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Primer

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Thoracic aortic aneurysm

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Abstract

Aortic medicine has undergone remarkable progress in recent decades with regard to our understanding and treatment of aortic disease. In the past decade, the scientific community has called for the aorta to be viewed as an independent organ, advocating for a holistic approach to understanding thoracic aortic disease, integrating its embryological development, wall composition, pathophysiological mechanisms, surveillance and treatment. Thoracic aortic aneurysm (TAA) is a potentially fatal disease characterized by abnormal dilation of the thoracic aorta, whereby the structural integrity of the vessel wall is compromised. Although epidemiological studies of TAA are confounded by its asymptomatic nature and diagnostic challenges, available evidence suggests that TAA prevalence and treatment outcomes vary according to race, sex and socioeconomic factors. Pathophysiological mechanisms involve interactions between vascular smooth muscle cells and the extracellular matrix, influenced by genetic predisposition and embryological factors as well as arterial hypertension. Diagnosis relies on advanced imaging techniques, with CT angiography considered to be the gold standard diagnostic tool and with genetic screening recommended for heritable conditions. Preventive measures focus on managing cardiovascular risk factors, whereas treatment includes medical management, as well as endovascular and open surgical repair. TAA has a major effect on quality of life, particularly in younger, female and genetically predisposed patients, necessitating further research and tailored interventions.

Sections

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Introduction

The aorta is the largest blood vessel that originates from the heart and is responsible for supplying blood to the entire body. Far more than a mere conduit for blood, the aorta has been classified as an organ given its self-contained nature and specific vital functions[1]. This aortic organ perspective emphasizes that the aorta should be studied in a holistic fashion, integrating its embryological origin, wall composition and associated functions of individual aortic segments, as well as the pathophysiological development of aortic disease, its surveillance and treatment (Fig. 1).

The aorta can be categorized into several anatomical and functional subclassifications. In this Primer, we describe the aorta based on Ishimaru zones, a classification system that divides the aorta into 12 zones, ranging from the proximal aorta beyond the aortic bifurcation (zone 0) to the iliac arteries (zone 11)[2] (Fig. 2). This primer focuses on aneurysms of the thoracic aorta (zones 0–5), comprising the aortic root, ascending aorta, aortic arch and the descending aorta. Beyond zone 5 are the thoracoabdominal and abdominal aortic segments, which are not the focus of this Primer.

Thoracic aortic aneurysm (TAA) is a serious vascular condition characterized by the abnormal dilation of the thoracic aorta, often due to progressive weakening of the arterial wall. Although the prevalence of TAA is relatively low compared with abdominal aortic aneurysms, its potentially fatal complications, such as rupture or aortic dissection, make it a crucial area of medical focus[3,4]. TAA is often referred to as a 'silent killer' because most patients do not have symptoms in its early stages. However, advanced cases can present with chest pain, back pain or compression-related symptoms, such as dyspnoea[5].

Risk factors for TAA include genetic conditions such as Marfan syndrome (MFS), Ehlers–Danlos syndrome (EDS) and bicuspid aortic valve (BAV), as well as acquired factors such as hypertension, smoking and advanced age[5]. Advances in imaging modalities, including CT and MRI, have substantially improved the early detection and monitoring of TAA.

Management strategies depend on aneurysm size, growth rate and patient-specific risk factors, ranging from pharmacological blood pressure control to surgical interventions such as open repair or endovascular stent grafting[1,5]. Despite these advances, the condition remains a challenge in terms of prevention and optimization of patient outcomes.

An arterial aneurysm is generally defined as a vessel diameter exceeding 1.5 times the predicted normal diameter. However, this cut-off might not be appropriate for the proximal thoracic aorta, as adverse events can occur before the aorta reaches 1.5 times its size[6–9]. Alternative scoring systems, such as the *z*-score, were introduced to reduce the risk of missing the most adverse aortic events (rupture and dissection) when applying the definition of 1.5 times the normal diameter[10]. Notably, demographic details should be considered, as larger aortic diameters are expected in men, as well as those who are overweight or of older age[9]. An absolute value to define TAA is therefore not recommended and instead patients should be assessed on an individual basis using nomograms[11–13]. Moreover, there are substantial differences in measurements of aortic diameter when comparing data derived from echocardiography and CT angiography[9,11,12], the latter being the gold standard for the assessment of thoracic aortic dimensions. Nevertheless, echocardiography remains essential for screening, especially of the proximal thoracic aorta[1,5].

In this Primer, we provide an overview of TAA, including its epidemiology, incidence and risk factors. We further describe its pathophysiological mechanisms and embryological factors, with a focus on vascular smooth muscle cells, genetics and related diseases. Finally, we provide an overview of its diagnosis, screening and prevention, the various treatment modalities and surveillance strategies, and we suggest directions for future research in the field of aortic medicine.

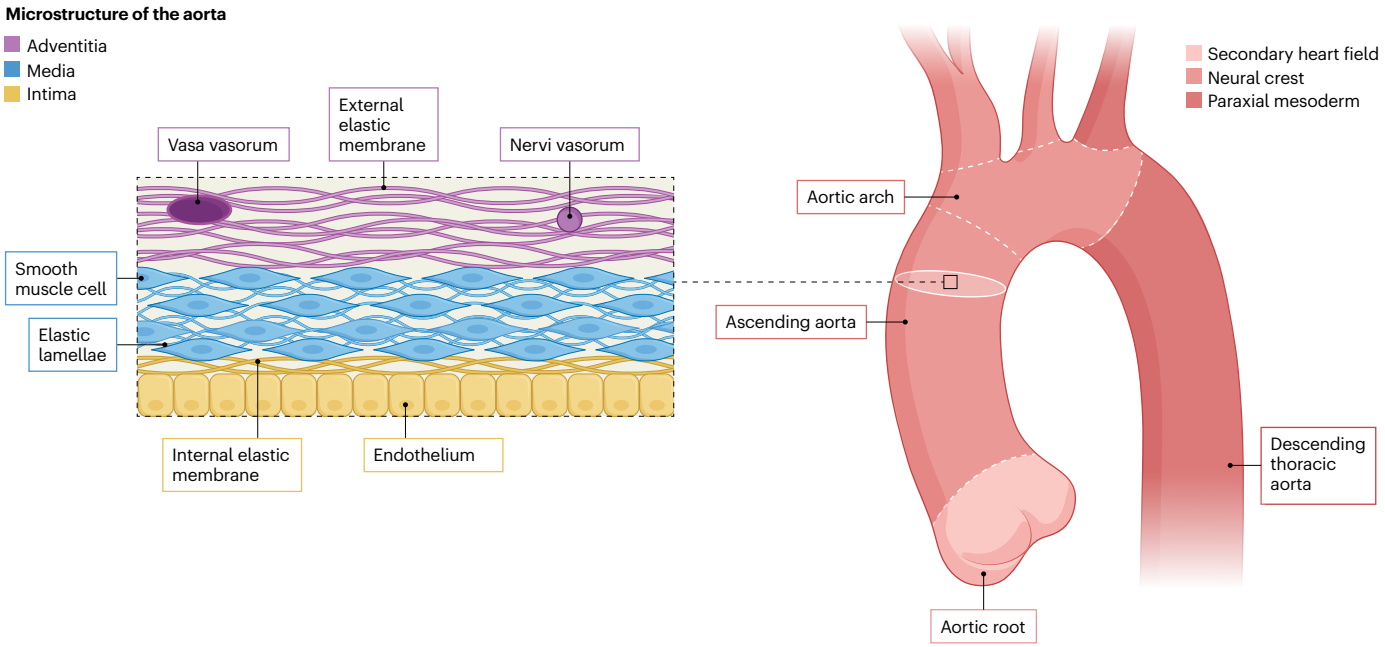

Fig. 1 | The developmental origin and microstructure of the aortic organ. The aortic root derives from cells of the secondary heart field. The ascending aorta and part of the aortic arch derive from the neural crest. The distal part of the aorta is of mesenchymal origin. The microstructure of the aorta consists of the intima, media (comprising the smooth muscle cells) and adventitia layers.

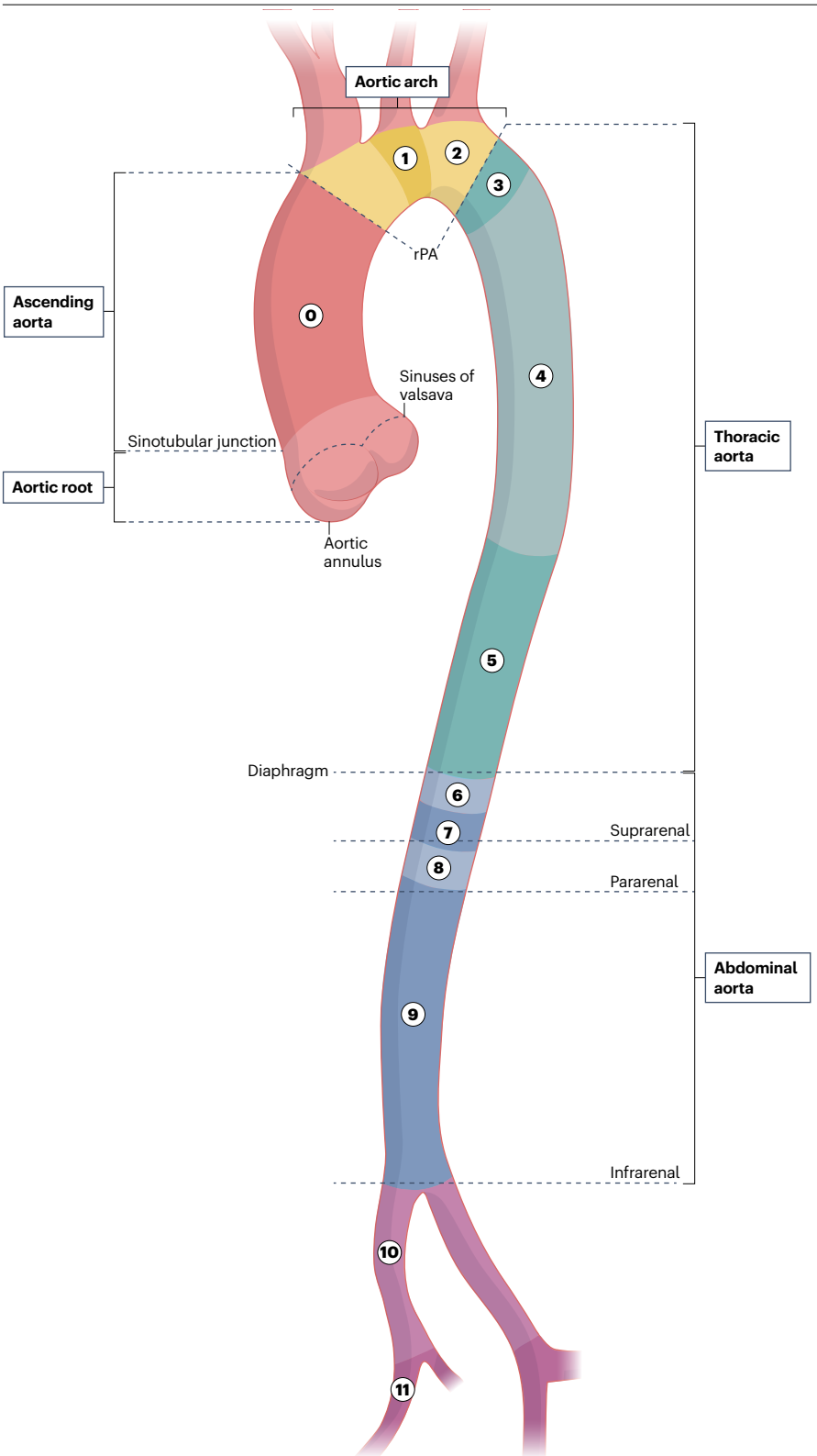

Fig. 2 | Ishimaru zones. The Ishimaru classification divides the thoracic and abdominal aorta into a total of 12 anatomical zones and is used to standardize the description and therapeutic planning of aortic dissections and aneurysms. Zone 0 comprises the ascending aorta, encompassing the brachiocephalic trunk. Zone 1 extends distally from the brachiocephalic artery to the origin of the left common carotid artery, which is included within this zone. Zone 2 spans from the left common carotid artery to the origin of the left subclavian artery. Zone 3 corresponds to the proximal descending thoracic aorta and typically measures approximately 2 cm in length. Zone 4 continues along the descending thoracic aorta down to the level of the sixth thoracic vertebra (T6). Zone 5 covers the descending thoracic aorta from this point to the aortic hiatus at the diaphragm, terminating just above the origin of the coeliac trunk. The remaining segments describe the abdominal aorta and iliac arteries. rPA, right pulmonary artery. Figure reprinted with permission from ref. 1, Oxford University Press.

Epidemiology

Epidemiological studies of thoracic aortic diseases are subject to several limitations. Aortic aneurysms are often asymptomatic and acute, with severe complications (such as aortic dissection) occurring without predisposing signs. As such, most epidemiological studies on thoracic aortic diseases have focused on post-onset disease and subsequent surgical treatment. These studies explore trends in demographic factors such as ethnicity, sex and age, but they inherently miss silent TAA that is not seen by health-care providers[14,15]. Moreover, a lack of unified opinion of the pathological diameter and morphology of TAA confounds the results of epidemiological studies. Combined with lack of diagnosis in lethal cases, the true incidence and prevalence rates of TAA are likely greatly underestimated.

The availability of diagnostic devices such as CT and MRI is directly related to the detection of thoracic aortic diseases. As a result, diagnosis and morbidity rates can vary according to factors that affect access to medical devices, such as socioeconomic status[16,17]. Ethnicity and racial differences seem to influence the incidence of TAA, although it remains unclear whether this is due to biological factors, lifestyle, economic reasons or access to preventive care[18]. Perhaps indicating a biological explanation, Black individuals tend to have greater aortic wall thickness compared with white individuals, as do men compared with women[19]. Interestingly, the prevalence of TAA in the Copenhagen General Population Study was 2.4%, with almost four times higher frequency in men than in women[20]. These data, published in 2015, revealed a markedly higher prevalence of TAA compared with previously published reports that describe prevalence rates of 1.2–1.4% in Iran and Sweden[21,22]. Most TAAs are located in the ascending aorta, followed by the aortic root and descending aorta[23–25].

Incidence

The incidence rate of thoracic aortic diseases has been reported to be 3.5–10 per 100,000 persons per year based on cohort studies in Canada, Sweden, USA and Japan[26–29] (Table 1). Focusing on TAA, a systematic review and meta-analysis of population-based studies revealed an incidence rate of 5.3 per 100,000 individuals each year, and a prevalence of 0.16%[14]. Of note, the prevalence was substantially higher in autopsy studies, highlighting the uncertainty of the true incidence rates of reports based on population-based evidence[14]. For example, post-mortem CT data from Japan revealed an aortic dissection prevalence of 7%, adding emphasis to the notion that many TAAs remain undiagnosed[30,31]. One study revealed a gradual increase in incidence from 3.5 to 7.6 per 100,000 persons between 2002 and 2014, probably explained by improvements in diagnostic techniques[26]. Adding further complication is the fact that the onset of TAA complications such as acute aortic dissection exhibit marked circadian and seasonal or monthly variations. Aortic dissection is more likely to occur in winter than in other seasons and seems to correlate with change in atmospheric pressure[32–34]. Most patients with acute aortic dissection or ruptured aneurysm will not survive without surgery.

Table 1 | Population-based incidence of TAA

Country	Time period	Aortic disease	Number of cases per 100,000	Ref.
Canada	2002–2014	Aneurysm	3.5–7.6	26[a]
Sweden	1991–1996	Dissection	15	27
USA	1995–2015	Dissection	4.4	28
Japan	2016–2018	Dissection	17.6	29

[a]This study estimated the incidence of thoracic aortic aneurysm (TAA) within a population, whereas the other studies have focused on aortic dissection specifically. Nevertheless, comparing incidence of TAA and aortic dissection provides important insights and suggests a relevant underestimation of TAA incidence and prevalence.

Natural course

The risk of natural complications from TAA, such as rupture or dissection, is greater with increasing aortic diameter. The annual risk of rupture or dissection is approximately 2% for TAAs measuring 4.0–4.9 cm, rising to nearly 7% for TAAs larger than 6.0 cm (ref. 3). Notably, a substantial increase in rupture or dissection risk was observed when the diameter exceeds 6.0 cm for ascending TAAs and 7.0 cm for descending TAAs[3]. In another study that included 6,372 patients with TAA, aortic dissection was reported to occur in 0.7% of the cohort, with an incidence rate of 0.22 events per 100 person-years[35]. However, larger aortic size was associated with an increased risk of aortic dissection and all-cause mortality, with a large rise in risk observed at an aortic diameter of 6.0 cm. The estimated adjusted 5-year risk of aortic dissection was 0.3% for TAA sizes of 4.0–4.4 cm, 0.6% for 4.5–4.9 cm, 1.5% for 5.0–5.4 cm, 3.6% for 5.5–5.9 cm, and 10.5% for sizes of 6.0 cm or greater[35].

Focusing specifically on the natural course of aneurysms in the ascending aorta, one study showed that aortic diameter of 3.5–3.9 cm, 4.0–4.4 cm, 4.5–4.9 cm, 5.0–5.4 cm, 5.5–5.9 cm and ≥6.0 cm was associated with an average annual risk of acute aortic events at a rate of 0.2%, 0.2%, 0.3%, 1.4%, 2.0% and 3.5%, respectively[36]. Correspondingly, 10-year survival rate free from adverse aortic events was 97.8%, 98.2%, 97.3%, 84.6%, 80.4% and 70.9%, respectively. The risk of adverse aortic events remained stable until an aortic size of 5 cm, at which point the risk began to markedly increase. The mean annual growth rate of ascending TAAs was estimated to be 0.1 ± 0.01 cm per year, with growth rarely exceeding 0.2 cm per year. These growth rate data suggest that ascending TAAs generally expand at a very slow pace[36]. Consequently, pre-emptive surgical intervention is crucial before the aorta reaches these critical diameter thresholds[4,37].

Mortality

Non-ruptured TAA is associated with a 30-day mortality rate of 10% (including operated and non-operated patients), which reduces to 7.6% in patients who undergo surgical repair[23]. The same study reported a long-term survival rate of 92% after 1 year, 76% after 5 years, 65% after 10 years and 41% after 15 years. Interestingly, mortality was shown to be associated with age but not with sex. With regard to the type of TAA complication, the prognosis for ruptured TAA is considerably worse than for dissection. A study reported that only 41% of patients with a ruptured TAA survive long enough to reach a hospital[38]. Moreover, for those who survive long enough to undergo surgery, data from a nationwide study showed a perioperative mortality rate of 28.6% for surgical repair of the descending aorta, compared with 23.4% for endovascular repair. Notably, the risk-adjusted mortality and complication rates were not significantly different between the two approaches[39]. Furthermore, owing to the potential misclassification of rupture-related deaths as cardiac arrests, the true mortality rate of aortic rupture is likely to be considerably higher than reported. These sobering statistics highlight the crucial importance of early detection and diagnosis of TAAs in the general population[37]. It is also noteworthy that although the major causes of death in patients with TAA are adverse aortic events such as rupture, other cardiovascular events (for example, myocardial infarction) or malignancy can occur during follow-up[23].

Risk factors

Hypertension, smoking, dyslipidaemia, advanced age, infectious diseases, heritable thoracic aortic disease (HTAD) and physical trauma are risk factors for thoracic aortic diseases[20,25,40]. Moreover, the risk of mortality from TAA is associated with smoking, systolic and diastolic blood pressure and dyslipidaemia. Interestingly, diabetes is inversely associated with TAA incidence[21,41] and mortality[42]. Patient outcomes are also related to the aortic segments at which the TAA occurs. Ascending TAAs in Ishimaru zone 0 are smooth and non-calcified, possibly protected from atherosclerosis, whereas descending TAAs beyond Ishimaru zone 1 are arteriosclerotic, irregular, calcified and full of debris[43]. Moreover, aortic valve stenosis, bicuspid aortopathy and HTAD are risk factors for ascending aortic aneurysms, whereas smoking, hypertension and dyslipidaemia are risk factors for descending aortic aneurysms[44].

Risk estimation

The risk of adverse aortic events, such as rupture and dissection, is affected by patient height and weight. Aortic diameter should therefore be considered in relation to body surface area (aortic size index) or to body height (aortic height index) when evaluating risk of adverse events in patients with TAA[45,46]. Furthermore, as total aortic diameter is a poor predictor of adverse aortic events and is insufficient for indication of elective prophylactic aortic surgery, additional morphological aortic parameters should be considered[6]. Such parameters include the ratio of ascending to descending aortic diameter, as well as ascending aortic length exceeding 11 mm (refs. 20,47–49). These parameters, combined with genetic testing, aim to improve the prediction or the course of acute thoracic aortic dissection[7,20,47–51]. In detail, an ascending aortic length of ≥13 cm was associated with a nearly fivefold higher yearly rate of aortic adverse events (AAEs) compared with an ascending aortic length of <9 cm (ref. 47). A notable increase in AAEs occurred between 11.5–12.0 cm and 12.5–13.0 cm, versus shorter lengths. The average annual aortic elongation rate was 0.18 cm per year. Accounting for aortic height index, which relates aortic diameter to body height, substantially improved the prediction of AAEs[47]. An aortic height index of <9.33, 9.38–10.81, 10.86–12.50 and ≥12.57 cm/m corresponded to a ~4%, ~7%, ~12% and ~18% yearly AAE risk, respectively[47].

Sex and hormones. Beyond the sex-related differences mentioned above, additional factors affect TAA incidence and outcomes in women. The lower incidence of TAA in women compared with men might be due to a vasoprotective effect and decreased vessel inflammation driven by female sex hormones, consistent with a greater density and upregulation of oestrogen receptor-α within the aortic wall[15,52,53]. In vitro, incubation of human aortic smooth muscle cells with male sex hormones substantially reduces the elastin to collagen ratio, providing evidence for a mechanism of unfavourable biomechanical vascular wall properties in men[54,55]. Moreover, compared with men, women with TAA experience a greater aorta growth rate and are more likely to suffer from acute aortic events, even with smaller diameters and after adjustment for body height[3,15,55,56].

Pregnant women are at higher risk of acute aortic syndromes compared with non-pregnant women, especially in the third trimester or after delivery[57]. Moreover, women diagnosed with HTADs such as MFS, vascular EDS (vEDS) or Loeys–Dietz syndrome (LDS) are at higher risk of aortic rupture and dissection during pregnancy and delivery, compared with women without HTAD[57,58]. Of note, outcomes for women during the peri-partum period are favourable[59,60].

Genetics. Mendelian inheritance studies from the late 1990s were the first to show the familial nature of TAA[61,62]. It is now generally accepted that approximately one-fifth of all TAA cases are hereditary (hence the term HTAD). The current genetic classification subdivides thoracic aortic disease into two main categories[63,64]: syndromic and non-syndromic.

Syndromic TAA involves abnormalities of the aorta and other organ systems that occur as part of a broader genetic condition, such as MFS, LDS or EDS. Although identification of patients with syndromic TAA is often more straightforward than identification of patients with non-syndromic TAA, syndromic cases often present at younger age and with more aggressive aortopathies, including faster aortic growth rates and aortic dissection or rupture at smaller size[65]. However, syndromic TAA cases represent a minority of all TAA cases.

Non-syndromic TAA refers to a condition that is restricted to the aorta, without other systemic abnormalities, and accounts for more than 90% of all cases of TAA[66]. Non-syndromic cases of TAA can be further subdivided into familial (also known as hereditary) and sporadic cases. Patients with non-syndromic TAA typically present later in life (at 50–60 years of age), and these cases are notoriously difficult to identify, given the asymptomatic nature of TAA.

Multiple genes have been associated with syndromic and non-syndromic HTAD[67,68]. However, known TAA-associated risk genes do not explain the entirety of HTAD cases, although there is substantial evidence that certain genetic alleles alter the natural history of aortic disease and predispose patients to earlier onset aortic dissection and rupture, often at smaller aortic sizes. The heightened risk associated with specific genetic alleles is reflected in the most recent iteration of the US and European guidelines on the management of thoracic aortic disease[1,69], both specifying earlier intervention criteria at smaller aortic size for a range of syndromic and non-syndromic HTADs associated with variants in specific risk genes.

Mechanisms/pathophysiology

The aortic wall consists of three interacting layers: the inner (intima) layer, medial (media) layer and outer (adventitia) layer (Fig. 1). The inner lumen is covered by a single layer of endothelial cells that regulate permeability for circulating cells in the bloodstream. Endothelial cells are anchored on a subendothelial basement membrane that contains various extracellular matrix (ECM) proteins, including laminin, collagen and fibronectin[70–72]. The medial layer represents the thickest portion of the aortic wall and is formed by several layers of vascular smooth muscle cells (VSMCs) that interact with elastin lamellae[73]. The 'lamellar unit', first described by Wolinsky and Glagov[74], is a fundamental structural and functional unit of the thoracic aortic wall, consisting of a concentric arrangement of VSMCs, elastin, collagen and proteoglycans (Fig. 3). These repeating units provide the aorta with its unique biomechanical properties, allowing it to withstand and adapt to pulsatile blood flow. The number of lamellar units varies along the aortic length, with a higher density in the proximal aorta and a gradual decrease towards the distal segments[74], contributing to regional differences in mechanical stress and susceptibility to aneurysm formation and dissection. The oblique anchoring of elastin lamellae to the surface of VSMCs allows the lamellar unit to minimize the biomechanical stress of pulsatile flow by tensile strength and at the same time ensure its elastic properties[63,67] (Fig. 3). The outer layer of the aortic wall comprises a collagen- and fibroblast-rich adventitia.

The natural course of TAA and dissection development is well understood[75,76] (Fig. 4). In some cases, the process begins with a

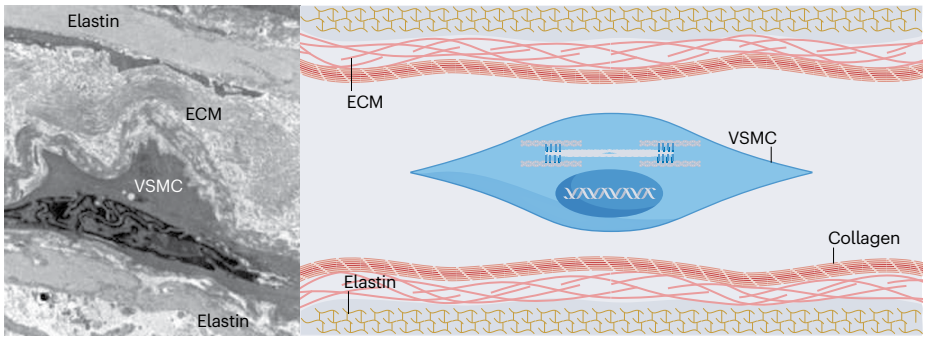

Fig. 3 | Electron micrograph of a single lamellar unit in the medial layer of the aortic wall showing a VSMC lying between two layers of elastin fibres and surrounded by ECM proteins containing microfibrils and proteoglycans. Lamellar units are intercalated by collagen bundles. The lamellar unit represents the basic structural and functional unit of the aortic wall. ECM, extracellular matrix; VSMC, vascular smooth muscle cell. Reprinted from ref. 63, Springer Nature Limited.

genetic predisposition, whereby inherited susceptibility creates a foundation for aortic aneurysm or dissection. Over time, this predisposition contributes to medial degeneration, characterized by inflammatory activation, loss of VSMCs and structural weakening of the aortic wall owing to cytokine-mediated damage[77]. As the medial layer deteriorates, the aorta undergoes aneurysm formation, in which progressive dilation imposes increasing mechanical stress on the vessel wall. Eventually, during a hypertensive episode — often triggered by extreme exertion or emotional stress — a sudden rise in blood pressure causes the aortic wall stress to surpass the tensile limits of the aortic tissue, leading to aortic dissection or rupture, in which the aortic layers separate and the dissection propagates along the vessel.

Vascular smooth muscle cells

Embryological origin. Based on the embryological development of the aortic organ, VSMCs — as the predominant cell type within the aortic wall tissue — derive from diverse embryological lineages depending on the location of the aortic segment. The aortic root (an anatomical segment that rises from the aortic annulus up to the sinotubular junction of the ascending aorta) mainly arises from the lateral plate mesoderm. The ascending aorta as well as the aortic arch find their embryological origin in the cardiac neural crest. Aortic segments distal to the left subclavian artery (LSA) are derived from paraxial mesoderm[78–82]. Clinically, diseases of the ascending aorta and arch present very differently from diseases of the descending aorta (with the separation point at the ligamentum arteriosum). Indeed, ascending aorta disease is often non-arteriosclerotic and likely genetic in nature and not related to traditional arterial risk factors, whereas descending aorta disease is often associated with irregular, calcified, arteriosclerotic disease[76]. Whether these differences in ascending versus descending disease manifestations are due to different embryological origins of VSMCs within these aortic segments remains unknown.

VSMC phenotypes. Irrespective of their embryological lineage, VSMCs interact with the ECM to facilitate aortic homeostasis. VSMCs exhibit remarkable phenotypic plasticity, allowing them to respond to environmental stimuli and mechanical stress by transitioning between multiple functional states beyond the two major contractile and synthetic phenotypes.

VSMCs are primarily aligned in a circumferential direction within the aorta, linked to the ECM within the media via integrins. Their contractile function is mediated by interactions between aortic smooth muscle actin (ACTA2) and myosin 11 (MYH11)[63], which regulate vessel tone and blood flow. Elastin not only provides mechanical support but also has a key regulatory role in VSMC proliferation and migration[83].

Under normal physiological conditions, VSMCs maintain homeostasis through balanced secretion of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) to regulate ECM turnover. However, pathological stimuli, such as mechanical stretch or genetic variants, can drive dysregulated VSMC plasticity, leading to excessive ECM degradation, fibrosis or inflammation[84]. The interplay between VSMCs and the ECM, along with the ability of VSMCs to integrate mechanical stimuli into biological responses, is essential to maintain the structural and functional integrity of the aortic wall. This dynamic regulation provides elasticity, compliance and wall strength, which are crucial to prevent aneurysm formation and dissection.

Pathophysiological changes in thoracic aortic disease. Thoracic aortic disease results from a disruption of aortic homeostasis within the medial layer. A pattern of increased levels of MMPs, especially MMP2, MMP9 and MMP12, and decreased abundance of smooth muscle cell proteins, have been described in thoracic aortic disease[85]. Mucoid ECM accumulation or elastic fibre fragmentation in combination with loss of contractile VSMCs is a common histopathological indication of medial degeneration in patients with aortic disease[86]. Degradation of the ECM further facilitates detachment of VSMCs from integrins and promotes cell migration, apoptosis and vascular remodelling[87].

Several cellular pathways have been implicated in the progression of aortic disease. Inflammatory cell infiltration, as well as oxidative or mechanical stress, can promote VSMC phenotypic switch towards synthetic VSMCs, ECM degradation, medial degeneration and aneurysm formation (Fig. 3). Advances in single-cell techniques have provided a more granular insight into VSMC phenotypes, leading to the identification of seven cell clusters involved in aortic disease[88]. In aortic tissue from people with ascending aortic aneurysms, a phenotype switch from a contractile phenotype to a pro-inflammatory phenotype was detected[88]. This alteration was also reflected in downregulated expression of genes involved in smooth muscle contraction (such as *MYLK* and *MYH11*) but upregulation of expression of inflammatory genes (such as *IL1R1*).

Based on the various embryological lineages, VSMCs also have the potential to switch into osteogenic phenotypes, creating a pro-calcifying environment in the setting of aortic disease[89]. Medial calcification, in contrast to intimal calcification associated with atherosclerosis, is not occlusive but increases vascular stiffness and reduces vessel compliance. Indeed, in an in vitro model of human pluripotent stem cells, increased ECM degradation was demonstrated

in VSMCs derived from the lateral mesoderm, which later form the aortic root, compared with VSMCs derived from neural crest or paraxial mesoderm[79].

Genetics

Genetic variants have an important role in the pathophysiology of aortic disease. The term HTAD has emerged as an umbrella category in clinical practice for genetically triggered inherited aortic pathologies, which account for at least 20% of thoracic aortopathies[90]. The development of whole-exome and whole-genome sequencing has paved the way towards extensive genetic testing in patients with a suspected genetic susceptibility to TAA, as well as to accelerating novel gene discovery in HTAD. To date, a large number of gene associations have been identified (Supplementary Table 1), and these can broadly be subdivided into four main groups, based on whether they encode ECM components (such as *FBN1*, *FBN2* and *COL3A1*), the contractile apparatus of smooth muscle cells (such as *MYH11*, *ACTA2* and *MYLK*), the TGFβ signalling pathway (such as *TGFBR1*, *TGFBR2* and *TGFB2*) or other proteins (such as *NOTCH1*). However, only 11 genes to date have been identified to cause HTAD: *ACTA2*, *COL3A1*, *FBN1*, *MYH11*, *MYLK*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, *LOX* and PRKG1 (ref. 68).

Heritable connective tissue disorders (syndromic TAA). Heritable connective tissue disorders are well-established causes of syndromic TAA and aortic dissection, resulting from pathogenic variants that compromise the structural integrity of the aortic wall. The three best-recognized syndromic aortopathies include MFS, LDS and vEDS, each of which is associated with distinct genetic variants and varying risks of aortic complications.

MFS is caused by pathogenic variants in *FBN1*, which encodes fibrillin 1, a key ECM protein that contributes to elastic fibre formation. *FBN1* variants lead to abnormal TGFβ signalling, ECM dysfunction and progressive aortic dilation, often necessitating surgical intervention at smaller aortic diameters[1,69]. Clinically, patients with MFS present with aortic root aneurysm, aortic dissection, thoracoabdominal aneurysm, mitral valve prolapse, skeletal features (such as scoliosis, arachnodactyly and pectus deformities), malpositioning of the lens of the eye (ectopia lentis), myopia, dural ectasia (ballooning of the dural sac) and pneumothorax (collapsed lung).

LDS is characterized by variants in genes encoding components of the TGFβ signalling pathway, including *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2* and *SMAD3*. These variants lead to increased TGFβ activity, abnormal vascular remodelling and aggressive aortic disease, often with aneurysm formation at younger ages and a higher propensity for dissection at smaller diameters compared with MFS[91,92]. Clinically, patients with LDS present with thoracoabdominal aneurysm, aortic dissection, mitral valve prolapse, arterial tortuosity, craniofacial features (such as craniosynostosis, hypertelorism, bluish sclera and bifid uvula), translucent skin and visible veins, dural ectasia, clubfoot and early-onset osteoarthritis.

vEDS is caused by pathogenic variants in *COL3A1*, which encodes type III collagen, an essential structural component of the arterial wall. vEDS is characterized by extreme vascular fragility, with arterial dissection and rupture occurring at unpredictable sites, leading to a high risk of sudden vascular events[93]. Clinically, people with vEDS present with thoracoabdominal aneurysm, aortic dissection, mitral valve prolapse, carotid–cavernous fistula, bowel and uterine rupture, pneumothorax and skin features (such as translucent skin and atrophic scars).

Beyond these classic syndromic aortopathies, variants in other ECM genes (such as *COL5A* and *LOX*), contractile apparatus genes (such as *ACTA*) and genes involved in vascular development (such as *NOTCH1*, *PKD1*, *PKD2* and *ABCC6*) have been associated with both syndromic forms of TAA, albeit with varying qualities of evidence. Although these conditions represent a small proportion of overall TAA cases, their identification is crucial for clinical management, as early recognition enables risk stratification, family genetic screening and timely surgical intervention to prevent life-threatening complications.

Heritable non-syndromic aortopathies. A large proportion of TAAs manifest in non-syndromic familial forms, often inherited in an autosomal dominant manner with variable expressivity and incomplete penetrance[67,68]. Unlike syndromic aortopathies, which are

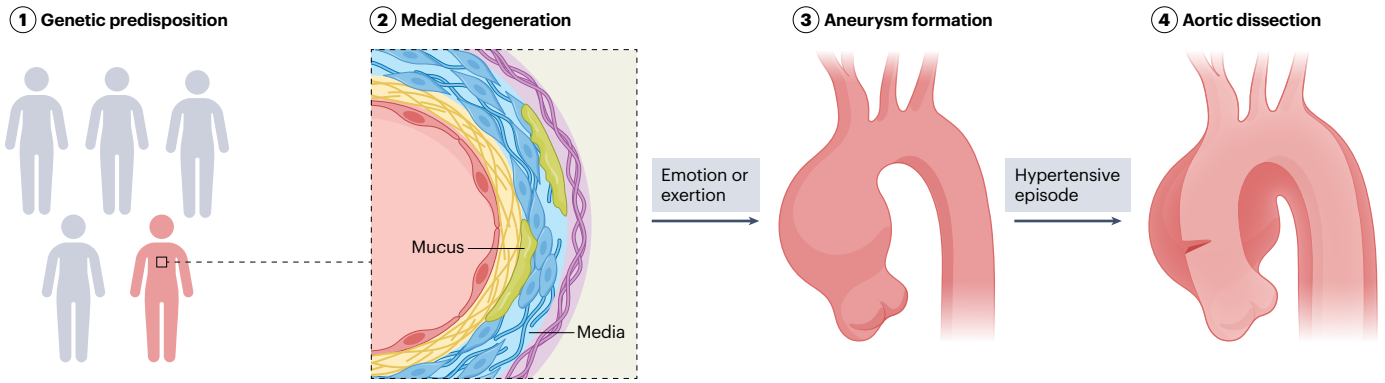

Fig. 4 | Schematic presentation of possible relationships underlying the instigation of an acute aortic dissection at one particular time. In certain instances, the process starts with a genetic predisposition, in which inherited susceptibility lays the groundwork for the development of an aortic aneurysm or dissection (1). Over time, this predisposition leads to medial degeneration – marked by inflammatory activation, loss of vascular smooth muscle cells, accumulation of mucus and structural weakening of the aortic wall due to cytokine-driven damage (2). As the medial layer deteriorates, the aorta begins to form an aneurysm, with progressive dilation causing increasing mechanical stress on the vessel wall (3). Eventually, during a hypertensive episode – often brought on by intense physical exertion or emotional stress – a rapid spike in blood pressure can cause the stress on the aortic wall to exceed its tensile strength. The ultimate result is an aortic dissection or rupture, whereby the layers of the aorta separate and the dissection extends along the vessel (4). Adapted with permission from ref. 75, Elsevier.

characterized by systemic features that affect multiple organ systems, non-syndromic familial TAAs primarily manifest with isolated aortic disease, with or without a family history of aortic dissection. Several key genes have been identified to contribute to these inherited aortopathies, broadly categorized into those that affect the contractile apparatus, ECM and TGFβ signalling pathways.

Pathogenic variants in genes encoding smooth muscle contractile proteins have a central role in non-syndromic familial TAA. Variants in *ACTA2* are among the most common causes (responsible for up to 14% of all non-syndromic aortopathies[94]), leading to early coronary artery disease, moyamoya-like disease, defective cytoskeletal function, increased aortic stiffness and a predisposition to early-onset dissection, often without notable aortic dilation. Similarly, variants in *MYH11* and *MYLK* (encoding myosin light chain kinase) impair VSMC contraction and increase susceptibility to aortic wall degeneration[67,95]. Variants in the *MYH11* gene are associated with impaired ability of myosin to polymerize into thick filaments[67]. *MYLK* variants are associated with an impairment of calcium influx or MYLK binding to calmodulin, resulting in diminished VSMC contractile function[87]. People with *MYLK* variants present with aortic dissection at normal or mildly dilated aortas[96,97]. Moreover, variants in *PRKG1*, which encodes a cGMP-dependent protein kinase that controls relaxation of VSMCs, are associated with acute aortic syndromes or aortic aneurysm at a young age, with additional vascular abnormalities in the abdominal aorta or coronary arteries[98].

Several familial TAAs have been linked to pathogenic variants in ECM-related genes, such as *LOX*, which encodes lysyl oxidase, an enzyme crucial for cross-linking collagen and elastin fibres[99,100]. Moreover, with regard to TGFβ signalling genes, although traditionally associated with syndromic aortopathies, variants in genes such as *SMAD3*, *TGFBR1*, *TGFBR2* and *TGFB2* have been implicated in non-syndromic familial TAAs, underscoring the role of dysregulated TGFβ signalling in both syndromic and non-syndromic disease[99,100].

These genetic discoveries have enhanced our understanding of familial aortic disease risk and have implications for genetic counselling, risk stratification and early surveillance in affected families. Although non-syndromic familial TAAs are less well characterized than their syndromic counterparts, ongoing genetic studies continue to uncover additional risk loci and pathways that contribute to disease pathogenesis.

Common genetic variants and GWAS studies. In the past 3 years, our understanding of the genetic basis of TAA has moved beyond the highly penetrant genes of HTAD, to include common genetic variants identified through genome-wide association studies (GWAS). Notably, one of the strongest GWAS signals for TAA maps to *FBN1* (ref. 101), the gene responsible for MFS, suggesting a potential shared genetic susceptibility between syndromic and non-syndromic forms of aortopathy. Additionally, large-scale biobank studies, including those leveraging MRI-based aortic measurements, from the UK Biobank[102] and the Department of Veterans Affairs Healthcare System biobank[103] (The Million Veteran Program), have identified common genetic variants associated with aortic enlargement, further highlighting the polygenic nature of aortic disease. However, unlike HTAD genes, which have directly influenced clinical risk stratification and surgical decision-making, GWAS findings have yet to translate into changes in clinical management, likely owing to their modest effect sizes and the complexity of polygenic risk. Nonetheless, these discoveries provide important insights into the genetic architecture of TAA and might serve as the foundation for future risk prediction models that integrate both rare and common genetic gene variants.

Summary. There is mounting evidence for a wide range of affected genes in aortic disease with varying penetrant risk. The cellular and molecular pathways affected by these genetic variants need to be further investigated, particularly given their potential as treatment targets.

Diagnosis, screening and prevention

Diagnosis

Especially over the past decade, aortic medicine has evolved from a purely surgical treatment into a multidisciplinary, lifelong treatment of the aortic organ. There is thus a need for standardized terminology and definitions that can be universally understood across cardiovascular surgeons, cardiologists, radiologists, anaesthesiologists, geneticists and the many more health-care providers involved in modern aortic medicine. The STORAGE guidelines were recently published by the editors of the *European Journal of Cardio-Thoracic Surgery* to define a common language for both open and endovascular aortic surgery[104]. The document defines aortic pathologies and provides standards to report interventions, radiological findings and outcome characteristics and was incorporated into the most recent guidelines from the European Association for Cardio-Thoracic Surgery (EACTS) and The Society of Thoracic Surgeons (STS)[1].

Imaging suggestions and recommendations have been made within recent ESC and EACTS–STS guidelines[1,5]. Alongside absolute diameters and lengths, *z*-scores or nomograms should be reported, as these enable correlation with expected values based on sex, age, height or body surface area[5,9,10,95,105]. Of note, there are several different formulas used to calculate *z*-scores and it should be stated which specific *z*-score was used. Websites are available that enable the calculation of *z*-scores[106]. Ishimaru zones are also highly useful to report the location of an aortic aneurysm and to facilitate further treatment[2].

Most TAAs remain asymptomatic for a long time and become symptomatic by compression of adjacent structures, impairment of the aortic valve function or as a sign of impending or ongoing rupture or dissection[23,107]. In patients with suspected TAAs, several imaging modalities are available (Table 2). CT angiography from the common carotid to the common femoral arteries is often the first-line diagnostic modality. MRI might be an alternative diagnostic tool, particularly in younger patients, to reduce radiation exposure. Transthoracic as well as transoesophageal echocardiography cannot currently be used to visualize the entire thoracic aorta, and may over- or underestimate the extent of the disease[1,108,109]. Nevertheless, echocardiography and coronary artery assessment remain a cornerstone of clinical risk assessment before invasive treatment planning[13].

Standardization of measurements according to aortic segment is also important. Aortic diameters should be measured at predefined levels to facilitate subsequent comparison (Fig. 5). Accuracy and uniformity of measurements are also crucial. In CT, it is recommended to measure outer edge to outer edge (including the aortic wall, an essential component of the disease process). In echocardiography, the leading edge-to-leading edge method is advocated by European and American societies[1,110,111]. Regarding the aortic root, two measurement methods are common: the sinus-to-commissure and the sinus-to-sinus measurements. The sinus-to-commissure method is carried out by drawing a line from the deepest point of a sinus to the opposite commissure, whereas the sinus-to-sinus method measures

Table 2 | Imaging modalities for thoracic aortic aneurysms

Imaging technique	Advantages	Disadvantages
CT angiography	Gold standard technique that enables high-resolution imaging of complete thoracic aorta Can detect concomitant coronary artery or branch vessel disease	Requires contrast agent administration Radiation exposure
MRI	Provides 3D images with good resolution and enables morphological analyses No radiation exposure	Requires contrast agent administration Artefacts in patients with implants and devices Image acquisition takes longer and spatial resolution is considerably lower than with CT angiography Limited practicability in patients who are haemodynamically unstable
Transthoracic echocardiography	Ideal for initial examination of the proximal ascending aorta Portable, bedside examination Concomitant cardiac evaluation including aortic valve	Unable to visualize complete aorta Results can vary between investigators
Transoesophageal echocardiography	Achieves high-resolution imaging of several zones of the thoracic aorta Concomitant cardiac evaluation including aortic valve	Invasive imaging modality Results can vary between investigators

the distance from the deepest points of two adjacent sinuses[110,111]. The sinus-to-sinus measurement usually yields higher values compared with the sinus-to-commissure measurement and is considered to be more representative of the highest wall tension within the root and consequently most appropriate to predict AAEs[110–112].

Screening

The diagnosis of TAA is usually incidental. To date, no general screening recommendation can be given for thoracic aortic pathologies, unlike for abdominal aortic aneurysms. Moreover, although a D-dimer test has diagnostic value for acute aortic dissections[113–115], it lacks accuracy in TAAs[116], and there is currently no blood test that can detect aortic disease sufficiently. Nonetheless, genetic screening and testing for HTAD in individuals or first-degree relatives of patients with thoracic aortic disease are a crucial component of the aortic team care model[1,5]. Screening by echocardiography is recommended in these patients and first-degree relatives and could be completed by CT or MRI imaging in the case of uncertainties[1]. Regarding genetic testing, patient family history should be gathered, the risk for HTAD assessed and if diagnosed with HTAD, at-risk biological relatives should be genetically tested[1,5]. Testing of relatives can be carried out by sequencing of the suspected genetic area, for cost-efficiency[1,117]. Detailed genetic screening pathways are illustrated in recent EACTS–STS and ESC guidelines[1,5].

Prevention

Non-surgical preventive measures aim to reduce the rate of TAA growth and are often the only option for individuals deemed too high risk for open or interventional surgery. Blood pressure control, as well as treatment of hyperlipidaemia and coexisting atherosclerotic disease, are cornerstones of medical aneurysm treatment[5]. Of note, there is currently no effective medical therapy available that can induce favourable remodelling of the aortic wall to slow or reverse aneurysmal dilation. Smoking cessation in those with TAA is highly recommended given the correlation between smoking and TAA progression[118]. With regard to recommendations of physical activity, data on exercise in people with aortic disease are limited. In general, collision sports and heavy exercise should be avoided owing to the impact on the body or in the case of weightlifting owing to high blood pressure peaks, whereas low-intensity physical activity is encouraged because of its long-term beneficial effect on heart rate and blood pressure[1,5,119]. Nevertheless, preventive open or endovascular surgery, if indicated, remains the definitive cornerstone to substantially reduce the risk of rupture or dissection at the affected segment[1,5,120,121].

Management

Management strategies for TAAs are commonly based on three major pillars. First, cardiovascular risk factors, such as high blood pressure, should be managed, as high blood pressure is often the most treatable risk factor and should be the focus of prevention. In addition, patients who are below the threshold for invasive treatment should be monitored (preferably in the same centre with the same imaging modality), as should patients deemed unfit for surgery or intervention[111,122,123]. The second pillar is endovascular treatment with increasing importance from proximal to distal aorta; the third is open surgical replacement of the diseased segments in those who are fit for surgery. Thresholds for endovascular or open repair have been reported[1] (Table 3). Of note, thresholds differ in patients with HTADs, which are not covered by this article but can be found elsewhere[1].

Aortic root

The treatment of aortic root aneurysms follows two major principles: surgical resection of the entire diseased aortic tissue, and maintenance of the functional unit consisting of both the aortic root itself and the aortic valve. Following both principles aims to prevent aortic dissection and rupture as well as to maintain regular valve morphology and function[124,125].

According to the current EACTS and STS aortic guidelines, aortic root dilation and aneurysms can be subclassified as 'root phenotype', 'ascending phenotype' and 'extended phenotype'[1]. A root phenotype is characterized by a root diameter that exceeds the ascending diameter, and surgical treatment consists of aortic valve and sinus replacement including re-implantation of the coronary ostia (modified Bentall–De Bono operation)[126]. This procedure is associated with favourable outcomes both in hospital and in the long term, with post-intervention survival of up to 93% at 10 years[125,126]. Of note, late adverse events occurring during follow-up often depend on whether a mechanical or biological valve is used[127].

Sparing the aortic valve in aortic root dilation or aneurysm is a surgical approach that has been increasingly adopted over past decades[128] (Fig. 6). Initially proposed for morphologically normal

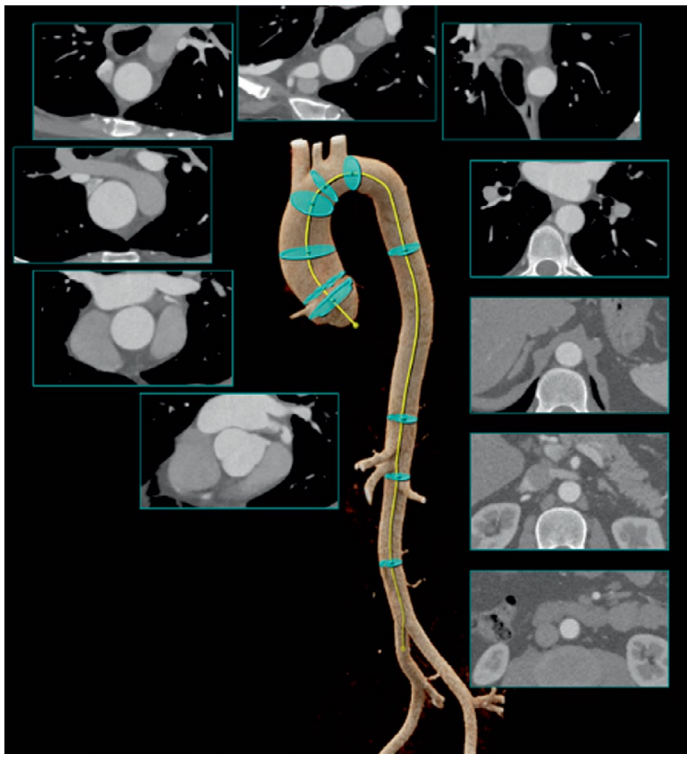

Fig. 5 | Standardized anatomical localizations for cross-sectional measurements of aortic dimensions. Boxes show CT angiography scans of the cross-sectional measurements from the aortic root, ascending aorta, aortic arch, thoracic descending aorta and the abdominal aorta. Reprinted with permission from ref. 1, Oxford University Press.

tricuspid aortic valves (TAVs) with root aneurysm, the indications were extended to all patients with aortic valves without severe calcifications or degeneration[69]. For both the re-implantation (in-hospital mortality of lower than 1%) and remodelling technique for valve-sparing aortic root replacement, lower in-hospital mortality rates have been reported compared with replacement with a valve-carrying conduit in elective patients[129]. Valve-sparing root replacement yields a long-term re-intervention-free survival rate of 69.1% at 20 years[130]. Moreover, sparing the valve is also associated with lower valve-related adverse events during follow-up, preserving valve durability and function with a low rate of aortic valve re-interventions for BAV as well as for TAV aortopathies[127,131–133]. Nevertheless, the long-term benefit of valve-sparing root replacements is dependent on surgeon expertise and should therefore be considered only when durable results are expected[1,129,131].

An ascending phenotype is characterized by a root diameter that is smaller than the ascending diameter. In these cases, the indication for concomitant aortic root replacement in addition to ascending aortic replacement is a root diameter of ≥45 mm[1] (measured by taking the largest diameter from sinus to sinus). Lower thresholds can apply in people with increased risk for aortic events, including young age, HTAD or family history of acute type A aortic dissection[1]. In comparison with extending the prosthetic replacement into the aortic arch, concomitant aortic root replacement seems not to increase mortality or the risk of adverse aortic events[134]. However, one should take into account that the growth rate of the native aortic root is slow and ranges between 0.4 and 0.8 mm per year after ascending aortic replacement[135,136]. Therefore, the remaining risk for aortic root re-operation after ascending aortic replacement is low[137,138]. Nevertheless, sinus dilation can be asymmetrical, with a higher incidence of non-coronary sinus dilation[139]. Selective prosthetic non-coronary sinus replacement is reasonable in selected patients[140,141]. In this scenario, the ascending graft is shaped meticulously to fit the resected part of the non-coronary sinus[1,136].

Ascending aorta

If the aneurysm is limited to the tubular portion of the ascending aorta without involvement of the root or the aortic arch, supracoronary ascending aorta replacement might be the simplest and most efficient surgical technique[1]. Nevertheless, patients with ascending aortic aneurysms frequently present with at least partial proximal involvement of the aortic arch, termed an extended phenotype. Based on the embryological origin from the neural crest of the most distal part of the ascending aorta, the proximal aortic arch should be resected and replaced with a dacron prosthesis. Hemiarch replacement, which involves an open distal anastomosis (distal anastomosis to the proximal hemiarch) without aortic cross-clamping, is favoured in this scenario[142,143] (Fig. 6). Moreover, ascending grafts should be chosen, to anticipate further distal endovascular treatment in terms of endovascular aortic arch repair to create an ideal proximal landing zone. The following two principles should be applied: a straight implantation of the prosthesis and a prosthesis length of ≥7 cm (ref. 1).

Aortic arch

Disease that is restricted to the aortic arch is rare, as most arch pathologies involve the ascending and proximal descending aorta. Isolated surgical replacement of the aortic arch is therefore uncommon. Aortic arch pathologies are addressed by open replacement or endovascular repair, the choice of which is dependent on the morphology and quality of the proximal and distal aorta, the origin and abnormalities of the supra-aortic vessels, as well as cerebral protection strategies. Nevertheless, limited data are available that compare the long-term outcomes of the two strategies; such research is greatly needed to inform surgical decision-making in the face of aortic arch pathologies[1].

Open surgical arch replacement. Aortic arch replacement is a complex and challenging procedure, although several technical refinements have been established over the past decade[144–146]. In the case of ascending aneurysms with involvement of the proximal aortic arch, selective replacement of the arch with re-implantation of one or more supra-aortic vessels is reasonable. The supra-aortic vessels can be re-implanted separately using a four-branched graft or a separate prosthesis in the case of limited arch replacement (for example, re-implantation of the brachiocephalic trunk). In this specific scenario, distal anastomosis can be carried out in Ishimaru zones 1–2 depending on the disease extension, thus requiring only one or two supra-aortic vessels to be implanted (the brachiocephalic trunk and/or also the left common carotid artery (LCCA))[1].

When total aortic arch replacement is needed, the so-called frozen elephant trunk (FET) technique is recommended[147–149], which combines the benefits of both open and endovascular repair (Fig. 6). The FET procedure involves a custom hybrid graft that consist of a proximal dacron part and a distal stent graft portion. The supra-aortic vessels can be re-implanted separately or using the island technique[145,146,148,150]. Aortic guidelines from 2023 and large cohort studies confirm the progressive

adoption of the FET procedure as the technique of choice for complex arch aneurysms, especially as it facilitates distal extension[1,149–153]. Using hybrid prostheses comprised of a dacron and a stent graft part has positive short-term outcomes including beneficial remodelling of the descending aorta[148,154,155]. Nevertheless, a relevant number of distal re-interventions were noted in several studies[156–158].

In patients at high risk of complications from surgery, a hybrid approach can be used to treat the aortic arch that potentially decreases surgical trauma[1]. The principle of this approach, which can be performed simultaneously or sequentially, is to surgically create an adequate landing zone for an endovascular prosthesis in proximal Ishimaru zones (zones 0–2). Owing to substantial variance in branching and fenestration patterns between individuals, as well as variation in underlying pathological conditions, the options for a hybrid approach in terms of supra-aortic vessel transposition are multiple[1,159,160]. Nevertheless, the risk of stroke and retrograde type A dissections remains, especially in patients after extensive debranching. Therefore, total arch rerouting should be avoided in favour of the FET technique, although stroke remains one of the major complications even after the FET technique owing to embolic events[161].

The LSA has a key role in distal aortic arch pathologies. Maintaining LSA perfusion subsequently preserves spinal cord perfusion. Therefore, routine LSA revascularization via a LSA–LCCA bypass or LSC–LCCA transposition is crucial to reduce the risk of spinal cord injury when the LSA is covered during thoracic endovascular aortic repair (TEVAR)[162]. Furthermore, arch configuration in terms of arch types and LSA anatomy have implications for endovascular aortic arch repair and should, therefore, be carefully assessed during preoperative planning[1,163].

Endovascular arch repair. The aortic arch is a highly complex anatomical and functional aortic segment. Advances in endograft technologies have led to the development of aortic arch endografts with various fenestration and branching patterns, as well as various delivery systems. All such approaches are targeted at patients at high risk for open surgical repair with total arch replacement (TAR)[164]. The most frequently used endograft designs are inner and outer branches, fenestrated grafts or physician-modified in situ fenestrations[165]. Although there are few studies available, retrospective case series studies suggest that the result of endovascular arch repair are comparable to those of open TAR via the FET technique[149,151,152,166]. A systematic review revealed mortality and stroke rates for endovascular arch repair of 16% and 14%, respectively[167], whereas a large case series reported mortality and stroke rates ranging from 10% to 20% in patients with TAA[150,151,161]. Of note, the FET cohorts often received concomitant cardiac procedures, and comparative studies of the two techniques are lacking. Therefore, further research on open versus endovascular arch repair is greatly needed[1].

Descending aorta

TEVAR is currently the preferred treatment for most conditions that affect the descending thoracic aorta, based on its positive outcomes and low invasiveness[50,168–170]. This minimally invasive procedure involves insertion of a transfemoral endograft either percutaneously or through open surgical exposure of the femoral artery, into the aorta. Advancements in low-profile (small sheath diameter) deployment systems and specialized large-bore closure devices have greatly facilitated TEVAR, especially the percutaneous approach, which can be performed without general anaesthesia[171–173].

The primary objective of TEVAR is to exclude descending aortic pathologies, such as descending TAAs and penetrating atherosclerotic ulcers (PAUs), from the circulatory system by covering the affected segment of the aorta. Achieving this exclusion relies on properly sealing the endograft in both the proximal sealing zone (PSZ) and distal sealing zone (DSZ), which represent the proximal and distal overlapping (ideally non-diseased) area between the native aortic tissue and the stent graft. This sealing process necessitates the complete apposition of the oversized endograft to the aortic wall. The term ‘proximal landing zone’ refers to the specific level at which the proximal end of the endograft is deployed relative to the supra-aortic vessels[1,174].

The selection of sealing zones is crucial to determine both the immediate and long-term success of TEVAR. A healthy PSZ in the descending aorta or the distal aortic arch should measure at least 25 mm. For the DSZ, a length of 25 mm is adequate if deploying in the native aorta, whereas 50 mm is necessary if deploying into a previously implanted prosthesis[1,175]. The length of the PSZ is measured along the inner curvature of the aorta, ensuring that the endograft completely apposes to the inner aortic wall. For cases in which the aorta features a type III arch with a small radius, incomplete apposition of the endograft in the PSZ, known as a ‘bird-beak’ configuration, can occur. This potential issue must be considered during the planning and decision-making stages of the procedure[174,176,177]. For example, it might be necessary to adjust the position of the proximal landing zone by debranching the supra-aortic vessels or by creating a stable PSZ by TAR using the FET technique. This approach creates a suitable foundation for subsequent endovascular interventions, ensuring a more secure and effective outcome[1,178,179].

A second major component is the quality of the aortic wall, which substantially affects outcomes after endovascular repair. Risk factors for aortic failure after TEVAR include HTAD, aortic diameter of the

Table 3 | Example thresholds for thoracic aortic intervention or replacement

Segment	Threshold	Condition
Ascending aorta	≥55 mm	Ascending aortic aneurysm within the root or tubular tract (TAV and BAV)
	>52 mm	Ascending phenotype dilation (TAV and BAV) in patients with low surgical risk
	≥50 mm	BAV and root phenotype TAV and root phenotype and low surgical risk BAV and ascending phenotype and low surgical risk and risk factors TAV and ascending phenotype and risk factors and low surgical risk and non-syndromic TAV and concomitant non-aortic valve cardiac surgery
	≥45 mm	Concomitant aortic valve surgery Aortic root dilation and surgery for ascending aortic aneurysm
Aortic arch	≥55 mm	Asymptomatic isolated aortic arch aneurysms
Descending aorta	≥55 mm	Asymptomatic descending aortic aneurysms

Based on data from ref. 1. Low surgical risk is based on both patient age and comorbidities, as well as surgeon expertise. Risk factors include below age 50 years, short stature (<1.69 m), an ascending aortic length of more than 11 cm, aortic diameter increase rate of >3 mm/year, family history of acute aortic syndrome, aortic coarctation, refractory hypertension, shared decision-making with the patient and concomitant non-aortic valve cardiac surgery[1]. An aortic diameter of 53 mm increases the risk of acute aortic events from <1% to 4–5%; therefore, a predicted perioperative mortality of less than 3% justifies elective surgery[1,45,199]. BAV, bicuspid aortic valve; TAV tricuspid aortic valve.

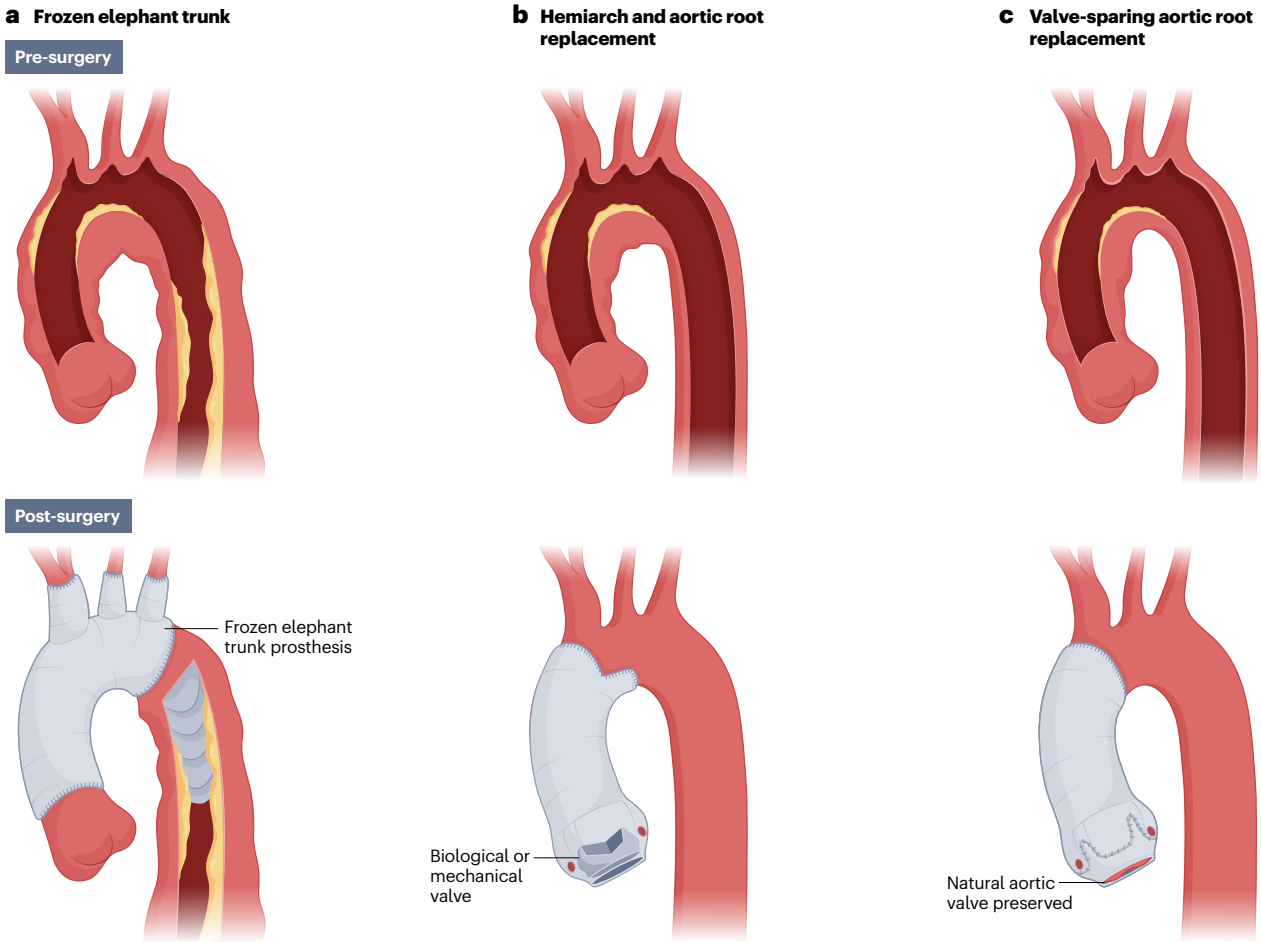

Fig. 6 | Surgical procedures of the ascending aorta and the aortic arch, including the proximal descending aorta. a, Pre- and post-surgical illustration of total aortic arch replacement using the frozen elephant trunk technique (resection of Ishimaru zone 0 to zones 1–3 and stent graft implantation into the descending aorta using a prefabricated hybrid prosthesis). **b**, Pre- and post-surgical illustration of a concomitant hemiarch and aortic root replacement with a biological valve-carrying conduit. **c**, Pre- and post-surgical illustration of a valve-sparing aortic root and ascending replacement. Reprinted with permission from ref. 1, Oxford University Press.

PLZ >40 mm, severe thrombus and calcification[1,50,180,181]. In particular, patients with HTAD undergoing TEVAR in native landing zones face major risks of complications and the need for additional interventions. However, positive outcomes for endovascular repair in these cases have been reported in small studies[182–186]. Patients with sealing zone diameters greater than 38 mm are at risk of further neck degeneration owing to the seal created by oversizing in an already dilated neck[187]. This condition can lead to type I endoleaks, which can be exacerbated by the presence of thrombus or calcification in the sealing zones[187,188]. The durability of the seal in TEVAR depends not only on the length and quality of the sealing zones but also on the appropriate degree of endograft oversizing. The extent of oversizing is mainly based on the underlying nature of the aortic pathology. To treat descending aortic aneurysms, a recommended stent graft oversizing of 15–20% in both the proximal and distal landing zones is advised[1].

In patients with unsuitable or unfavourable aortic anatomy for descending endovascular repair, creating a proximal landing zone with open repair is reasonable. In this scenario, the FET technique with its distal stent graft component facilitates further downstream treatment[156,189]. The FET procedure might also be reasonable even in patients without arch pathologies but with proximal descending involvement[1,190]. Isolated open descending replacement yields a higher perioperative risk compared with endovascular repair[170], and, therefore, is limited to selected patients, such as those with HTAD or in the case of failed endovascular repair[1,191].

Surveillance

Patients with TAA who do not meet surgical criteria require consistent follow-up, combining clinical evaluations and imaging. The optimal imaging modality depends on the location of the aneurysm[5,111,122]. For dilation of the aortic root or proximal ascending aorta, transthoracic echocardiogram (TTE) can be used for follow-up if there is agreement with MRI or CT measurements; otherwise, MRI or CT is preferred. In cases that involve the aortic arch or descending thoracic aorta, where TTE is less precise, follow-up relies on MRI or CT, and should be conducted with the same imaging technique and at the same

centre to ensure comparability. For moderate-sized aneurysms that remain stable, follow-up with MRI is preferred, to minimize radiation exposure[5].

After the initial diagnosis, follow-up imaging is recommended at 6–12 months, depending on baseline diameter and aetiology. For aneurysms <40 mm that are stable, follow-up might be conducted annually, whereas those of 40–49 mm should be monitored every 6–12 months. Aneurysms of 50–55 mm require imaging every 6 months until they reach the size threshold for surgical or endovascular intervention. Rapid growth (≥3 mm per year) or diameters nearing surgical criteria necessitate closer evaluation. Stable aortic dimensions over several years, particularly for non-genetic aneurysms of <45 mm, might allow for extended imaging intervals[5].

Surveillance after TAA surgery or intervention is crucial, as untreated aortic segments remain prone to disease progression and complications. Distal and proximal segments can continue to dilate, particularly in patients who have undergone endovascular repair. Although growth rates in untreated segments are slower in patients with TAA compared with patients with dissection, re-interventions, such as arch or descending aortic repairs, are often required, especially in high-risk populations[192].

Endovascular repair carries risks of complications, including endoleaks and aortic dilation, necessitating lifelong surveillance with imaging. Early identification of risk factors for complications on post-treatment CT scans is crucial, and surveillance frequency should be tailored on the basis of residual untreated segments and patient risk[1]. For patients undergoing endovascular treatment, regardless of the underlying aortic condition, CT angiography imaging is recommended at 6 months, 12 months and then annually for 5 years if stability is maintained. In contrast, patients treated with open surgery for TAA should undergo imaging at 12 months and 24 months, with extended intervals thereafter if stable[1].

Quality of life

Data on the quality of life (QoL) of patients with thoracic aortic disease is limited and conflicting. Most studies have used small sample sizes, with variable response rates and some include populations with unverified diagnosis and usually patients with TAA and dissection[193–195].

People with thoracic aortic disease have markedly lower health-related QoL compared with the general population[193]. Several scores have been used to assess QoL in people with thoracic aortic disease. The short form 36 (SF-36) and hospital anxiety and depression scale (HADS) have been used to show impaired QoL in both male and female patients, with worse QoL in women and younger patients. Interestingly, disease-related factors such as previous aortic dissection or the presence of HTAD have less of an affect compared with employment status or coping style (including acceptance of the disease). Baseline QoL in people with untreated TAAs was strongly influenced by factors such as New York Heart Association (NYHA) functional class, smoking status and the need for formal or informal care, with higher NYHA class and current smoking associated with worse QoL. Over time, QoL remained stable for fit, non-smoking patients of average age, but older age and smoking were associated with faster decline, with smoking having a greater impact than a 10-year age difference[196]. Nevertheless, data are still limited to a small number of studies and warrant further research[193,197].

Medical therapy for patients with TAA primarily focuses on managing risk factors to prevent aneurysm progression and rupture. Although such medical management substantially reduces mortality, its direct impact on QoL is less pronounced than that of surgical interventions[198]. Studies indicate that without surgical intervention, patients with TAA can experience a gradual decline in health-related QoL over time, particularly with regard to mobility and self-care. Therefore, although medical therapy is essential for management of TAAs, it may not markedly enhance QoL, and patients might still face a decline in certain health aspects over time[198].

A 2019 systematic review of QoL in people with HTAD and dissection reported that most studies indicate a negative impact on QoL in patients with MFS compared with the general population[195]. Patients presenting with thoracoabdominal aortic aneurysms have lower baseline QoL compared with the general population[194]. Postoperatively, these patients can experience a decline in postoperative QoL persisting across repair types, even in long-term follow-up. Comorbidities, peri- and postprocedural complications, and the duration of hospital stay aggravate adverse effects on postoperative QoL[194].

Outlook

The latest EACTS and STS aortic guidelines are based on retrospective data or expert opinion, which has not changed substantially over the past decade[1]. Nonetheless, there continues to be debate on treatment strategies, especially in terms of the technical and conceptual aspects of aortic repair. To address this issue, we propose a two-step approach. First, there is a need for large multicentre or registry data that focus on specific questions related to aortic disease (Box 1). Example areas that warrant research include determination of the extent of repair in acute aortic dissections and evaluation of the use of hybrid or endovascular treatment in patients with HTAD, who are at substantially higher risk for the development of adverse aortic events such as aortic rupture and dissection, leading to more frequent follow-up as well as a potentially higher incidence of subsequent aortic re-interventions[65]. Second, multicentre randomized controlled studies should be carried out based on these results, especially comparing open with endovascular treatment options in the aortic arch or prospective insights into cerebral perfusion strategies during aortic arch replacement in terms of optimal core temperature and cerebral inflow strategies such as antegrade versus retrograde as well as bilateral versus unilateral cerebral perfusion. Moreover, the development of diagnostic biomarkers that can identify patients with, or at risk of, thoracic aortic disease is another milestone for the upcoming decade.

Aortic disease is often efficiently treated but not cured. Untreated segments remain and these are at risk of both disease and treatment-related collateral events for which more prospective evidence is

Box 1 | In the next decade, thoracic aortic aneurysm research should focus on

- Standardizing evidence-based follow-up protocols specific to each disease and treatment modality
- Evaluating the use and efficiency of endovascular treatment in patients with heritable thoracic aortic disease
- Creating automated measurements of aortic dimension
- Forming interdisciplinary teams for diagnosis and treatment of the aortic organ as a functional unit
- Multicentre randomized controlled trials to obtain robust data regarding treatment modalities for patients and health-care providers

needed, leading to uniform and evidence-based follow-up protocols, individualized for each patient according to the respective location and type of aortic disease, as well as treatment modality received. Moreover, the most common complication of TAA is acute aortic dissection. The incidence of aortic dissection in western countries remains uncertain owing to its highly lethal nature; thus, the substantial rate of lethal TAA course that is undiagnosed might lead to underestimation of true incidence and prevalence rates. This necessitates focused health service research and campaigns that aim to increase awareness of aortic diseases in the upcoming years. The rapid advancement of machine learning and artificial intelligence (AI) has now firmly established these tools in medicine, including aortic medicine. Although the full scope of these tools remains to be determined, they will undoubtedly have a central role in the coming years. Research areas in which machine learning and AI are already being used include the evaluation of aortic dimensions and their automated analysis. In the near future, we foresee that these technologies will extend to disease-specific evaluations of patients with aortic dissections, potentially reaching the point of evaluating and suggesting personalized treatment options for individual patients. In addition, the aorta should globally be seen and treated as a functional unit from the aortic root to the aortic bifurcation. The aorta has been defined as the 24th organ of the human body and should be interpreted accordingly, especially in terms of involved specialities that are encouraged to act as a functional unit for the diagnosis and treatment of aortic pathologies.

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Author contributions

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Additional information

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