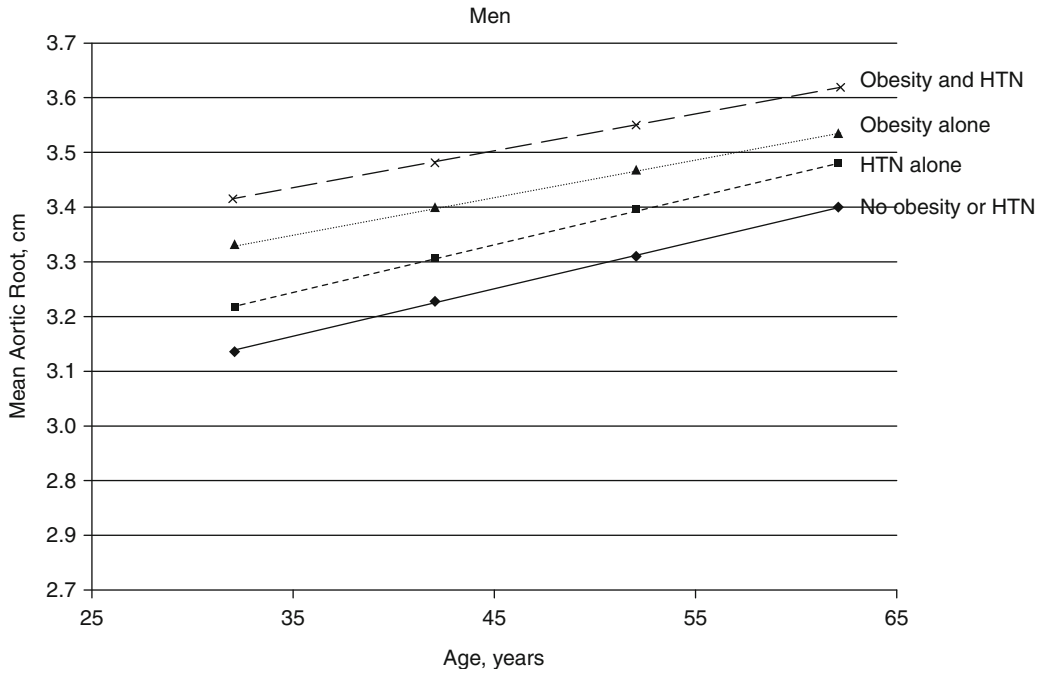

Fig. 4.2 Predicted mean aortic root growth curves in men with and without obesity or hypertension (From Lam et al. [11])

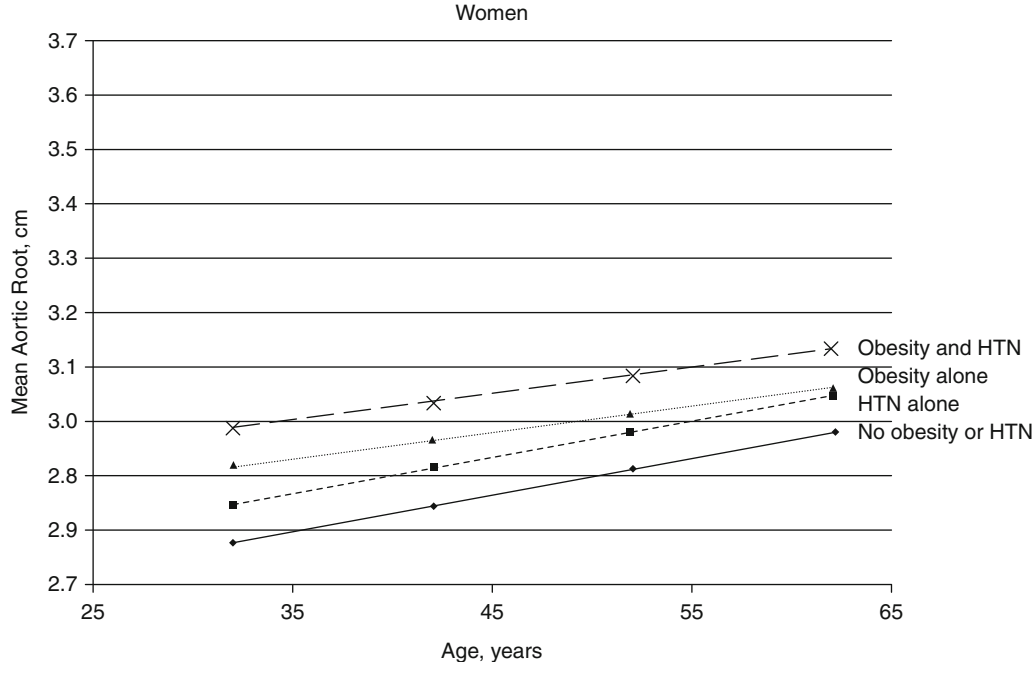

Fig. 4.3 Predicted mean aortic root growth curves in women with and without obesity or hypertension (From Lam et al. [11])

(LDS) and TAAD. So more or less the same process is acting in the aortic wall in aging as well as in pathological conditions.

What Is an Abnormal Diameter? Echocardiographic Methods

An aneurysm is defined as a cross sectional diameter of more than 1.5 times its normal value. For the ascending aorta this definition does not seem to be so useful. The ascending aorta begins with a natural dilatation at the level of the Sinus of Valsalva. So there is no proximal reference diameter available, as is the case in the distal aorta or in muscular arteries. Mean diameter with confidence intervals derived from a normal population are better applicable. The size of the ascending aorta is related most strongly to body surface area (BSA) and age [4, 5]. Relation with sex and height is conflicting. Therefore, BSA may be used to predict aortic root diameter in several age intervals. In 52 children and 135 adults, Roman et al. established normal values in three age strata: younger than 20 years, 20–40 years, and older than 40 years by published equations (Figs. 4.4 and 4.5). These values with 95 % confidence have been included in guidelines as reference values to date [1, 3, 12].

However, the sample size of the study of Roman et al. was limited and a sufficient number of healthy subjects whose height exceeds the 95th percentile, as is usually the case in MFS patients, was not included. Data for children and for adults under the age of 40 with a large BSA were extrapolated, not based on real measurements! In an adjusted nomogram for tall children, developed by Rozendaal et al., a wider range of aortic root diameter is considered to be normal [13] (Fig. 4.6). Radonic et al. examined 38 healthy controls with a large BSA and found a maximal aortic root diameter of 38 mm [14]. The aortic root diameter tends to plateau at 40 mm (Fig. 4.7). This has also been demonstrated in tall men and women [15] and in athletes [16, 17]. Radonic et al. conclude, referring to other publications,

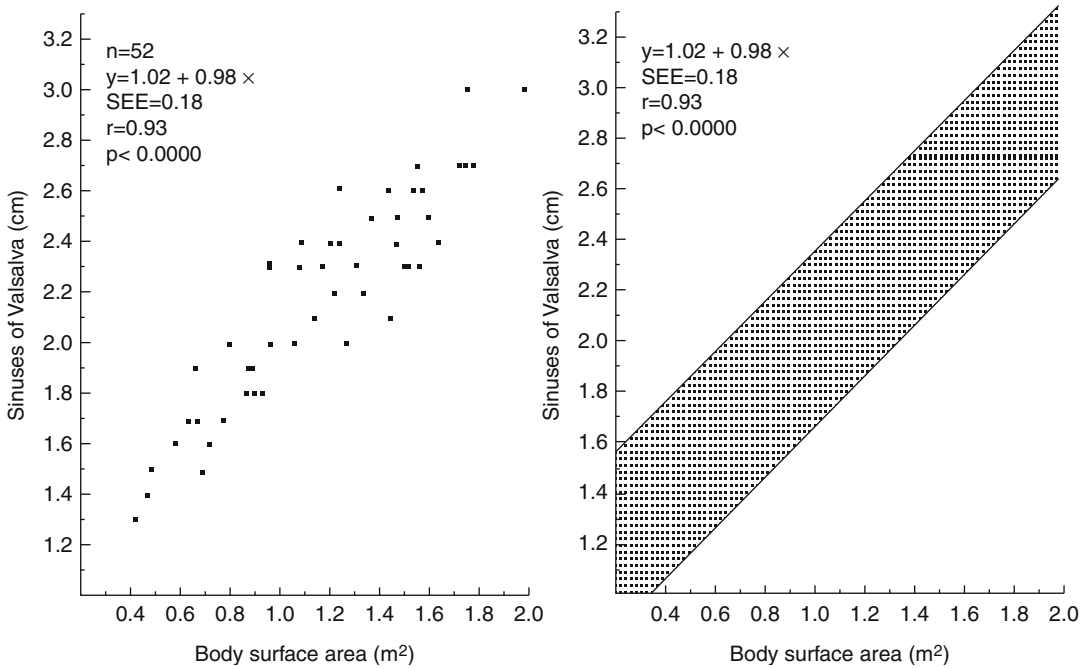

Fig. 4.4 Aortic diameter at the sinuses of Valsalva in Children (From Roman et al. [4]). *Left*: Relation of body surface area to aortic root diameter at the sinuses of Valsalva in normal infants and children. *Right*: 95 % normal confidence limits for aortic root at the sinuses of Valsalva in relation to body surface area in normal infants and children

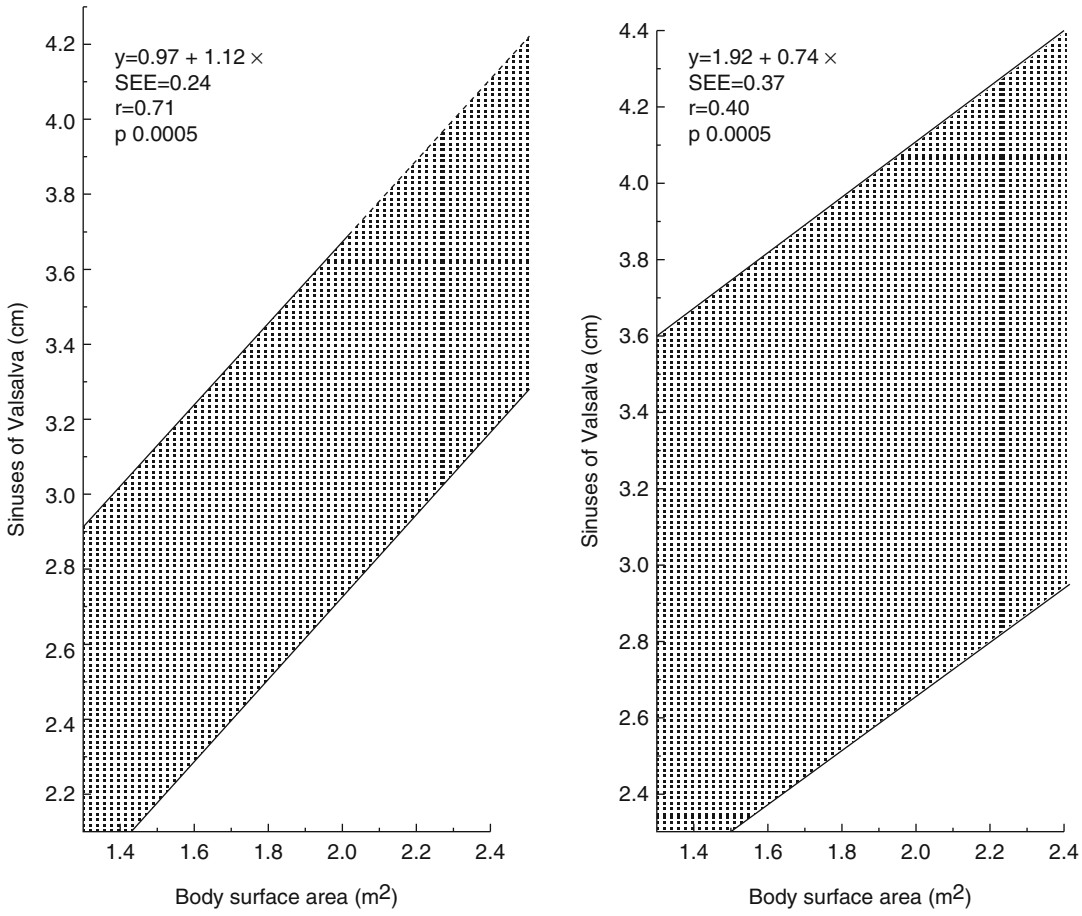

Fig. 4.5 Aortic diameter at the sinuses of Valsalva in Adults. Ninety five percent normal confidence limits for aortic root diameter at the level of the sinuses of Valsalva in relation to BSA. *Left* in adult younger than 40 years of age. *Right* in adults 40 years of age and older (From Roman et al. [4])

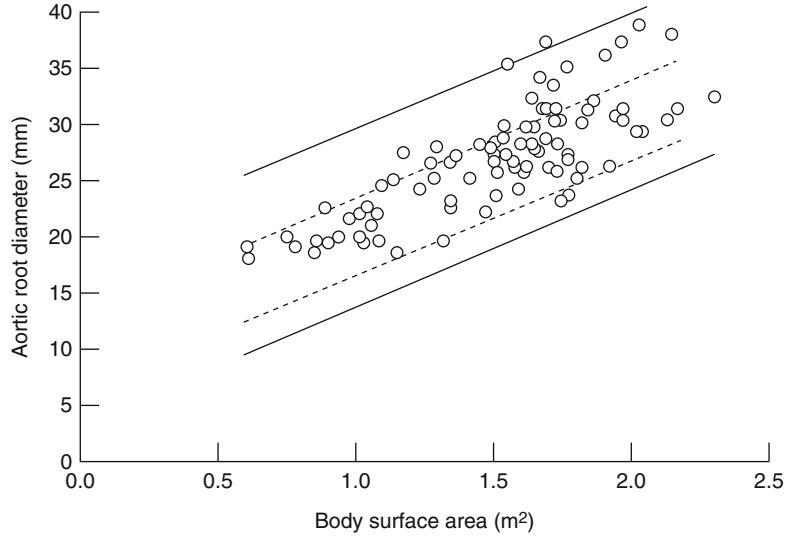

Fig. 4.6 Relation between aortic root diameter and body surface area (BSA) (*empty circles*) and 95 % reference limits for aortic root diameter in relation to BSA (*solid lines*), in subjects aged 3.2–18.4 years (From Rozendaal et al. [13]). The upper and lower limits of normal of the standard nomogram (4) are shown in *dashed lines*

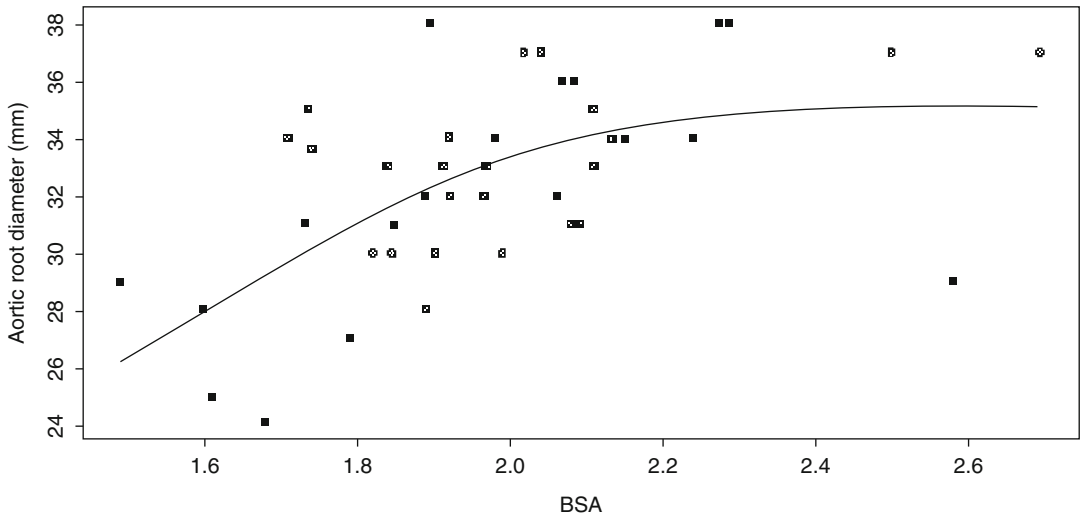

Fig. 4.7 Correlation of BSA (m^2) and aortic root diameters in 38 healthy volunteers (From Radonic et al. [14])

that with the use of the Z-score, the diagnosis of MFS wrongly would be missed in patients with a large BSA. So, the authors are critical against the use of these nomograms of Roman et al. in adults.

The clinician has to be aware that the diameters are measured in different ways. Roman et al. measured aortic diameters *enddiastolic* using the *leading edge to leading edge* technique (with inclusion of the anterior wall) conform the 2005 ASE-recommendations for adults [18]. The 2010 ASE guideline for paediatric echocardiography on the other hand recommends measurements to be done *midsystolic* and *inner edge to inner edge* [19]. The 2010 ACCF/AHA Guideline for Thoracic Aortic Disease also recommends the internal diameter (whereas for CT and MRI the external diameter is advised) [3].

Transthoracic echocardiography (TTE) suffices to quantify maximum aortic root and proximal ascending aorta diameters when the acoustic window is adequate. For the mid- and distal part of the ascending aorta other techniques may be needed. TEE overcomes problems with a bad acoustic window, except for a small portion of the distal ascending aorta [20]. But also CT en MRI are increasingly used, but for the aortic root, they are not well suitable, when performed without ECG-gating.

The revised Ghent nosology for the diagnosis of MFS has made a Z-score of ≥2 for the aortic root an important diagnostic criterium [12]. For childhood and young adulthood standardization to body surface (BSA) is usual, although aortic dimensions seem to have good correlation with height also [21]. Newer reference values for children based on measurements in larger groups have been developed for both *leading edge* method (also in diastole) [22] and the *inner edge* method (in systole) [23]. From these reference values, scores can be calculated. For adults however application of the Z-score may not be a good approach.

Aortic Size and MRI

In 2008 reference values for children and adolescents [24] and for adults [25] have been published.

Aortic Size and CT

CT is increasingly used nowadays for diagnosis or exclusion of dilatation of the ascending aorta. Earlier studies were limited by sample

Table 4.1 Summary of data regarding mean ascending aortic diameter, using CT

Author (Ref. #)	Year	Sample size	Age range (years)	Anatomic landmark of aorta	Ascending aorta diameter (cm)*
Aronberg et al.	1984	102	21–61	Caudal to aortic arch	3.5 cm
Hager et al.	2002	70	17–89	Caudal to aortic arch	3.1 ± 0.4
Kaplan et al.	2008	214	24–87	Pulmonary artery level	3.4 ± 0.5
Lin et al.	2008	103	51 ± 14	Pulmonary artery level	3.0 ± 0.3
Mao et al.	2008	1442	55 ± 11	Pulmonary artery level	3.4 females 3.6 males
Wolak et al.	2008	2952	26–75	Pulmonary artery level	3.3 ± 0.4
Kälsch et al.	2010	4129	45–75	Pulmonary artery level	3.45 ± 0.4 females 3.71 ± 0.4 males

Table 4.2 Normal CT values for aortic annulus, sinus of valsalva, sinotubular junction

Aorta	Normal values		Author	Year
Aortic annulus	25–37 mm (95 % CI)	End diastolic	Lin et al.	2008
	26.3 ± 2.8 (coronal) 23.5 ± 2.7 (sagittal)		Tops et al.	2008
Sinus of valsalva	34.2 ± 4.1 (2SD)		Lu et al.	2009
	36.9 ± 3.8 (2SD)	End diastolic, gated	Ocak et al.	2009
Sinotubular junction	29.7 ± 3.4 (2SD)		Lu et al.	2009

size, only pure axial slices and non-contemporary imaging technology [9]. In recent years newer reference values have been developed, not only in patients referred for various cardiac and non-cardiovascular reasons [26, 27] but also in the general population [28]. Age, gender, and especially BSA were the major determinants of ascending aortic diameters. Data of several studies are summarized in Tables 4.1 and 4.2.

The clinician must be aware that also in CT different methods of measurement are used: *enddiastolic* (Kälsch et al. [28] or *endsystolic* (Mao et al. [26], *with* inclusion Kälsch et al. [28] or *without* inclusion Mao et al. [26] of the aortic wall. Traditionally cross sectional imaging with CT or MRI includes the vessel wall. For contrast enhanced CT or MR however intraluminal diameter measurements are used. In 107 healthy persons Mao et al. showed that the mean diameter of the ascending aorta was endsystolic 1.7 mm greater than enddiastolic. The mean aortic wall thickness in 85 persons appeared to be 1.2 mm (range 0.75–1.75). So the luminal diameter was 2.4 mm less than the total diameter.

The clinician must also be careful to perform accurate measurements perpendicular to the long axis of the aorta. Especially in cases of an elongated thoracic aorta, the plane of the aortic valve can be nearly vertical instead of horizontal; the ascending aorta also gets more of a C-shape. Double oblique reformatted images, obtained perpendicular to the aortic lumen (i.e. true short axis images of the aorta) allow a more accurate measurement of the aortic diameter [29]. When comparing cross-sectional dimensions in standard axial planes and in reformatted double oblique planes, Mendoza et al. demonstrated significant size differences with impact for surgical decision making [30]. During hypovolaemic shock aortic diameters may be decreased [31].

Aortic Growth and Pathologic Conditions

At younger ages, dilatation of the ascending aorta is often associated with various connective tissue diseases and has a hereditary cause, either syndromal (e.g. MFS, Loeys Dietz syndrome [LDS], Ehlers Danlos syndrome type IV) or non-syndromal (e.g. TAAD). Osteoarthritis Aneurysm syndrome is a recently recognized autosomal dominant syndromic form of thoracic

aortic aneurysms and dissections characterised by the presence of arterial aneurysms and tortuosity, mild craniofacial, skeletal and cutaneous anomalies, and early-onset osteoarthritis. It is caused by mutations in SMAD 3 [32–34]. Other causes of aortic dilatation are hypertension, chronic dissection, aortic surgery (false aneurysm), cardiopulmonary resuscitation and lastly infectious and non-infectious aortitis. Atherosclerosis more often causes aneurysms of the *descending* aorta and particularly aneurysms of the abdominal aorta, not the ascending aorta [7, 35].

There is evidence that many patients with bicuspid aortic valve (BAV) or Aortic Coarctation (CoA) have disorders of vascular connective tissue as well, involving loss of elastic tissue and leading to dilatation of the proximal aorta [36, 37]. The exact mechanism behind dilatation of the proximal aorta in isolated BAV is however still a matter of debate, For a long time this has been attributed to a genetic cause. Lately there is increasing evidence for a haemodynamic mechanism, either a poststenotic dilatation, or abnormal flow patterns and asymmetrically increased wall stress by a clinically normal BAV. Probably, it is a combination of these aforementioned components, because also different phenotypic forms of aortopathy have been described: dilatation of only the tubular part of the ascending aorta, dilatation of only the aortic root and combinations with dilatation of the aortic arch [38–42].

When Can Aortic Dissection Occur?

Although a virulent disease, thoracic aortic aneurysm (TAA) is an indolent process. Yale data pointed out that a thoracic aneurysm grows very slowly, approximately 0.12 cm per year (ascending aorta 0.1 cm/year, descending aorta 0.3 cm/year [43].

TAA-patients with positive family trees (but no MFS) show a higher growth rate than patients with sporadic TAA or MFS [44, 45]. Aortic dilatation may lead to aortic dissection or aortic rupture. The risk of aortic dissection is related to the aortic diameter. In 2002, Davies et al. [46] identified that the median aortic diameter at the time of rupture for the ascending or aortic arch was 6.0 cm. This diameter is still considered a 'hinge point' at which dissection or rupture can occur and yearly rate of rupture, dissection or death reaches maximal levels [43, 47] (Figs. 4.8 and 4.9). Intraoperative experiments with epiaortic echography has shown that as the aorta enlarges, distensibility of the aortic wall decreases, so that by approximately 6 cm in size, the aorta becomes a rigid tube [48]. There is, however, also evidence that a substantial number of patients have aortic diameters of less than 5.5 cm at the time of dissection; 15 % of the MFS patients have aortic dissection at a size of less than 5.0 cm [49]. In the analysis of Parish et al. 42 % (74/177) of patients without MFS or BAV had diameter <5 cm at moment of type A dissection [50]. In the International Registry of Acute Aortic Dissections (IRAD), more or less the same results: nearly 60 % of the 591 type A dissection patients

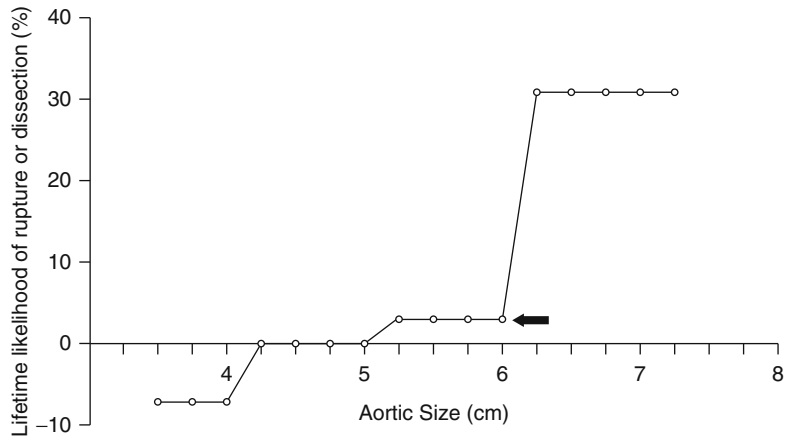

Fig. 4.8 Estimated effect of ascending aortic aneurysm size on risk of complications. Cumulative lifetime likelihood of rupture or dissection (y-axis) plotted against aortic size (x-axis). Note the abrupt "hinge point" at 6 cm (Adapted from Coady et al. [47])

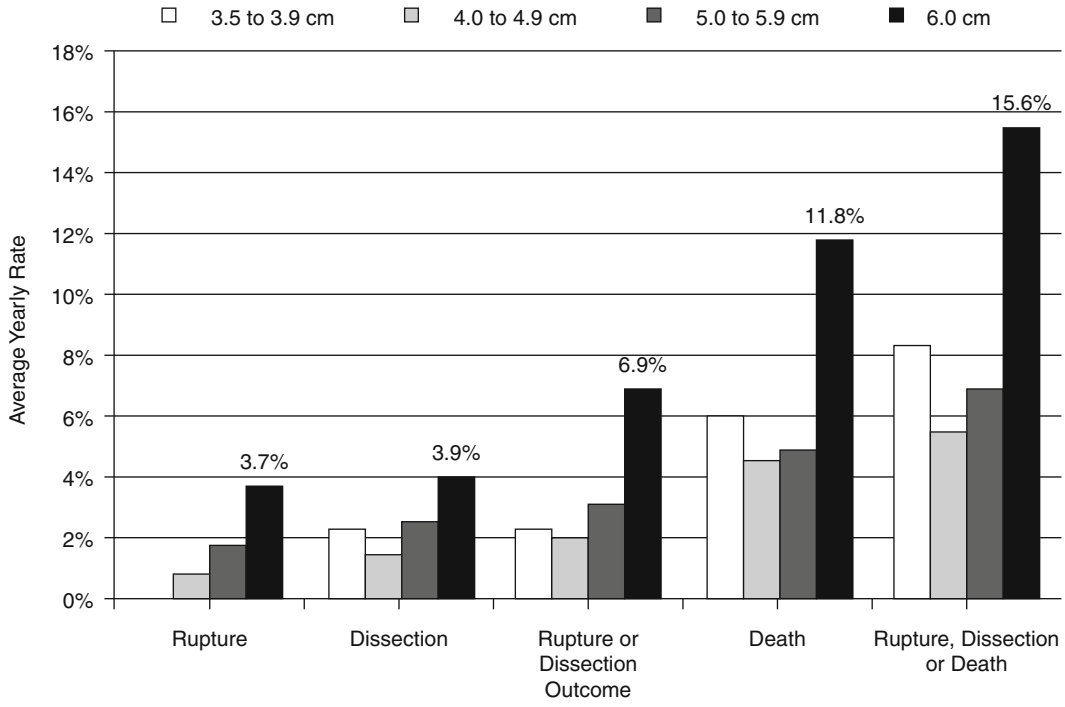

Fig. 4.9 Yearly rates of rupture, dissection, death, and combined events, related to aortic size. Note again the critical criterion dimension of 6 cm (From Elefteriades et al. [43])

had diameters <5.5 cm, and 40 % had diameters <5.0 cm [51] (Fig. 4.10). Given these facts, the aortic diameter alone is not sufficient to explain aortic dissection, and there is need for additional risk markers. Aortic elasticity has been identified as an additional risk factor for aortic dissection [52]. Whether this has implications for management has to be awaited.

Aortic Dissection and BAV

Early publications indicated that aortic dissections occur more frequently in patients with BAV compared with tricuspid aortic valve (TAV) [53], even after AVR when there was a seemingly normal ascending aorta diameter at time of surgery [54]. Dissections occurred in patients with BAV at smaller size than 5.0 cm [49] and at a younger age [55]. However, in the IRAD-data it was unclear if the results were corrected for the effect of hypertension with and without BAV compared with TAV [56].

Recent studies however indicate that the dissection rate in patients with BAV is low [37, 57–59], does not differ from patients with TAV [60] and that life expectancy of adults is not shortened, when compared with the general population [57, 58]. Also after isolated AVR, dissection rate is low for patients with preoperative ascending aorta diameter of <50 mm [61, 62] or 40–50 mm [63, 64] (Table 4.3). Aortic enlargement may still occur post AVR, but appeared not to be a predictor for adverse aortic events [61–65]. Only the small subgroup with a 'root phenotype' seemed to be at higher risk [38, 65–67].

When Is Operation Indicated in Asymptomatic Patients? What do the Guidelines Say?

Until recently, it was generally agreed that prophylactic replacement of the aortic root should be performed at a diameter of 5.5 cm in patients with MFS [47, 68]. In the recommendations from

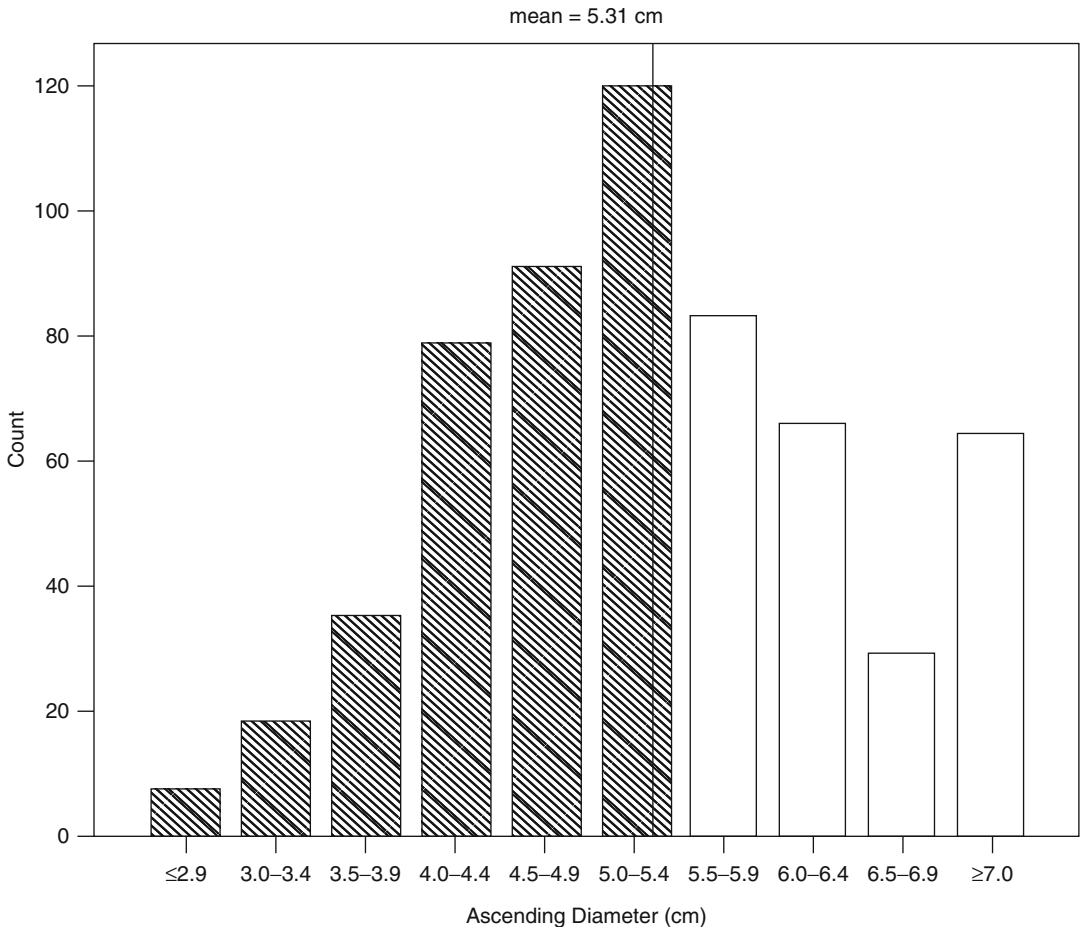

Fig. 4.10 Distribution of aortic size at time of presentation with acute type A aortic dissection (cm). *Shaded bars* indicate 59 % of patients with diameters <5.5 cm (From Pape et al. [51])

the ESC Task Force on Aortic Dissection in 2001, this was broadened to all cases of dilated ascending aorta with inherited disease (MFS, EDS, annulo aortic ectasia) [1]. In cases with a *family history of type A-dissection*, the replacement of the aortic root should be performed earlier, at a diameter of ≤5.0 cm [1]. These ESC guidelines received ACC endorsement in 2001.

Between 2006 and 2008, four guidelines were published, not focussed on aortic dissection/dilatation, but with additional advice for patients with Dilated Ascending Aorta in combination with MFS, BAV or Aortic regurgitation. The 2006 ACC/AHA Guidelines for the management of Valvular Heart Disease (VHD) [69], the 2007 ESC Guidelines on the management of VHD [70], the 2008 ACC/AHA Guidelines for the management of Adults with Congenital Heart Disease [71] and the 2010 ESC Guidelines for the management of Grown-Up Congenital Heart Disease (GUCH) [72]. All guidelines give practically the same recommendations: (1) Repair of the aortic root (ARR), or replacement of the ascending aorta (AAR) if the diameter of the aortic root or the ascending aorta exceeds 5.0 cm or if the rate of increase is 0.5 cm/year or more. (2) In patients undergoing AVR, ARR, or AAR is indicated if the diameter is greater than 4.5 cm. (3) Lower thresholds may be considered for patients of small stature [69]. (4) Prepregnancy counselling is advised at 4.0/4.5 cm.

Table 4.3 Follow-up studies on BAV patients after aortic valve replacement

Authors	Sample size	Age (years)	Study period	Follow-up (years)	Dissection/rupture	Aortic reoperations	Sudden deaths	Cumulative aortic events	15 year survival
Russo et al.	50	51 ± 12	1975–1985	19.5 ± 3.9	5 (10 %)	3 (6.0 %)	7 (14.0 %)	15 (30.0 %)	
Borger et al.	201	56 ± 15	1979–1993	10.3 ± 3.8	1 (0.5 %)	18[a] (9.0 %)	3 (1.5 %)	22 (11.0 %)	
Goland et al.	252	61 ± 15	1971–2000	8.9 ± 6.3	0 (0 %)	1 (0.4 %)	11 (5.6 %)	12 (4.8 %)	
McKellar et al.	1286		1960–1995	12 (0–38)	13 (1 %)	11 (0.9)	No data	160[c](11 %)	52 %
Girdauskas et al.	153	54.2 ± 10.5	1995–2001	11.5 ± 3.2	0	5[b](3.3 %)	3 (2.0 %)	8 (5.2 %)	78 %

[a]11/18 simultaneous aortic valve replacement for structural deterioration of bioprosthesis
[b]2/5 additional indication for redo by complications of the aortic valve prosthesis
[c]Including 127 documented cases (9.9 %) of progressive aortic enlargement

The ESC Guidelines on GUCH gives this recommendation for MFS. The other three Guidelines gives the same recommendations for BAV, which has been criticized by many authors [56, 64, 73, 74] and is still matter of debate [53, 75]. Because the low risk of aortic dissection with BAV, the size of the BAV population and (often) the impossibility of valve sparing surgery, the ESC has become recently more conservative in her policy towards aortic root dilatation with BAV. The Revised ESC Guidelines on VHD (version 2012) advices operative treatment of the aortic root at a size ≥5.0 cm only if risk factors are present (family history, systemic hypertension, aortic coarctation, increase in aortic diameter >2 mm/year) [76]. Without risk-factors operative treatment is adviced at a diameter ≥5.5 cm, just as for other patients. In MFS, also family history, size increase 2 mm/year, severe AR, desire to become pregnant, are risk factors to consider operative treatment for aortic root diameter ≥4.5 cm instead of 5.0 cm in MFS without risk factors [76].

In between, the 2010 ACCF/AHA Guidelines for the management of Thoracic Aortic Disease were published. They recommended similar thresholds for surgery. New in was the statement that for patients with LDS or confirmed TGFBR1 or TGFBR2 mutation, it is reasonable to undergo aortic repair when the aorta diameter exceeds 4.5 cm [3]. The experience of the surgical team may influence this decision making.

Given the recent data about type A dissection at diameters <5.0 cm, the lowered operative risk in large surgical centres, and the current possibilities of valve-sparing surgery, operative treatment at a diameter of 4.5 cm or more may be advised in some cases of connective tissue disease, especially when pregnancy is desired, when there is a family history of dissection, or when there is an indication for elective aortic valve replacement [3, 22, 35, 49, 50, 54, 69–72, 77] (Table 4.4). Replacement of the aortic root has also been suggested starting from 4.0 cm in LDS (in particular when it can be done valve-sparing) [78–80] and when there is an indication for elective aortic valve replacement [35].

Table 4.4 What to do with ascending aorta diameters >4.0 cm: advice for the clinician caring for patient with aortic dilatation

Diameter >4.0 cm	Search for connective tissue disorder, initiate beta-blocker-therapy, strict blood pressure control, moderate restriction of physical activity, pre-pregnancy counseling, yearly follow up by TTE and/or CT/MRI
Diameter >4.5 cm and aortic valve surgery	Operative treatment of valve and ascending aorta simultaneously
Diameter >4.5 cm in case of connective tissue disorder	Consider operative treatment in cases of desired pregnancy, family history of aortic dissection, LDS or TGFBR1/TGFBR2 mutation, or progressive aortic growth >0.2 cm/year
Diameter >5.0 cm in case of connective tissue disorder,	Operative treatment
Diameter >5.0 cm and BAV	Consider operative treatment of valve and ascending aorta simultaneously, when risk factors are present
Diameter >5.5 cm in other cases	Operative treatment

Management and Follow-Up in Case of Aortic Dilatation

For adults the authors consider an aortic root (AR) or tubular ascending aorta (AA) diameter above 4.0 cm as abnormal. This is supported by many authors: Pellicia 2010 AR [17], Reed 2010 AR [15], Kinoshita 2000 AR [16], Radonic2011 AR [14], Agarwal 2009 AA [29] and many published reference values (Hager 2002 AA [81], Kaplan 2007 AA [82], Lin 2008 AA [83], Mao 2008 AA [26], Lu 2009 AR+AA [84], Mendoza 2011 AR+AA [30]).

In our opinion dilatation due to aging is not a *normal* process. Aortic sizes of young adults might be taken as reference value for older adults as well. Also for tall persons the aortic root

diameter does not increase linearly with increasing BSA but tends to plateau. For women a value somewhat below 4.0 cm may be considered as upper limit of normal. The same applies to persons with small stature [69].

Last but not least, the tight hinge point for dissection at 6.0 cm, the solid criteria for surgical intervention from 5.0 to 5.5 cm and in some cases earlier, ask for a tight upper limit of normal size.

From a dilatation of the ascending aorta above 4.0 cm, the patient should be monitored regularly. Evaluation of a possible connective tissue disease should be performed by a multidisciplinary team (cardiologist, geneticist, and ophthalmologist). Patient and family history should be investigated, physical examination should be undertaken, and eventually DNA testing should be carried out. TTE should be performed to examine the aortic valve and to quantify aortic regurgitation. It cannot be stressed enough that also the entire aorta should be visualized using MRI or CT [85, 86]. Especially in TAAD or BAV patients, aneurysms tend to occur more frequently in the tubular ascending aorta, which may be difficult to visualize by TTE. Risk factors such as hypertension, cigarette smoking, and hypercholesterolemia should be managed. Blood pressure level should be lowered to 120/80 mmHg or less. Presently, beta-blockers are still the preferred medical therapy [35, 87, 88], but large prospective multicenter trials on the effect of ATII receptor antagonists or ACE inhibitors on aortic growth in patients with Marfan syndrome are being performed worldwide [35, 88, 89]. An overview of current studies has recently been published by den Hartog et al. [89] (Table 4.5).

Moderate restriction of physical activity should be advised [1, 88]. Patients should avoid exertion at maximal capacity and specifically, should not engage in competitive, contact, or isometric sports [90, 91]. Yearly follow up of the aortic diameter by TTE and/or by means of MRI or CT should be performed. In case of LDS or TGFBR1/TGFBR2 mutation, MRI of the thoracic, abdominal, cervical and cerebral vessels should be performed more frequently. Patients with LDS often have a more widespread and malignant course of aneurysmal disease.

Operative Treatment

The aortic valve and ascending aorta are replaced simultaneously by using a so-called composite valve graft with reimplantation of the coronary ostia into the prosthesis. The most frequent cause of late death is aneurysmal formation at the downstream aorta. The draw-back of composite graft replacement are thrombo-embolic, infectious and bleeding complications. With BAV as exception, valve sparing aortic root replacement is now first choice with excellent medium-term results. In the remodelling technique described by Yacoub [92], the graft is sewn to the remaining aortic wall around the commissures. This creates neo-sinuses and leaves the annulus mobile but unsupported. In the re-implantation or David technique, [93] the graft is fixed at the subannular level, and the valve and commissures are reimplanted inside the fabric. Both procedures offer a reasonable alternative to composite valve grafting with excellent short- and medium-term results, but long-term durability is not yet established. All aspects of surgery are treated in more detail in other chapters.

Genetic Counseling

Most connective tissue disorders are inherited in an *autosomal dominant* manner, which means that first degree relatives have a 50 % risk of inheriting the disease, although the severity cannot be predicted. For BAV, the genetics are complex and studies have demonstrated that BAV is likely related to mutations in different genes. First-degree relatives, also of patients with BAV, should, therefore, be evaluated for manifestations of connective tissue disorder, including a comprehensive clinical examination and TTE [71, 76]. If a disease-causing mutation in the index patient is known, molecular genetic testing of

Table 4.5 Overview of current studies with ATII receptor antagonists with regard to aortic disease in MFS

Institution (study)	Start date	Follow up	Design	Age range (years)	Target no. cases	Clinical endpoints	Tool
Boston Children's Hospital, Pediatric Heart Network	January 2007	36	DB, RCT; losartan vs atenolol	0.5–25	604	Change in AoR diameter	Ultrasound
Lacro et al.							
National Taiwan University Hospital (LOSARTAN)	February 2007	Un-known	OF, RCT; losartan and atenolol vs propanolol	≥1	44	Change in Aor diameter	Ultrasound
Wu et al.							
Brigham and Women's Hospital	October 2007	6	DB, RCT; losartan vs atenolol	≥50	50	Aortic biophysical properties	Ultrasound + arterial tonometry
Creager et al.							
Heart and Stroke Foundation of Canada	January 2008	12	DB, RCT; losartan vs atenolol	12–25	30	Aortic biophysical properties	Ultrasound
Sandor et al.							
Academic Medical Center (COMPARE)	February 2008	36	OB, RCT; losartan vs no losartan	≥18	330	Change in AoR diameter	Ultrasound + MRI
Mulder et al.							
Policlinico St. Matteo Hospital	July 2008	48	OB, RCT losartan vs nebivolol or combined	1–55	291	Change in AoR diameter	Ultrasound
Gambarin et al.							
Hospital Bichat Paris (Marfan Sartan)	September 2008	36	DB, RCT losartan vs placebo	≥ 10	300	Change in AoR diameter	Ultrasound
Detaint et al.							
Ghent Hospital (Ghent Marfan Trial)	June 2009	36	DB, RCT losartan vs placebo	≥10	174	AoR diameter at any level, CA diameter	Ultrasound + MRI
Moberg et al.							
Hospital Universitario Vall d'Hebron	October 2010	36	DB, RCT losartan vs atenolol	5–60	150	Change in AoR, CA diameter	Ultrasound + MRI
Forteza et al.							

From Hartog et al. [89]
AoR Aortic root, *CA* carotid artery, *DB* double-blind, *echo* echocardiography, *MRI* magnetic resonance imaging, *OB* open label, blinded endpoints, *OF* open factorial, *RCT* randomized controlled trial

family members is possible, and prenatal testing can be performed.

Conclusion

An ascending aortic diameter above 4.0 cm should always be considered as abnormal. The clinician should be aware of the need for an aggressive preventive approach in patients with aortic dilatation, specifically in case of a connective tissue disorder. Due to recent insights, criteria for operative treatment of aortic dilatation have been liberalized in the relevant guidelines. Furthermore, the clinician should realize that first-degree relatives of

patients with thoracic aortic dilatation are also at risk and should be evaluated for manifestations of connective tissue disorders.

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