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The ascending aortic aneurysm: When to intervene?

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ABSTRACT

Background: Thoracic ascending aorta aneurysms (TAA) are an important cause of mortality in adults but are a relatively less studied subject compared to abdominal aortic aneurysms (AAA). The purpose of this review is to explain the main aspects (etiology, pathophysiology, diagnosis) of this disease and to summarize the most recent developments in its management.
Methodology: Literature was obtained through online health related search engines (PubMed, MEDLINE) by including the following keywords: ascending aorta aneurysm, thoracic aneurysms, Marfan syndrome, bicuspid aortic valve, familial thoracic syndrome, aortic dissection, aorta imaging and aortic aneurysm guidelines. We included articles dating from 1980 to 2014.
Findings: Literature revealed how lethal this disease can be and how simple steps such as follow-up and prophylactic surgery can significantly reduce morbidity and mortality. This review also allowed us to realize the many developments that have been made in recent years in the understanding of pathologic mechanisms of this disease.
Conclusion: TAA is a silent disease that needs to be recognized early in its course and followed closely in order to recommend appropriate preventive and prophylactic therapy in a timely manner.

1. Introduction

The dilation of the ascending aorta is a common incidental finding on transthoracic echocardiography performed for unrelated indications. While the potential complications of aortic rupture and dissection are well recognized, most physicians are trained for the treatment of heart and coronary artery diseases, with limited knowledge and experience in the optimal management of patients with a dilated ascending aorta. The purpose of this article is to review the current understanding of the etiology, diagnosis, medical management and timing of surgical intervention in the patient with a dilated ascending aorta or ascending thoracic aortic aneurysm (TAA).

1.1. Anatomy

The aorta is divided into two main segments: thoracic and abdominal. The thoracic aorta is further divided into 3 parts: ascending, arch and descending. The ascending aorta originates beyond the aortic valve and ends right before the innominate artery (brachiocephalic trunc). It is approximately 5 cm long and is composed of two distinct segments. The lower segment, known as the aortic root, encompasses the sinuses of Valsalva and sinotubular junction (STJ). The upper segment, known as the tubular ascending aorta, begins at the STJ and extends to the aortic arch (innominate artery). More than 50% of TAA are localized to the ascending aorta, which may affect either the aortic root or tubular aortic segment [1].

1.2. Definition of aortic aneurysm

Published data on arteries diameter in healthy population are often scant or variable because of different imaging modalities used for measurement. Nevertheless, by common convention, aortic dilatation refers to a dimension that is greater than the 95th percentile for the normal person age, sex and body size. In contrast, an aneurysm is defined as a localized dilation of the aorta that is more than 50% of predicted (ratio of observed to expected diameter ≥ 1.5). Aneurysm should be distinguished from ectasia, which represents a diffuse dilation of the aorta less than 50% of normal aorta diameter.

An official cutoff for the definition of aortic dilatation has not been determined because of the variability of this measure, but most experts agree that ascending aorta size should be correlated to size and gender. In addition, some authors suggest using the aortic size index [2] which takes into account the body surface area, thus

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minimizing classification of normal aorta as pathologically dilated and vice versa.

1.3. Epidemiology

Thoracic aortic aneurysms (TAA) and its associated complications are life threatening clinical entities that rank in the top 20 leading causes of mortality in the United States (15th leading cause of death in people over 65 years old) (*CDC*, http://webapp.cdc.gov/cgi-bin/broker.exe). Unfortunately, the mortality rate of patients presenting with complications of TAA has remained relatively stable in the last two decades, in contrast to the improved survival observed in patients presenting with complications of coronary artery disease (CAD). As Clouse et al. pointed out, the prognosis of patients with TAA is indeed improved if they are treated before complications occur [3].

The incidence of TAA has been reported to be only 5.9 cases per 100,000 person-years in the early 1980s, however recent advances in imaging modalities, aging of the population, increased use of transthoracic echocardiography and routine screening have resulted in a twofold increase in the incidence [4]. According to the CDC, the incidence of ascending TAA is estimated to be around 10 per 100,000 person-years. Women and men have similar incidences of thoracic aortic aneurysm but the age at diagnosis is a decade higher in women (70s) than in men (60s).

1.4. Pathophysiology

The aorta is an elastic vessel composed of three main layers: the tunica intima, the tunica media and the tunica adventitia. The internal elastic lamina separates the intima from the media.

Elastic fiber in the medial layer of the aorta allows continuous forward flow during the whole cardiac cycle. During systole, expansion of the aorta allows kinetic energy from left ventricular contraction to be stored as potential energy in the aortic wall. In diastole, recoil of the aorta transforms the stored potential energy back to kinetic energy, propelling the blood distally into the arterial bed. With aging, there is fragmentation of elastic fiber, smooth muscle dropout and replacement by amorphous material (known as cystic medial degeneration), which leads to increased stiffness and weakening of the aortic wall which predisposes to dilatation of the ascending aorta. In addition, according to Laplace's law, the dilation of the aorta increases wall tension, triggering vascular wall remodeling and even further aortic dilatation.

Recent developments have helped better explain the cellular changes that lead to aneurysmal ascending aortas. The different conditions that cause TAAs either affect structural components of the aortic wall or alter the intracellular signaling cascade that maintains vascular wall integrity. The main culprit in this disease seems to be the *TGF-B1* signaling mechanism that is responsible for activating matrix degradation through increased production of plasminogen activators and release of matrix metalloproteinases [5].

For example, mutations in ACTA2 alter the function of smooth muscle cell actin and are responsible for 14% of inherited TAAs [6]. In addition, the MYH11 gene affects the C-terminal coiled-coil region of the smooth muscle myosin heavy chain, a specific contractile protein of smooth muscle cells [7] and increases TAA formation.

Other mutations can affect both the structure and the metabolic homeostasis of the vascular wall. For instance, the mutation of fibrillin 1 in Marfan syndrome weakens the vascular wall given that it is a reinforcing structure [8] and it also alters the regulation of the bioavailability of TGFB1 [9].

Other mutations affect the TGF-B signaling pathway directly by affecting the TGF-B receptors such as in Loeys–Dietz syndrome [10]. Other mutations alter the regulatory mechanisms that inhibit the activity of the TGF-B pathway such as the mutation of GLUT10, a glucose transporter whose deficiency is associated with arterial tortuosity syndrome [11] or the mutation of the SMAD3 gene that encodes a protein necessary for the signaling downstream of the TGF-B pathway [12].

Many other structural anomalies and metabolic alterations have also been implicated in the pathogenesis of TAAs but will not be extensively reviewed in this article.

1.5. Etiologies

The process of cystic medial degeneration can be either due to an innate defect or an acquired one. As can be seen in Table 1, ascending TAA is frequently seen with connective tissue diseases such as Marfan syndrome, Ehlers–Danlos syndrome, or familial aneurysms syndrome [13]. Data suggests that this process can also occur in congenital disease such as tetralogy of Fallot [14] and bicuspid aortic valve (BAV). Hypertension and smoking appear to accelerate the process by increasing elastolytic enzymes in the aortic medial layer [13]. Atherosclerosis has long been considered as a second cause of aortic aneurysm formation, with atheromatous plaques destroying small muscle cells and elastic fiber architectures, resulting in weakening of the aortic wall. However, this concept has recently been challenged; and it is now thought that atherosclerosis is not a primary cause, but a concomitant process in the diseased medial layer of the aortic wall [13].

Other less common etiologies can contribute to TAA formation. These include post-traumatic aortic transection, aortic cannulation post-CABG surgery, chronic aortic dissection, bacterial or syphilitic infection and vasculitic aortitis. These uncommon etiologies are not discussed in this review.

1.6. Risk factors

Different studies have shown that the ascending aorta diameter significantly correlates with age, waist circumference, smoking history and hypertension; the latter being the most prevalent risk factor for acute aortic dissection [15]. In a recent study, mean carotid intimal media thickness as well as epicardial adipose tissue were associated with ascending aorta dilatation [16]. In a study examining 833 autopsy cases, six risk factors (age, sex, body height, smoking history, hypertension and severe atherosclerosis) have been associated with ascending aorta dilations with age being the most important predictor of dilatation [17].

2. Diagnosis

2.1. Presentation

Dilatation of the ascending aorta is a very indolent process as it takes many years to develop and it is asymptomatic initially. In patients who develop an ascending aortic aneurysm secondarily to a systemic disorder, signs of the primary disease are the ones who lead the clinician to look for the dilatation such as in Marfan syndrome. Otherwise, this pathology remains quiet until its catastrophic complications occur or when it is incidentally seen on cardiovascular imaging related to other causes. We can prevent these complications by screening asymptomatic patients. Feared events include aortic dissection or rupture, pericardial hemorrhage, cardiac tamponade and occlusion of aortic branches. In addition, some patients, in a lesser proportion, can also develop intramural hematomas or penetrating aortic ulcers.

As shown in Tables 2.1 and 2.2, these complications do not manifest at the same age or at the same ascending aortic size. They are greatly dependent on the predisposing condition and, as discussed later, on the management of this disease.

Table 1
Etiologies of ascending aortic dilatation.

Congenital	Hereditary	Acquired
Bicuspid aortic valve Tetralogy of Fallot	Connective tissue disease	Hypertension Infectious
	- Marfan syndrome - Ehlers–Danlos syndrome - Loeys–Dietz syndrome - Arterial tortuosity syndrome - Aneurysms osteoarthritis syndrome	- Syphilitic - Bacterial infections - Viral - Fungal
	Familial aortic syndromes	Auto-immune
	- Autosomal dominant - Sporadic	- Takayasu - Behçet disease - Idiopathic aortitis
		Post-traumatic Chronic aortic dissection AV fistula Post-stenotic

2.1.1. Imaging

As can be seen in Table 3, many imaging modalities can be used to image the ascending aorta. We will discuss the advantages and disadvantages of each of these modalities in this section.

2.1.2. Chest X-ray

TAA produces a widening of the mediastinum characterized by a width on AP film of greater than 8 cm at the T4 or carinal level. In the lateral view, there is loss of the retrosternal space. However, this simple and non-invasive test is not neither sensitive nor specific. CXR could be normal in 15–20% of patients with TAA or aortic dissection.

2.1.3. Echocardiography

Transthoracic echocardiography (TTE) provides a simple non-invasive technique to evaluate the aortic root, proximal ascending aorta, aortic valve and left ventricular morphology and function in the vast majority of patients. For aorta assessment, images should be obtained in the parasternal long axis view and the aorta size measured at the onset of the QRS complex at 4 levels of the ascending aorta: annulus, sinuses of Valsalva, ST junction, and ascending tubular aorta (maximal diameters). Aortic dimensions can be obtained using a leading-to-leading edge technique [18]. Measurements obtained from two-dimensional images are preferred as m-mode techniques may underestimate the size of the aorta due to translation of the heart during the cardiac cycle.

Even though TTE does not provide consistently an adequate imaging of mid and distal segments of the ascending aorta, nor does it well visualize the descending aorta, it is the recommended imaging technique for screening of patients with suspected aortic aneurysm (root or proximal aorta) and for follow-up. A recent study [19] showed that TTE can substitute TEE in the follow-up of TAA dilatation with both modalities having relatively the same accuracy and a very little inter-observer variability.

Although, transesophageal echocardiogram (TEE) provides better view of almost the entire thoracic aorta, it is a semi-invasive technique and it is not the preferred routine study for follow-up or screening.

2.1.4. CT scan

Since the introduction of CT scanning in the 80s, it has become the preferred imaging technique to define aortic anatomy and its side branch vessels because of its easy accessibility and of its rapid results. With 3D reconstruction, the accuracy is further enhanced for measurement of aneurysms and the diagnosis of dissection, penetrating ulcer or intramural hematoma. The sensitivity and specificity of angioscans have increased greatly in the last few years reaching up to 100% [20], thus becoming comparable to MRI. Recently, a published study [21] demonstrated that dual source CT scan is as accurate as MRI in documenting TAA diameters in patients with BAV and a stenotic aortic valve which comes to reinforce the role of CT scanning in the diagnosis of TAA dilatation.

The main disadvantages of CT scanning are the radiation exposure and the risks related to contrast injection such as contrast induced nephropathy (CIN), carcinogenicity and teratogenicity. While CIN can be easily prevented with adequate hydration and reduction of contrast volume, carcinogenicity remains an important issue to consider especially in younger patients (i.e. Marfan syndrome patients) who require serial evaluations even in the context of newer generation low dose CT scanners. For this reason, screening with CT scanning is not routinely recommended, but it is the imaging method of choice to diagnose complications of ascending TAA dilatation and for preoperative visualization of the entire aortic anatomy.

2.1.5. MRI

MR angiography is an imaging modality that provides accurate measurement and definition of the entire aorta anatomy. Combined with cardiac MRI, this technology can better assess ventricular function, aortic valve function and aortic root anatomy. While it has the advantages of not requiring any radiation exposure, it is a less accessible and a more time consuming imaging technique. In addition, it is contraindicated in patients having metallic parts in them and in patients with advanced renal failure because of the possible risk of systemic nephrogenic fibrosis related to gadolinium injection.

3. Natural history

Normal aorta grows slowly with age. From the Framingham Heart Study (echo sub-study), aorta diameter increases 0.1 cm per 10 years

Table 2.1
Age of complication for TAA.

	Mean age at presentation (years)	Source
Hypertensive	64.2	(Davies, Kaple et al., 2007) [16]
Marfan syndrome	24.5 34.4 (age at prophylactic surgery) 39.4 (age at aortic dissection)	(Jondeau, Detaint et al., 2012) [17]
Bicuspid aortic valve	49	(Davies, Kaple et al., 2007) [16]
Familial (non syndromic)	56.8	(Albornoz, Coady et al., 2006) [18]
Loeys–Dietz syndrome	19.8 (age at complications)	(Loeys, Schwarze et al., 2006) [8]
Ehlers–Danlos syndrome	No data	No data

Table 2.2
Diameter of ascending aorta at timing of complications.

	Mean size at complications (mm)[a]	Source
Hypertensive	60	(Davies, Kaple et al., 2007) [16]
Marfan syndrome	51	(Roman, Rosen et al., 1993) [19]
	56	(Kornbluth, Schnittger et al., 1999) [20]
	50–59	(Jondeau, Detaint et al., 2012) [17]
Bicuspid aortic valve	52	(Davies, Kaple et al., 2007) [16]
Familial (non-syndromic)	No data	No data
Loeys–Dietz syndrome	40–50	(Loeys, Schwarze et al., 2006) [8]
Ehlers–Danlos syndrome	No data	No data

[a] It is to be noted that the risk of complications is higher for bigger diameters in each of the preceding conditions.

at the aortic root after the age of 25 [22]. Similar rate of growth is also observed for the tubular portion of the ascending aorta [23]. By the age of 75, normal ascending aorta diameter is approximately 3.6–3.7 cm for women (BSA: 1.95 m^2) and 4.1–4.2 cm for men (BSA: 2.35 m^2).

3.1. Hypertension related ascending thoracic aortic aneurysms

Nearly all studies found that hypertension increases ascending aorta dilatation in pre-existing TAAs and predisposes to the formation of TAA. Unlike inherited forms of ascending aortic aneurysms, hypertension related TAAs complicate at diameters over 6.0 cm and the risk of complications increases exponentially with the further increase in diameter [13].

Once the aorta becomes aneurysmal, its rate of growth is somehow accelerated and is strongly influenced by its size. The database from the Yale Center shows that aneurysms of the thoracic aorta grow at approximately 0.12 cm/yr (all patients confounded). The annual growth varies from 0.08 cm for small aneurysm (4.0 cm) to 0.16 cm for large aneurysm (8 cm) [24]. The rate of growth is also affected by the location of aneurysm. Aneurysms arising from ascending aorta grow slower (0.07 cm/yr) than the one from descending thoracic (0.19 cm/yr).

3.2. Bicuspid aortic valve (BAV)

Bicuspid aortic valve (BAV) disease is the most common congenital heart disease, occurring in 1–2% of the population. Bicuspid aortic valve is associated with valvular complications (aortic stenosis or regurgitation) as well as vascular complications such ascending aorta dilatation beyond the sinotubular junction and up to 33% will develop serious complications [25]. Up to 83% of patients with BAV will develop ascending aorta dilatation [26]. Nistri et al. found that 52% of patients with a normally functioning bicuspid valve have aortic dilatation [27].

While the valvular complications are directly related to the valve anatomy and its underlying embryological defects, the pathophysiology of the vascular complications is still under debate. Aortic dilatation could be easily attributed to hemodynamic abnormalities across an abnormally shaped valve but many studies seem to show that valvular dysfunction is not significantly related to increased aortic size. For instance, Ferencik and Pape showed that in patients with BAV with normal valve function, progressive aortic dilatation was more severe than in patients with tricuspid aortic valve (TAV) [28]. In a case–control study done by Keane et al., BAV patients were matched with TAV patients with similar valve function (AR, AS, normal) and the results showed that patients with BAV had aortic dilatation at a younger age and earlier than their matched controls [29]. Most studies done so far seem to show an underlying congenital anomaly in the aortic media associated with BAV that predisposes these patients to develop aortic dilatation with an aggravation induced by the valve dysfunction.

Very few studies succeeded in establishing a growth rate pattern for patients with BAV, and the evidence remains contradictory. A prospective TEE study has compared the growth rates of the dilated ascending aorta (4.0–6.0 cm) between patients with normal functioning aortic bicuspid and tricuspid valve. Among the 113 patients studied, 86 had bicuspid and 27 had tricuspid valve and there was no difference in the rate of growth between the two groups [30]. In contrast, another study involving 514 patients comparing patients with BAV (70) to patients with TAV(445) showed that patients with BAV had a higher growth rate (0.19 cm/yr compared to 0.14 cm/yr) and higher surgical repair rate than TAV patients (72.8% vs 44.8%). In addition, a recent study at the Montreal Heart Institute showed that ascending aortas in patients with BAV had a growth rate of 0.1 cm per year 1 cm beyond the sinotubular junction [31].

While it may seem that the natural history of TAA in patients with bicuspid aortic valve disease remains ill-defined, there seems to be a great tendency towards faster growth rate in this population.

3.3. Marfan syndrome

Marfan syndrome, first described by Antoine Marfan in 1896, is a connective tissue disorder with manifestations mainly involving the cardiovascular, respiratory, skeletal and ocular systems. It is caused by a mutation of the *FBN-1* gene that is inherited in an autosomal dominant pattern, although, 25% of cases seem to be sporadic. While Marfan syndrome predisposes to many other conditions, its most serious complications are related to aortic valve regurgitation and ascending root dilatation. Aortic dissection constitutes the most common cause of death in these patients. Up to 80% of patients with Marfan syndrome have ascending TAA dilatation [32]. Plus, women often complicate at smaller ascending aorta size compared to men [33].

Different studies have tried to establish the growth rate of the ascending aorta in these patients. As shown in Table 4, the results

Table 3
Advantages and disadvantages of different imaging modalities[a].

	Ultrasound	CT-scan	MRI
Advantages	Widely available Allows for estimating valve function No radiation exposure	Rapidly available Nearly 100% specific and sensitive Can diagnose dissection Can visualize entire aorta	Nearly 100% specific and sensitive No radiation exposure Can visualize entire aorta
Disadvantages	Time consuming compared to CT-scan (center dependent) Inter-observer variability Arch not visualized Difficulty visualizing portions distal to the sinotubular junction	Radiation exposure Contrast nephropathy	Time consuming compared to CT-scan Many contraindications Contraindicated in advanced renal failure More expensive

[a] Chest X-ray has not been included in this table for the reasons outlined below.

varied widely, ranging from 0.027 cm per year up to 0.2 cm per year. The largest study on this issue (n = 762) by Jondeau et al. shows that mean annual ascending aorta growth rate is 0.050 +/− 0.089 cm [34]. It has also been noted in certain studies that there are two specific subsets of patients in terms of growth rate: fast growers and slow growers. In a study by Meijboom et al., 1 in 7 men had a faster yearly growth rate (0.15 cm compared to 0.036 cm) and 1 in 9 women (0.18 cm compared to 0.027 cm) [33]. Higher diastolic and systolic blood pressure, older age and larger initial aorta size were all associated with being a "fast grower" as shown in another related study by Lazarevic et al. [35] and they were associated with a higher rate of complications which are: aortic dissection, aortic regurgitation and death. In the study by Roman et al., the extent of the dilatation was also associated with a higher rate of complications (33% in generalized dilatation compared to 6% in dilatation confined to the sinuses of Valsalva) [32].

3.4. Familial thoracic syndromes

Genetic predisposition other than Marfan syndrome appears to be linked with the development of ascending TAA. Biddinger et al. were the first who reported familiar aggregation of TAA [36]. In this study, patients with family history of TAA, aortic dissection or sudden death exhibited higher prevalence of TAA development and sudden death. Recently, similar studies support the role of genetic factors in the familial aggregation of TAA [13,37,38]. Albornoz et al. demonstrated that 21.5% of TAA was found in patients with family history of TAA [37]. It seems to be transmitted in an autosomal dominant pattern with variable degree of penetrance. The following mutations have been associated with TAA and dissection: MYH11, MYLK, SMAD3 and ACTA2 [39]. The age at presentation of complicating TAA or diagnosis of TAA is different as compared to patients with Marfan syndrome or patients with sporadic TAA. They are older than Marfan group but younger than sporadic group. The observed annual growth of TAA for familial TAA is 2.1 mm/yr, which is higher than any other subgroups of population. In some cases, familial TAA appears to be an aggressive aortic disease and family history of TAA, aortic dissection or sudden death needs to be considered as risk factor for rapid growth of TAA and its complications.

3.5. Loeys–Dietz syndrome

Loeys–Dietz syndrome is an autosomal dominant genetic disorder mainly associated with mutations of the genes responsible for the *transforming growth factor B receptors 1 and 2*. It is a rather rare disease characterized by the triad of hypertelorism, a bifid uvula, cleft palate or both, and generalized arterial tortuosity with widespread vascular aneurysm and dissection [11]. This disorder is nearly always associated with aortic root aneurysm and they tend to have complications very early on in life. In the study by Loeys et al. the mean age of death of these patients was at 26 and was caused by thoracic aortic dissection and the mean age for first vascular surgery was 19.8 years. In addition, women with this disease have higher tendency to have aortic dissection during pregnancy.

3.6. Ehlers–Danlos syndrome (EDS)

Ehlers–Danlos regroups a multitude of connective tissue disorders characterized by laxity of the Joints and skin disorders. Up to 28% of patients with EDS (all types confounded) present with ascending aorta dilatation [40]. This population has not been extensively studied but the associated TAA seems to be of little clinical importance as a recent retrospective study suggested that these aortas seem to normalize in size when children with EDS become adults [41]. However, type IV Ehlers–Danlos syndrome (autosomal dominant disorder) is characterized by characteristic skin manifestations associated with arterial, uterine and intestinal dissection and rupture [42]. Arterial complications are usually preceded by aneurysm formation but they can also occur spontaneously. This syndrome is associated with the COL3A1 mutation and the diagnosis can be made by DNA amplification or by collagen analysis.

Table 4
Mean increase in aorta size in patients with Marfan syndrome.

Source	Sample size	Growth rate (mm per year)[a]	
		Men	Women
(Jondeau, Detaint et al., 2012)	N = 762	0.50 ± 0.89	
(Lazarevic, Nakatani et al., 2006)	N = 43	1.5 ± 1.3	
(Meijboom, Timmermans et al., 2005)	N = 221	0.42	0.38
(Kornbluth, Schnittger et al., 1999)	N = 57	Up to 2 mm per year	
(Shores, Berger et al., 1994)	N = 70	0.84	
(Roman, Rosen et al., 1993)	N = 113	1.4 ± 0.5 (complications group)	
		0.9 ± 0.8 (no complications group)	
(Hwa, Richards et al., 1993)	N = 40	1.5	1.8
		0.36	0.27

[a] Compared to the 1 mm per decade observed in normal patients (refer to natural history section).

3.7. Arterial tortuosity syndrome

Arterial tortuosity syndrome is an autosomal recessive disorder characterized by tortuosity and aneurysm formation in the major arteries caused by a deficiency in glucose transporter GLUT 10 causing an upregulation of TGFBR1 signaling [11].

3.8. Aneurysms osteoarthritis syndrome

Aneurysms osteoarthritis syndrome is an autosomal dominant syndromic characterized by thoracic aortic aneurysms and dissections associated with the presence of arterial aneurysms, early-onset osteoarthritis and cutaneous manifestations. AOS is caused by mutations in the SMAD3 gene [43,44].

4. Management

4.1. When to intervene

As has been previously mentioned, complications of ascending aorta aneurysms can be disastrous even if diagnosed promptly and properly managed. It is therefore essential to diagnose a pathologically dilated ascending aorta in a timely fashion and to ensure a proper follow-up in order to start medical therapy and recommend prophylactic surgical repair.

Elective surgery is the mainstay "curative" treatment. Several studies have demonstrated the reduction in mortality associated with prophylactic surgery (Table 5). Corrective surgery is recommended when the aorta reaches a size where the risk of complications equals or exceeds the risk related to the surgery.

There have been many studies that tried to establish a specific size at which surgery should be performed, but it has been shown that this criterion depends on the underlying pathology, the rate of growth, the family history and to some extent the individual morphology of each patient. A retrospective study (that included a few patients with Marfan syndrome) showed that the median size associated with an increased risk of aortic dissection, rupture or sudden death was 6.0 cm [45]. In the same study, we see that the odds ratio of acute dissection for an aorta between 5.0 and 5.9 cm was not significantly increased but that it jumps to a statistically significant 8.84 when it exceeds 6.0 cm.

It is therefore safe to recommend prophylactic surgery when the aorta reaches a diameter of 5.5 cm unless the patient falls under the

category of Marfan syndrome, bicuspid aortic valve, positive family history or fast growers in accordance with the newest American guidelines [46].

Some authors have even cited the need to be more aggressive in the criteria for elective repair citing data from the International Registry of Aortic Dissection [47] showing that 60% of aortic dissections occurred in aortas with diameters under 5.5 cm and that 40% of them had diameters under 5.0 cm. These results led some experts to develop other measures that can possibly better predict the risk of complications. For example, a novel method that takes into account the body surface area called the aortic size index (ASI), measured by MRI, by dividing the maximal aortic diameter with the body surface area [2]. This formula allowed to identify 3 different risk groups: those with an ASI higher than 4.25 cm/m^2 experienced a sevenfold increase in the incidence of aortic complications. This index allows a certain individualization of the size at which people should be recommended surgery.

As of today, it is recommended to offer prophylactic ascending aorta repair to patients without predisposing conditions other than hypertension when the aorta reaches 5.5 cm or if the growth rate exceeds 0.5 cm per year or if patient is undergoing another major cardiac surgery with an ascending aorta over 4.5 cm.

As has been already mentioned in this review, patients with Marfan syndrome tend to have acute aortic syndromes at a younger age and at smaller aortic diameters than other patients (refer to Table 2.2). The newest American guidelines recommend prophylactic surgery for patients with Marfan syndrome in 6 settings [46]:

1 When the aorta reaches a diameter of 5.0 cm.
2 When the aorta reaches a diameter of 4.5 cm with either a positive family history of complications.
3 When the patient is undergoing aortic valve replacement, if the aorta exceeds 4.5 cm.
4 Associated significant aortic valve regurgitation, if the aorta exceeds 4.5 cm.
5 When the annual rate growth exceeds 0.5 cm.
Women with childbearing potential (see section on pregnancy).

Some references even suggest lowering the threshold for surgery to all patients with Marfan syndrome to 4.5 cm based on data showing that some dissections occur below the threshold aforementioned and given the reduction of mortality associated to the surgery in high volume centers. Choice of surgical procedure is discussed in the following section.

For patients born with a bicuspid aortic valve, data is still somewhat contradictory about the diameter at which complications occur. It is now widely accepted that this is a heterogeneous population. Therefore, there is variability with the determination of a specific diameter at which the risk of complications increases. Most centers recommend elective replacement when the ascending aorta reaches 5.0 cm. Choice of surgical procedure has not been extensively studied.

In patients diagnosed with Loeys–Dietz syndrome, complications from TAA occur at a much younger age and at smaller ascending aortic diameters than most other patients, thus requiring even more aggressive prophylactic therapy. The authors of the main study on aneurysm syndromes in patients with Loeys–Dietz syndrome recommend prophylactic surgery at experienced centers when the aorta reaches 4.0 cm [10]. Likewise, the latest guidelines from the ACCF recommend prophylactic surgery when the ascending aorta reaches 4.2 cm (measured by transesophageal ultrasound) albeit being based on a "C" level of evidence [46].

4.2. International recommendations

Tables 6, 7 and 8 compare Canadian, European and Japanese guidelines in the management of ascending TAA in general as well as in patients with Marfan syndrome or patients with a BAV. As can be noticed, all international guidelines recommend prophylactic surgery for TAA at sizes somewhat equivalent.

4.3. Medical management

If diagnosed early, mild to moderate dilated ascending aortas can certainly benefit directly from medications such as beta blockers and ACE inhibitors. In addition, it is very important to prevent and treat risk factors such as hypertension and metabolic syndrome. There is no official recommendation for the target blood pressure, but it would be preferable to aim for blood pressure under 120/80 mm Hg [48].

According to ACC guidelines, "antihypertensive therapy should be administered to hypertensive patients with thoracic aortic disease to achieve a goal of less than 140/90 (patients without diabetes) or less than 130/80 (patients with diabetes or chronic renal disease) to reduce the risk of stroke, myocardial infarction, heart failure and cardiovascular death" [46].

In patients with Marfan syndrome, a landmark trial by Shores et al. [49] demonstrated the efficacy of the beta blocker propranolol in reducing the rate of dilation of the ascending aorta (0.023 cm per year compared to 0.084 cm per year with $p < 0.001$) as well as increasing survival. The physiological effect of beta blockers on the natural history of the dilated ascending aorta is not clearly understood, and a combination of reduced wall stress and vascular remodeling has been proposed. As mentioned earlier, patients with mildly dilated ascending aorta are those who benefit the most from beta blockade as shown in a study by Haouzi et al. [50].

In addition, many authors have shown interest in the effect of angiotensin converting enzyme inhibitors (ACEIs) on the rate of dilation of TAA. In one study, the addition of perindopril to beta-blockers significantly reduced the aortic diameter as well as the aortic stiffness in a small sample of 10 patients with Marfan syndrome [51]. This finding is also corroborated by another study, in which beta blockers are compared to the ACEI enalapril [52], the latter showing slower rate of aortic growth, fewer adverse outcomes and decreased side effects in patients with Marfan syndrome. The effect of ACEIs is thought to be due to the decreased activity of the angiotensin II receptors which increase cystic medial degeneration.

Table 5
Mortality rates for timing of surgical therapy.

	Sample size	Elective (>7 days)	Urgent (1–7 days)	Emergent (<24 h)
Gott et al. NEJM 1999 (M)[a]	675	1.5%	2.6%	11.7%
Coady et al. J thorac Surg 1997	230	4.3%	20.5%	
Achnek et al. Ann Thorac Surg 2007	506	4.4%	21.6%	
Kallenback et al. Circulation 2005	284	1.3%	9.3 ± 2.5%	

[a] (M) = studies on patients with Marfan syndrome.

Table 6
Comparison of national guidelines for the management of TAA in patients without any genetic predisposition.

Canadian society for vascular surgery	Japanese Circulation Society 2011 guidelines	ESC 2007 guidelines
"*Intervention should be considered when the diameter of a thoracic aortic aneurysm reaches 5.5 cms in men, and 5.0 in women. Smaller aneurysms under surveillance typically grow by 10% per year. Faster growing aneurysms should be considered for intervention sooner than the usual operative threshold.*" http://canadianvascular.ca	The following situations warrant surgical intervention: • Aneurysms with a maximum minor-axis diameter of 60 mm or greater • Aortic aneurysms accompanied by pain where the maximum minor-axis diameter is 50 to 60 mm (Group 2013)	The following situations warrant surgical intervention: • Aortic root diameter greater than 55 mm. • "For patients who have an indication for surgery on the aortic valve, lower thresholds can be used for combining surgery on the ascending aorta." (Vahanian, Baumgartner et al. 2007) [44]

Table 8
Comparison of national guidelines for the management of TAA in patients with bicuspid aortic valve.

Canadian guidelines	Japanese guidelines	ESC 2012
Based on American guidelines	*Based on American guidelines*	The following situations warrant surgical intervention: • Ascending aorta diameter greater than 50 mm with any of the following risk factors: 1. Coarctation of the aorta 2. Systemic hypertension 3. Family history of dissection 4. Progressive dilation of more than 2 mm per year as confirmed by repeated measurements (Vahanian, Alfieri et al., 2013) [44]

At the 2013 European Society of Cardiology Congress, authors of the COMPARE trial (prospective randomized study which included 233 patients with Marfan syndrome) revealed that losartan slowed aortic root enlargement [53]. However, the study did not show a reduced rate of events in the treatment group. This larger study confirms the findings of a smaller study (n = 17) that showed a beneficial effect of losartan on the rate of progression of TAAs [54].

While the use of Statin has been soaring in the past decade for the treatment of abdominal aortic aneurysms (AAA), no study has found a beneficial effect on the outcomes associated with TAA.

Most studies have examined the effect of long-term medical therapy on the progression of idiopathic aortic dilation in patients with Marfan syndrome. However, there are very few studies on patients with other etiologies. Thus, it is unclear whether extrapolation of the results of patients with Marfan syndrome can be done. Nevertheless, it is very important to encourage cardiovascular risk factor reduction in patients with TAA especially hypertension and dyslipidemia.

4.4. Surgical intervention

As has been already mentioned, surgery and ideally prophylactic surgery remain the cornerstone of the treatment of the pathologically dilated ascending aorta. Different surgical procedures can be performed depending on the site of aortic dilation and the function of the aortic valve. Dilation without implication of the Valsalva sinuses can be managed by tube graft replacement, however when the sinuses of Valsalva are involved, the Bentall procedure (composite valve graft replacement with re-implantation of the coronary arteries) or the valve sparing procedure can be performed [55]. The valve sparing procedure can be done following the David technique (aortic valve reimplantation) or the Yacoub technique (aortic valve remodeling). The David technique is the one used preferentially [56]. In some cases, the Ross procedure can also be performed, if the native aortic valve is diseased and cannot be reimplanted.

In general, all three procedures are associated with lower mortality and morbidity if performed electively. Post-operative morbidities including stroke, myocardial infarct, bleeding and aortic insufficiency have been estimated at less than 5%.

Choice of procedure depends on many factors, but, in general, most studies show an early and late mortality and morbidity advantage associated with the valve sparing surgery at the expense of a slightly higher re-operation rate. As Tables 9 and 10 show, there is decreased 30-day and 5 years mortality in patients who undergo the valve sparing procedure. As previously stated, freedom from re-operation for aortic insufficiency is slightly lower in patients who undergo the valve sparing procedure (VSP). In one study [57]

Table 7
Comparison of national guidelines for the management of TAA in patients with Marfan syndrome.

Canadian Cardiovascular Society 2009 Consensus	Japanese Circulation Society 2011 guidelines	ESC 2010
The following situations warrant surgical intervention: • A maximal aortic root/ascending aorta diameter of greater than 50 mm. • A maximal aortic root/ascending aorta diameter of greater than 45 mm to 50 mm with the following: 1. Rapid aortic root growth of more than 5 mm per year. 2. Progressive aortic regurgitation, especially if the surgeon believes the aortic valve can be spared and an aortic valve-sparing procedure is planned. 3. Family history of premature aortic dissection of less than 50 mm. 4. Severe mitral valve regurgitation that requires surgery. • A maximal aortic root/ascending aorta diameter of greater than 44 mm if pregnancy is desired. • A maximal dimension of other parts of the aorta of 50 mm to 60 mm or progressive dilation. • Severe mitral regurgitation with symptoms or progressive LV dilation/dysfunction as per the current guidelines on valvular heart disease. (Silversides, Kiess et al., 2010) [45]	The following situations warrant surgical intervention: • Aortic root replacement when aortic root diameter exceeds 45 mm • Aortic root replacement in an individual with a history or family history of dissection when aortic root diameter is 40 mm or greater • Aortic root replacement in women contemplating pregnancy when aortic root diameter is 40 mm or greater (Group 2013)	The following situations warrant surgical intervention: • Ascending aorta diameter greater than 50 mm. Consider surgery if greater than 45 mm. • Ascending aorta diameter between 46 and 50 mm with: 1. Family history of dissection 2. Progressive dilation of more than 2 mm per year as confirmed by repeated measurements 3. Severe AR or MR 4. Desire of pregnancy • Patients should be considered for surgery if other parts of the aorta are over 50 mm. (Baumgartner, Bonhoeffer et al., 2010) [46]

Table 9
Mortality rates for surgical repair with valve replacement.

	Sample	30 days mortality	5 years mortality	10 years mortality
Gott et al. NEJM 1999 (Marfan patients) [53]	675	3.5%–4.8%	–	–
Karck et al. J Thorac Cardiovasc Surg 2004 (Marfan patients) [52]	119	6.8%	11 +/− 4%	–

following patients who underwent either VSP or valve replacement surgery (VRS), there is an increased freedom from re-operation in patients with VRS (96%) compared to patients who underwent VSP (63%). In another study [1], freedom from re-operation was approximately 90% in patients who underwent VSP.

4.4.1. Surgical management in patients with Marfan syndrome

Several studies have examined the benefits of VSP versus VRP in patients with Marfan syndrome (refer to Tables 9 and 10). While some retrospective single center studies found that the VSP shows superiority in survival and morbidity, there seems to be a tendency towards higher rates of re-operation and re-exploration therapy [58]. In a 2011 meta-analysis analyzing data from 1385 patients, there was a statistically significant difference in reintervention rates in patients undergoing VRP [59]. In addition, some authors have reported that patients with Marfan syndrome might not be ideal candidates for VSP because they believe that these patients have innate structural disorders of the aortic valve requiring replacement later in life.

5. Ascending aortic dilatation and pregnancy

There have been many cases reported about ascending aorta dilatation during pregnancy and the increased rate of complications during this period. While this subject is not very well studied, pregnancy seems to predispose to arterial wall degeneration by the excess release of estrogen and progesterone [60]. In select women, this process is aggravated by the very well known cardiovascular changes during pregnancy (increased circulating volume, increased stroke volume and increased heart rate). In addition, women with predisposing conditions such as those mentioned in Table 3 (Marfan syndrome, BAV, etc.) are at increased risk of complications during pregnancy.

According to the newest guidelines, all pregnant women with TAA should be under strict blood pressure control (<120/80 mm Hg) and a monthly or bi-monthly echocardiographic measurement of the ascending aorta should also be performed to follow the growth rate [46].

While there were no official guideline and no prospective study to confirm it, most experts agree that women who wish to become pregnant should get prophylactic surgery at earlier stages of their disease. For example, patients with Marfan syndrome should get prophylactic repair when the ascending aorta reaches 4.0 to 4.5 cm and patients with BAV should get it when the aorta reaches 4.5 to 5.0 cm.

6. Follow-up and screening

As noted above, the natural history of TAA is that of progressive expansion. Patients with aortic root or ascending aortic dilation that has not yet exceeded the threshold for surgical intervention require serial evaluations. The size of the aortic root and ascending aorta should be evaluated annually or biannually, although more frequent studies are warranted (3–6 months) when the aorta exceeds 4.5 cm or the growth rate > 0.5 cm/yr. Patient who is newly diagnosed of TAA needs to have another imaging in 6 months to determine the growth rate. If patient is a fast grower, imaging assessment needs to be every 3–6 months. Otherwise if TAA is stable, imaging will be annually.

Patients who already had their TAA repair still require medical attention. These patients could develop aneurysm in other segments of aorta, particularly in patients with chronic dissection at the distal anastomosis of tube graft. It has been reported that patients with chronic dissection had late reoperation rate as high as 30%. Annual imaging assessment of the entire aorta is recommended.

According to ACC guidelines, all patients with Marfan syndrome and Loeys–Dietz syndrome should receive screening for ascending TAA when diagnosed with this disease and 6 months thereafter to determine the rate of growth. Afterwards, annual imaging is recommended to document the progression of the dilation. If the aorta reaches 4.5 cm or if the rate of progression increases, the imaging follow-up should become more frequent [46].

As mentioned earlier, familial thoracic aneurysm disease can occur in different patterns. It is therefore reasonable to recommend screening for first degree relatives of affected people.

All patients with a BAV should undergo TAA screening. Family members of these patients should be screened for BAV.

Screening of first-degree relatives is considered warranted for many of these conditions; however, at what age the investigation should be started, how often the imaging should be repeated and how long the screening should last are still debatable at the present time as well as the cost effectiveness of the methods.

7. Exercise restriction

Patients with aorthopathy associated with Marfan syndrome should avoid isometric exercise because of sustained elevation of blood pressure and wall stress applied on aortic wall during exertion [61]. Isometric exercises include weight lifting, sit-ups, and push-ups. Patients are encouraged to perform aerobic exercise with moderation. These recommendations should be given to all patients with other aortopathies since the shear stress needs to be kept minimal once aorta becomes aneurysmal.

Table 10
Mortality rates for surgical repair with valve sparing surgery.

	Sample	Early mortality	5 years mortality	10 years mortality
Gott et al. NEJM 1999 (Marfan patients) [53]	675	0%	–	–
David et al. Journal of Thoracic and Cardiovascular surgery 2006	220	–	6 +/− 1%	88 +/− 3%
Karck et al. J Thorac Cardiovasc Surg 2004 (Marfan patients) [52]	119	0%	4 +/− 4%	–
Kallenbach et al. [1]	284	3.2%	9.3 +/− 2.5%	–
Kallenback et al. [54] (Marfan patients)	35	0%	8.5%	–

8. Conclusion

Ascending aortic aneurysm is a lethal disease. Elective surgical repair remains the mainstay for the management of symptomatic aneurysm or asymptomatic aneurysm of which the diameter > 5.5 cm. Lower threshold of aortic diameter for surgery should be considered for patients with aortopathy related to congenital etiologies. Medical treatment as well as lifestyle changes and risk factor control, and serial imaging assessment of aortic aneurysm constitute the second part of the management of these patients.

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