



Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes

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Abstract | The aorta is the ‘greatest artery’, through which oxygenated blood is delivered from the left ventricle to end organs with each cardiac cycle (200 million litres of blood transported in an average lifetime). The aorta can be affected by a wide spectrum of acute factors (such as cocaine use, weight lifting and trauma) and chronic acquired and/or genetic conditions (such as systemic arterial hypertension and pheochromocytoma), which variously lead to increased aortic wall stress. The medial layer of the aorta can also be subject to abnormalities (such as Marfan syndrome, bicuspid aortic valve, inflammatory vasculitis, atherosclerosis and infections). Despite important advances in diagnostic and therapeutic interventions, data derived from registries and population-based studies highlight that the burden of aortic diseases remains high. Therefore, specific resources need to be allocated to design and implement preventive strategies (healthy lifestyles, modifications to cardiovascular risk factors, and educational and screening programmes) at individual and community levels. In this Review, we discuss the epidemiology, management and outcomes of the most common aortic diseases, namely, aortic aneurysms and acute aortic syndromes.

The aorta — the ‘greatest artery’ — is the ultimate conductance vessel through which oxygenated blood is delivered from the left ventricle to end organs with each cardiac cycle (200 million litres of blood transported in an average lifetime). The aortic wall is composed of three layers: the thin tunica intima, the thickest musculoelastic tunica media and the outer fibrous tunica adventitia (FIG. 1a). Anatomically, the aorta is divided into thoracic and abdominal components, above and below the diaphragm, respectively. The thoracic aorta includes the aortic root and the ascending aorta, the aortic arch and the descending segments. The abdominal aorta includes the suprarenal and infrarenal segments; the aorta then ends at the level of the fourth lumbar vertebra, where it bifurcates into the left and right common iliac arteries (FIG. 1b). In addition to conductance and pumping functions, the aorta has an important role in the regulation of systemic vascular resistance and heart rate interaction through pressure-responsive receptors located in the ascending aorta and aortic arch segments^{1–4}.

As a whole organ, the aorta can be either acutely or chronically affected by various congenital or acquired diseases involving the thoracic and/or abdominal components^{2,3}. Aortic diseases can be broadly classified as thoracic aortic aneurysm (TAA), abdominal aortic aneurysm (AAA) and acute aortic syndromes (AAS).

These diseases are variously associated with one or more conditions leading to increased aortic wall stress (such as systemic hypertension, cocaine use or trauma) and/or aortic media abnormalities (such as Marfan syndrome, bicuspid aortic valve (BAV), inflammatory vasculitis and atherosclerosis)^{2,3,5} (BOX 1).

During the past two decades, the overall global death rates from aortic disease (including TAA, AAA and acute aortic dissection (AAD)) have increased from 2.49 per 100,000 (95% CI 1.78–3.27) in 1990 to 2.78 per 100,000 (95% CI 2.04–3.62) in 2010 (REF.⁶). This increase seems to be more evident in developing countries, with a median death rate of 0.71 (95% CI 0.28–1.40) compared with 0.22 (95% CI 0.10–0.33) in developed nations⁶. Interestingly, age-specific data indicate a decrease in death rates between 1990 and 2010 in all age groups⁶ (TABLE 1). The overall increase in global death rates is perhaps related to the increasing mean age of the global population.

In this Review, we describe the epidemiological profile (the incidence, prevalence, demographics and risk factors) and the management of TAAs, AAAs and AAS. We also discuss trends in the presentation, diagnosis, management and outcomes of AADs on the basis of data from the International Registry of Acute Aortic Dissection (IRAD)^{7,8}.

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Key points

- The aorta can be affected by various congenital and acquired diseases, either acutely or chronically, and involving the thoracic and/or abdominal components.
- Despite remarkable progress in diagnostic and therapeutic techniques, the global burden of aortic diseases remains high.
- Designing and implementing prevention and screening programmes at the individual and population levels are required.
- Advances in genetics, proteomics and imaging might allow more precise diagnosis, prevention and treatment in the future.

Aortic aneurysms

Aortic aneurysm is the second most common disease affecting the aorta after atherosclerosis², the fifteenth leading cause of death in individuals aged ≥ 55 years and the nineteenth leading cause of death overall^{9,10}. Aortic aneurysm is defined as a $\geq 50\%$, localized increase in the observed diameter of the aorta compared with the same aortic segment in age-matched and sex-matched healthy individuals (that is, a ratio of the observed to the expected diameter of ≥ 1.5)¹. Of note, a true aneurysm is characterized by an abnormal dilatation involving all aortic layers, whereas a false aneurysm (or pseudoaneurysm) consists of a periaortic haematoma between the tunica media and tunica adventitia, with a persistent communication with the aortic lumen¹. Although traditionally divided into thoracic and abdominal aneurysms (the dichotomy approach) (TABLE 2), tandem lesions of both the thoracic and abdominal aorta can

occur (the holistic approach)^{2,11–13}. Furthermore, thora-coabdominal aneurysms extending from the chest to the abdomen have also been described^{2,3}. Therefore, when an aortic aneurysm is diagnosed at any anatomical segment, a comprehensive assessment of the aortic valve complex and the entire aorta with the use of trans-thoracic echocardiography (TTE) plus CT or MRI is warranted (FIG. 2), before planning the appropriate therapeutic interventions^{2,3}.

Thoracic aortic aneurysms

Epidemiology and risk factors. The large majority (~95%) of patients with TAAs are asymptomatic before an acute event occurs, so the epidemiology of TAAs is difficult to ascertain^{14–19}. The overall incidence of TAAs ranges from approximately 5 to 10 per 100,000 person-years, with an upward trend, probably related to the ageing of the general population and the increased use of advanced imaging techniques (which increases detection)^{14,16,17}. TAAs are more frequent in men, but women have worse outcomes (a threefold higher risk of aortic dissection and rupture). In this regard, preliminary studies have pointed out that degenerative TAAs seem to grow faster in women than in men, perhaps owing to greater aortic stiffness in men^{19–23}. Declining levels of oestrogen as women age and transition to the menopause might lead to a loss of the protective effects of oestrogen on the aortic wall and impairment of its elastic properties²². Moreover, AAS occur at smaller aneurysm diameters (indexed to body size) in women

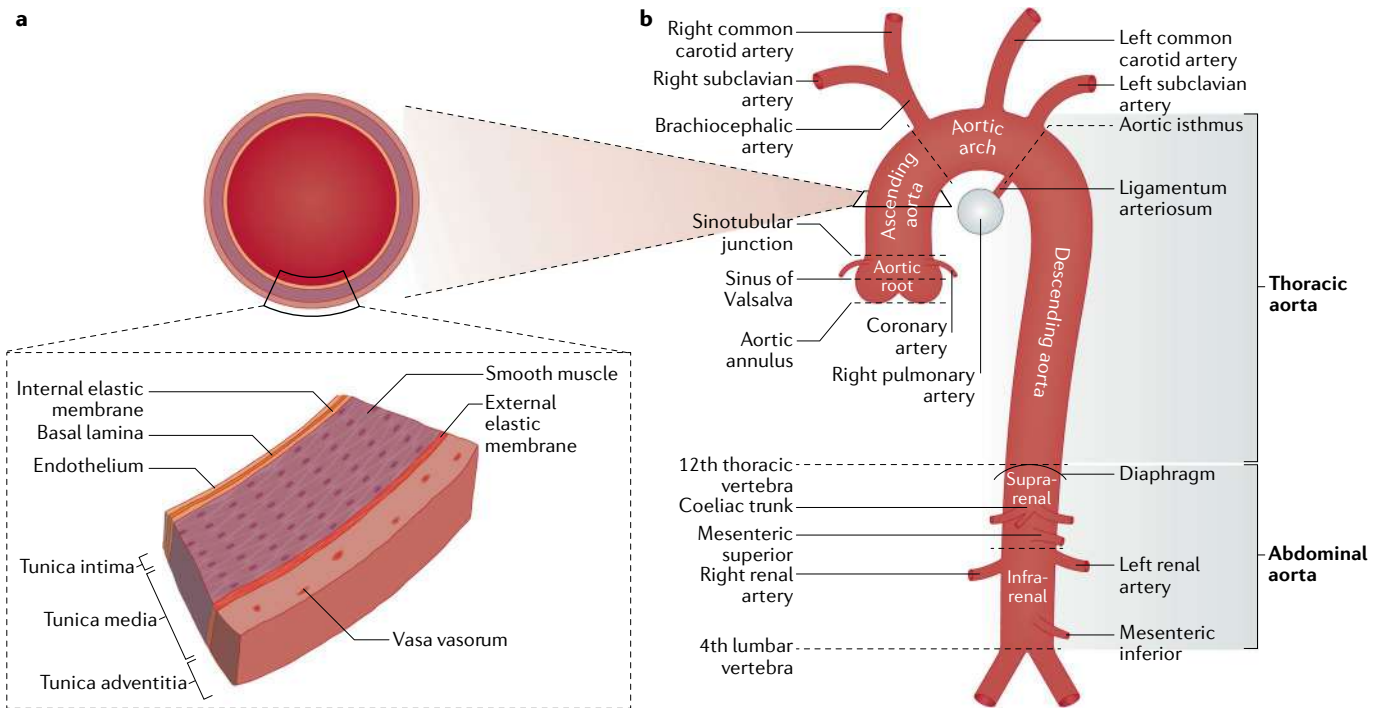


Fig. 1 | The structure and anatomy of the aorta. a | The aortic wall is composed of three layers: the thin tunica intima, the thickest musculoelastic tunica media and the outer fibrous tunica adventitia. **b** | Anatomically, the aorta is divided into thoracic and abdominal components, above and below the diaphragm, respectively. The thoracic aorta includes the aortic root and the ascending aorta, the aortic arch and the descending segment. The abdominal aorta includes the supra-renal and infra-renal segments; it then ends at the level of the fourth lumbar vertebra, where it bifurcates into the left and right common iliac arteries.

Box 1 | Conditions associated with aortic syndromes and aneurysms

Conditions associated with increased aortic wall stress

- Hypertension, particularly if uncontrolled
- Phaeochromocytoma
- Cocaine or other stimulant use
- Weight lifting or other Valsalva manoeuvre
- Coarctation of the aorta
- Traumatic aortic injuries (partial or complete transection of the aorta)
 - High-speed motor vehicle accidents
 - Falling from a great height

Conditions associated with aortic media abnormalities

- Genetic syndromes
 - Marfan syndrome
 - Loeys-Diez syndrome
 - Ehlers-Danlos syndrome, type IV or vascular type
 - Turner syndrome
 - Arterial tortuosity syndrome
 - Aneurysms-osteoarthritis syndrome
 - Others
- Genetic, non-syndromic familial thoracic aortic aneurysm and dissection syndrome

- Known genetic variants in *ACTA2*, *FBN1*, *MYH11*, *MYLK*, *PRKG1*, *SMAD3*, *TGFBR1* or *TGFBR2*
- Unknown genetic variants
- Bicuspid aortic valve (including previous aortic valve replacement)
- Non-genetic conditions
 - Inflammatory vasculitis (Takayasu arteritis, giant cell arteritis or Behçet arteritis)
- Other
 - Atherosclerosis
 - Pregnancy
 - Polycystic kidney disease
 - Chronic corticosteroid or immunosuppression agent administration
 - Fluoroquinolone exposure
 - Infection involving the aortic wall from either bacteraemia or extension of adjacent infection

Iatrogenic

- Cardiac surgery
- Coronary angiography
- Coronary intervention

REF.³.

than in men^{8,24–26}. One of the largest, population-based, hospital analyses of thoracic aortic disease (retrospective, not including out-of-hospital deaths), involving >13.5 million residents in the province of Ontario, Canada, over a 12-year time frame (2002–2014), found an overall incidence of 7.6 and 4.6 per 100,000 for TAAs and thoracic aortic dissections, respectively²⁷. The incidence increased on an annual basis during the 12-year study period (from 3.5 to 7.6 per 100,000 ($P < 0.0001$) for TAAs and from 2.7 to 4.6 per 100,000 ($P < 0.0001$) for thoracic aortic dissections)²⁷. Of note, the incidence of thoracic aortic disease during the 12-year study was higher in men than in women, but women had higher in-hospital mortality for TAAs and aortic dissections involving the ascending aorta (type A)²⁷. By contrast, no significant difference in in-hospital mortality was observed between men and women for aortic dissections not involving the ascending aorta (type B)²⁷.

Approximately 60% of TAAs involve the aortic root and/or ascending aorta, 10% involve the aortic arch, 40% involve the descending aorta and 10% involve the thoracoabdominal aorta (some aneurysms involve multiple aortic segments)¹⁵. Atherosclerosis is the most prevalent risk factor for descending TAAs (as for AAAs), whereas ascending TAAs are most commonly associated with either connective tissue disease (most frequently Marfan syndrome) or BAV^{2,9,15} (TABLES 3, 4). Interestingly, non-syndromic familial TAAs comprise 21% of all cases of TAAs (77% have an autosomal dominant inheritance pattern with variable expressivity and penetrance) and usually occur at younger ages than sporadic TAAs (56.8 years versus 64.3 years)^{9,15,28–31} (TABLE 5). Other causes of TAAs include mechanical (traumatic) injury,

inflammatory conditions (such as giant cell arteritis, Takayasu arteritis and Behçet arteritis), chronic corticosteroid and/or immunosuppression agent administration and fluoroquinolone exposure^{1–3,5,32,33} (BOX 1). Furthermore, several microorganisms, including *Staphylococcus aureus*, *Salmonella* spp., *Escherichia coli*, *Streptococcus* spp., *Neisseria* spp., Gram-negative bacilli and fungi, have been associated with aortic aneurysm, producing rare but lethal conditions¹. Although rare nowadays, tertiary syphilis (resulting from *Treponema pallidum* infection) can cause ascending TAAs in about 40% of patients¹. Ascending and descending aortic aneurysms have also been reported in the context of HIV vasculopathy secondary to multifactorial pathophysiological processes including bacterial infections, such as *Salmonella*-related mycotic aneurysmal disease^{34–36}.

The diabetes paradox. Although diabetes mellitus is a major cardiovascular risk factor, epidemiological studies have highlighted an inverse association between the presence of diabetes and the incidence of aortic aneurysms and dissections^{37–40}. Data suggest that glycated crosslinks in the aortic tissue might have a protective role in preventing the progression of aortic diseases in patients with diabetes³⁷. Metformin therapy seems to limit the early progression of AAA disease^{41,42}. However, further studies are needed to confirm these observations and to clarify the potential underlying mechanisms.

Screening. Unlike for AAAs, screening for TAAs in the general population is not usually recommended^{2,3}. However, clinical screening with the use of imaging (TTE and, if indicated, MRI or CT) should be performed in high-risk cohorts: patients with intracranial aneurysms (the high prevalence (~20%) of thoracic aortic dilatation or aneurysm in these individuals might be linked to similar pathogenic pathways) or AAAs, individuals with a family history of sudden cardiac death, those with persistent atypical chest pain, and relatives of patients with a known aneurysm or first-degree relatives of patients with Marfan syndrome^{2,3,9,15,31,43–45} or other genetic aortopathies. Screening should also be considered in first-degree siblings of individuals with a BAV².

Natural history. TAAs are characterized by a long-term, silent growing phase (growth rate of ~1.2 mm per year). Interestingly, on average, ascending TAAs grow more slowly (0.7 mm per year) than descending TAAs (1.9 mm per year; larger diameters seem to expand more rapidly than smaller diameters)^{9,17,25,46}. Of note, aneurysm growth is faster in patients with familial or syndromic TAA than in those with degenerative TAA^{2,28,47}. Ascending TAAs with a diameter of ≥ 60 mm and descending TAAs with a diameter of ≥ 70 mm are widely regarded as being at very high risk of aortic dissection or rupture^{2,3,9,48} (FIG. 3).

Diagnosis. The diagnosis of a TAA is usually made accidentally during an imaging test (usually chest radiography, TTE or CT) performed for other indications^{2,3}.

Table 1 | Global death rates from aortic disease stratified by age and sex

Age (years)	Men		Women	
	1990	2010	1990	2010
25–29	0.18 (0.10–0.32)	0.16 (0.10–0.27)	0.10 (0.04–0.17)	0.07 (0.04–0.11)
30–34	0.29 (0.16–0.52)	0.25 (0.15–0.47)	0.18 (0.07–0.35)	0.11 (0.06–0.18)
35–39	0.48 (0.28–0.89)	0.43 (0.25–0.74)	0.30 (0.12–0.65)	0.19 (0.1–0.35)
40–44	0.84 (0.51–1.44)	0.78 (0.46–1.4)	0.53 (0.23–1.20)	0.35 (0.19–0.65)
45–49	1.54 (0.91–2.65)	1.42 (0.88–2.37)	0.82 (0.37–1.75)	0.58 (0.32–1.15)
50–54	2.86 (1.71–4.87)	2.64 (1.60–4.51)	1.44 (0.67–3.01)	1.02 (0.60–1.88)
55–59	5.44 (3.16–9.13)	5.02 (3.05–8.43)	2.20 (1.21–3.83)	1.69 (1.05–2.7)
60–64	10.37 (6.48–16.4)	9.41 (5.92–15.21)	4.35 (2.34–7.93)	3.31 (2.03–5.55)
65–69	19.79 (12.62–31.32)	17.19 (10.90–28.76)	8.47 (4.63–14.91)	6.37 (3.97–10.25)
70–74	33.52 (20.73–54.78)	29.11 (18.81–46.81)	17.09 (8.9–33.07)	12.33 (7.37–20.84)
75–79	53.62 (34.66–80.46)	46.70 (29.85–73.76)	26.63 (16.46–44.07)	21.02 (13.4–33.43)
≥80	88.93 (59.35–130.7)	86.82 (57.06–128.59)	59.65 (38.74–93.08)	52.46 (34.88–80.33)

Aortic disease includes aortic aneurysms and aortic dissections. Estimates are expressed as mean death rates per 100,000 of the general population, with 95% CIs. Adapted with permission from REF.⁵ CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

Signs and symptoms of a TAA can vary depending on the involvement of adjacent organs and/or structures and include: hoarseness (left recurrent laryngeal nerve), stridor (trachea and/or bronchi), shortness of breath (lung), dysphagia (oesophagus), plethora and oedema (superior vena cava). Patients might also complain of back, interscapular, left shoulder (descending TAA) and/or neck or jaw pain (aortic arch TAA). An aortic regurgitation murmur can be heard in the presence of aortic root or ascending TAA, owing to dysfunction of the aortic valve complex. Hypotension or shock usually signals haemorrhage (leaking or rupture) into the pleural and/or pericardial space. Rarely, gastrointestinal haemorrhage (aorto-oesophageal fistula) or haemoptysis (ascending TAA rupture into the left lung bronchus) can also be present^{1–3}. An unstable haemodynamic clinical scenario should trigger an emergency imaging test (CT) and subsequent therapeutic interventions, as for traumatic aortic injury (TAI).

Therapeutic interventions. The decision-making on timing and type of therapeutic intervention (thoracic endovascular aortic repair (TEVAR) and/or open surgery) for TAA is dependent on the patient’s clinical features and risk profile (presence or absence of Marfan syndrome or other elastopathy and major comorbidities), the anatomy of the aneurysm (location, size and growth rate) and expertise of the local aorta team.

Open surgery is indicated in patients with an asymptomatic ascending TAA (mostly associated with the aortic root and/or aortic arch) with an aneurysm maximum diameter of ≥55 mm and no elastopathy; perioperative mortality is 3–7%^{2,3,15,44}. Lower thresholds of aneurysm maximum diameter (40–50 mm) should be considered for repair in the presence of genetic disease and/or in patients undergoing aortic valve replacement^{2,3,15,44}. At present, endovascular repair for ascending TAAs

remains experimental and is the last resort for patients at very high surgical risk or in those presenting with isolated ascending lesions due to pseudoaneurysm or penetrating aortic ulcer (PAU)^{44,49,50}.

In patients with a descending TAA, intervention should be considered if the aneurysm maximum diameter is ≥60 mm (REF.¹¹). A lower threshold (50–55 mm) needs to be used for women and/or in the presence of connective tissue disorders¹¹. TEVAR should be preferred to open surgery in both ‘fit’ and ‘unfit’ individuals with a suitable anatomy but without associated elastopathy¹¹. Open surgery can be a valid alternative in ‘fit’ individuals, those with Marfan syndrome or other elastopathies, and/or those in whom TEVAR is not feasible (no adequate arterial access, the presence of a hostile abdomen (changes to the physiological proportions of the intra-abdominal organs and structures, usually caused by substantial adhesions), severe aorto-iliac disease, or the absence of proximal or distal landing zones)¹¹. Perioperative mortality is lower with TEVAR than with open repair (1.9% versus 5.7%) but overall mid-term survival does not differ significantly between the two approaches^{2,3,44,51}. In addition, definitive data on long-term outcomes are lacking^{2,3,44,52}. Given that no randomized trials have compared endovascular and open repair of descending TAAs, the above recommendations are derived from meta-analyses, single-centre studies, registries and administrative databases^{2,3,15,44}.

Abdominal aortic aneurysms

Epidemiology and risk factors. AAAs are defined as a localized enlargement of the abdominal aorta to a diameter of ≥30 mm imaged using abdominal ultrasonography or CT, are mostly localized at the level of the infrarenal aorta and are a degenerative disease of ageing^{2,3}. Indeed, the incidence of AAAs increases substantially in men aged >55 years and in women aged >70 years^{2,3,15,53}. Of note, although the incidence of TAAs and AADs has been stable or even increasing over time^{2–4,6,14–19,54–59}, a decline in the global prevalence and incidence rates of AAAs has been observed, particularly in Australasia, (high-income) North America and Western Europe⁶⁰ (TABLE 6). Population-wide screening programmes targeting men aged 65 years in Sweden and the UK have shown a prevalence of AAAs as low as 1.0–1.5%^{61,62}. This epidemiological pattern might be related to the increasing implementation of cardiovascular disease prevention programmes, including smoking-cessation strategies^{40,60}. Indeed, the risk of developing AAAs and aneurysmal growth is strikingly higher among current smokers (potentially also those using e-cigarettes) than among former smokers. The risk increases with smoking duration and intensity (number of cigarettes smoked per day) and decreases over time after quitting^{63–66}.

Additional risk factors include male sex (the male-to-female ratio ranges from 4:1 to 5:1), concomitant atherosclerotic cardiovascular diseases (coronary heart disease, peripheral arterial occlusive disease or stroke), systemic arterial hypertension, dyslipidaemia and obesity^{67–70}. A reduced risk of AAAs has been reported among African American, Asian and Hispanic

individuals compared with white individuals⁶³. About 20% of patients with AAAs have a family history of AAAs, suggesting a genetic predisposition to the disease^{1,2}.

Screening. Given the natural history of AAAs and data from epidemiological studies, the ESC guidelines on aortic diseases recommend population screening with the use of abdominal ultrasonography in all men aged >65 years². In addition, abdominal ultrasonography screening can also be considered in women aged >65 years who smoke or have a history of smoking and in first-degree siblings of patients with an AAA². If no structured screening programme exists, performing a quick ‘ultrasound check’ of the abdominal aorta in patients at risk of AAA who are undergoing TTE examination for other indications is advised (opportunistic screening). This strategy seems to be cost-effective in detecting otherwise-unknown AAAs².

Natural history. As with TAAs, AAAs are usually characterized by a long-term asymptomatic phase (growth rate ~1–6 mm per year). Aortic expansion and impending rupture should be suspected in the presence of a steady, gnawing pain or discomfort in the lower back and/or hypogastrium^{1–3}. AAA rupture causes 150,000–200,000 deaths each year worldwide⁶. Mortality is 60–70%, with hypotension and shock being common². Of note, symptomatic AAA is a surgical emergency, similar to TAI².

Diagnosis. The diagnosis of an AAA is usually made by chance during imaging tests (mainly abdominal ultrasonography or CT angiography) performed for other reasons, as part of ultrasonography screening programmes, if a patient complains of pain with an aortic origin or during routine physical examination².

Therapeutic interventions. Given the high morbidity and mortality associated with ruptured AAAs, timely diagnosis and elective AAA repair are essential to prevent an acute aortic event^{2,12,13,44,71}. The elective repair of asymptomatic AAAs is indicated if the AAA diameter is >55 mm in men or >50 mm in women (inner-to-inner maximum anterior–posterior aortic diameter on ultrasonography)^{13,72}. Furthermore, prompt referral to a vascular surgeon should be considered if the AAA growth rate is >10 mm per year¹³. In patients who are eligible for either endovascular aneurysm repair (EVAR) or open repair, the final therapeutic decision should be made by the aorta team on the basis of a comprehensive clinical evaluation that includes the patient’s preference^{2,12,13,44,71,72}. Randomized trials, large observational studies and meta-analyses have shown lower perioperative morbidity and mortality with EVAR than with open surgery (in-hospital mortality 1.4% versus 4.2%)^{44,73–79}. However, the short-term survival benefit of EVAR over open surgery is counterbalanced by higher rates of long-term complications and death^{44,80,81}.

Patient factors favouring open repair of AAAs (the preferred strategy according to the 2020 NICE guidelines⁷¹) include younger age, long life expectancy (>10 years), few or no medical comorbidities, the presence of a connective tissue disorder and an anatomy not suitable for EVAR^{44,72}. Conversely, factors favouring EVAR (the preferred strategy according to the 2019 European Society for Vascular Surgery guidelines¹³) include older age, reasonable life expectancy (the majority of candidate patients), multiple medical comorbidities, previous aortic surgery and/or previous abdominal surgery^{44,72}. Of note, AAA repair is not recommended in patients with limited life expectancy (for example, those with terminal cancer or severe heart failure)^{13,72}. For symptomatic AAA, urgent (emergency, if a rupture is present) open or endovascular repair is indicated after an imaging evaluation (CT angiography in the majority of patients or, much less commonly, MRI)^{2,12,82}. Perioperative mortality is ~38% with open repair and ~25% with endovascular repair; the risk of death also depends on the complexity of the AAA^{2,12,82}.

Table 2 | Features of TAAs and AAAs^{2,11–13}

Feature	TAA	AAA
Male-to-female ratio	2:1 to 4:1	4:1 to 5:1
Risk factors	Atherosclerosis, smoking, syndromic disorders (such as Marfan syndrome), non-syndromic disorders, bicuspid aortic valve, infectious or non-infectious aortitis, and traumatic injury	Smoking, age >60 years, atherosclerosis, hypertension, male sex, AAA in first-degree relatives, dyslipidaemia and obesity
Preventive measures	Healthy lifestyle, cardiovascular risk-factor modifications, and educational and screening programmes	Healthy lifestyle, cardiovascular risk-factor modifications, and educational and screening programmes
Screening	TTE	A-US
Signs and symptoms	Long asymptomatic phase; back, interscapular or left shoulder pain (descending TAA), or neck or jaw pain (aortic arch TAA); involvement of adjacent organs and/or structures In the event of rupture: hypotension and/or shock, gastrointestinal haemorrhage (rare) or haemoptysis (rare)	Long asymptomatic phase, pulsatile abdominal mass, atypical abdominal or back pain In the event of rupture: intense pain, hypotension and fast pulse
Diagnostic test	TTE plus CT angiography or MRI	A-US plus CT angiography or MRI
Surveillance	Using TTE plus MRI if needed, annually if TAA diameter is <45 mm, or every 6 months if TAA diameter is 45–55 mm	Using A-US, every 3 years if AAA diameter is 30–39 mm, annually if AAA diameter is 40–49 mm, or every 3–6 months if AAA diameter is ≥50 mm
Treatment	TAA repair is indicated if TAA diameter is ≥50 mm in women or in patients with connective tissue disorders; or if TAA diameter is ≥55 mm in patients with no connective tissue disorder TEVAR is often preferred to open surgery for anatomically suitable descending aorta aneurysms ≥55 mm in patients without connective tissue disorders	AAA repair is indicated if AAA diameter is >55 mm in men or >50 mm in women or aneurysm growth is >10 mm per year Among patients with an aneurysm that is anatomically suitable for EVAR and who are at an acceptable surgical risk, either open or endovascular aortic repair is recommended

AAA, abdominal aortic aneurysm; A-US, abdominal ultrasonography; EVAR, endovascular aneurysm repair; TAA, thoracic aortic aneurysm; TEVAR, thoracic endovascular aortic repair; TTE, 2D transthoracic colour–Doppler echocardiography.

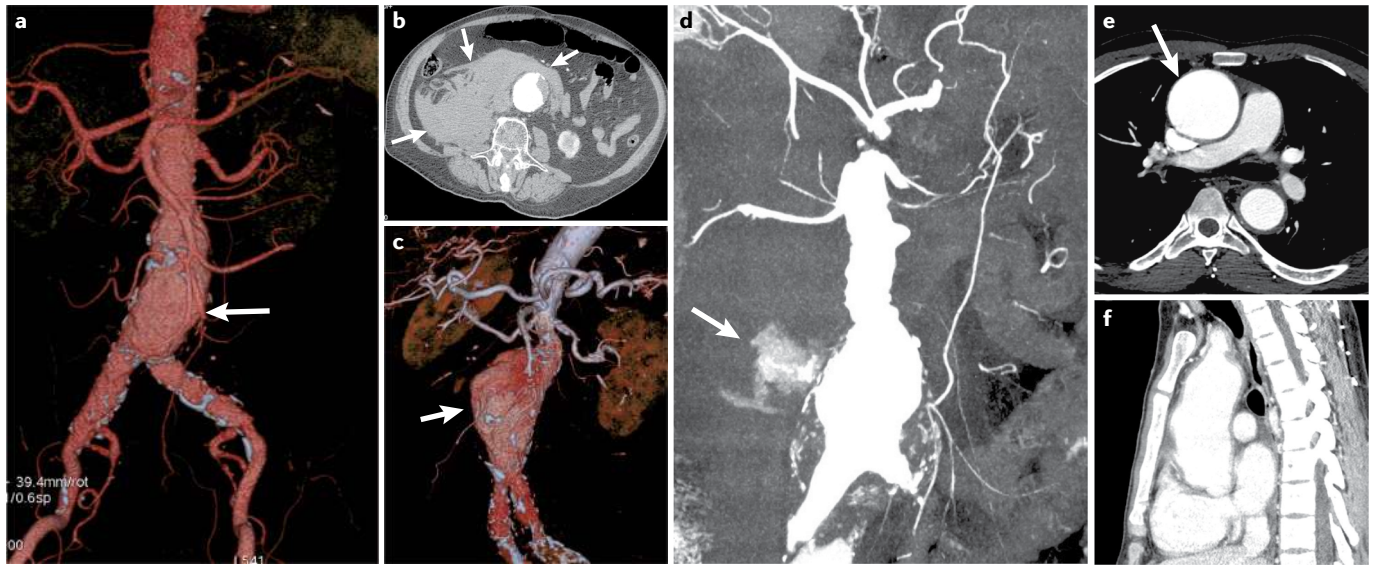


Fig. 2 | Imaging of aortic aneurysms. **a** | Volume-rendered, contrast-enhanced CT reconstruction showing an abdominal aortic aneurysm (AAA) in the subrenal segment (arrow), without leakage. There is evidence of atherosclerotic disease of the aortic wall, with multiple calcified plaques. **b** | Axial contrast-enhanced CT image showing an AAA complicated by wall leakage and active bleeding. The aneurysm is surrounded by a large haematoma contained by retroperitoneal fasciae (arrows). No blood is present inside the peritoneal cavity. **c** | Volume-rendered, contrast-enhanced CT reconstruction showing an AAA complicated by wall leakage

(arrow) and extraluminal spread of contrast medium. **d** | Maximum-intensity projection reconstruction depicting the extravasation of contrast medium outside the aortic wall (arrow) owing to aneurysm wall rupture. **e** | Axial contrast-enhanced CT image showing a large aneurysm in the thoracic ascending aortic segment (arrow). **f** | Maximum-intensity projection sagittal reconstruction showing an ascending aorta aneurysm extending from the valvular plane up to the beginning of the aortic arch. Images courtesy of L. Romano (A. Cardarelli Hospital, Naples, Italy).

Acute aortic syndromes

AAS are a group of interrelated, life-threatening conditions that encompass classic aortic dissection, intramural haematoma (IMH), PAU, aortic pseudoaneurysm and TAI affecting the aortic wall (predominantly the intima and media). AAS are characterized by similar clinical manifestations and have shared diagnostic and management pathways^{2,3} (FIGS 4,5).

AAS are classified by anatomical and temporal features. The DeBakey and Stanford systems are the most commonly used anatomical classifications. The DeBakey system takes into account the origin of the intimal tear and the extent of dissection; the Stanford system divides AAS into two categories regardless of the site of origin: type A involving the ascending aorta and type B not involving the ascending aorta^{2,3} (FIG. 6). The term non-A-non-B AAD has been introduced to indicate any involvement of the aortic arch extending to the descending aorta, independent of the primary location of the entry tear⁸³.

In terms of temporal considerations (from initial onset of symptoms to hospital presentation), the ESC guidelines on aortic diseases distinguish between acute (<14 days), subacute (15–90 days) and chronic (>90 days) dissection^{2,3}. Conversely, the IRAD published a time survival classification in relation to dissection location (type A versus type B) and therapy provided (medical, endovascular or open surgery). Four time domains characterized by progressively lower overall survival rates were identified: hyperacute (<24 h), acute (2–7 days), subacute (8–30 days) and chronic (>30 days)⁷. This approach seems to be a comprehensive

method to characterize patients with AAD and to plan appropriate therapeutic interventions.

Acute aortic dissection

Incidence

Classic AAD (comprising 80–90% of all AAS) is characterized by the presence of an intimal flap separating the true lumen from the false lumen^{2–4}. Population-based studies suggest an incidence of 2.6 to 3.5 cases per 100,000 person-years (6,000 to 10,000 cases annually in the USA)^{54,55}. A higher incidence of AAD (6 per 100,000 person-years including out-of-hospital deaths) was reported over a 10-year period (2002–2012) in the Oxfordshire (UK) population ($n=92,728$; 94% white)⁵⁶. Furthermore, on the basis of the 2010 Office for National Statistics population projections, an increase in incident dissection events from 3,892 in 2010 to 6,893 in 2050 has been predicted in the UK in both men and women, mainly among those aged >75 years^{56,57} (FIG. 7). Data from the Swedish National Patient Register and the Cause of Death Register (a retrospective population-based registry study from 2002 to 2016 involving autopsy information and a total of 8,057 patients with AAD receiving in-hospital or out-of-hospital care) indicate a mean annual incidence of AAD of 7.2 per 100,000 of the general population (9.1 per 100,000 men versus 5.4 per 100,000 women; $P<0.001$)⁸⁴. Trend analysis highlighted a decreasing incidence over time in men ($P=0.005$) but no change in women ($P=0.105$)⁸⁴. From these studies, the number of cases of AAD seems to be increasing in Western countries, probably related to heightened clinical awareness of the condition as well as an exponential increase in the

availability and use of imaging techniques (particularly CT) in emergency departments^{7,85}. However, high-quality epidemiological data of AAD remain insufficient, owing to the lack of comprehensive, global, prospective population studies². In addition, identifying cases of AAD that result in sudden cardiac death and/or pre-hospital death is objectively challenging, unless autopsies are undertaken^{2-4,56}. Of note, the occurrence of AAD shows chronobiological patterns⁷. In particular, the frequency of AAD is higher in the morning hours (with a peak between 0800 and 0900 hours) and in the winter (with a peak in January in the northern hemisphere)⁷.

Demographics

The majority (~65%) of patients with AAD are male, with AAD most commonly occurring in the seventh decade of life (mean age 63 years)^{2,3,7,86}. Older patients (aged ≥70 years) present less frequently with typical signs and symptoms⁸⁷. Systemic hypertension, atherosclerosis and iatrogenic causes are more prevalent in older patients, whereas Marfan syndrome is seen predominantly in younger patients (aged <70 years)⁸⁷. Patients

aged ≥70 years have an overall higher in-hospital mortality than patients aged <70 years (type A AAD, 43% versus 28%, *P* = 0.0006; type B AAD, 16% versus 10%, *P* = 0.07)^{7,87}.

AAD occurs less frequently in women than in men (women comprised ~32% of all patients enrolled in the IRAD) but women are significantly older than men at the onset of AAD (AAD occurs on average 6 or 7 years later in women; 50% of women with AAD are aged ≥70 years)²⁶. In patients with AAD, systemic hypertension is more common in women than in men (77.5% versus 69.2%; *P* = 0.006) whereas previous cardiac surgery is less frequent in women than in men (16.9% versus 24.0%; *P* = 0.02)²⁶. Furthermore, a delayed time from onset of AAD symptoms to hospital presentation has been reported in women compared with men²⁶. Overall in-hospital mortality is higher in women than in men (30.1% versus 21.0%; *P* = 0.001), mainly driven by higher mortality with surgical treatment of type A AAD (31.9% versus 21.9%; *P* = 0.013)^{7,86}.

African American individuals (14% of 1,354 patients with AAD enrolled in the 13 US centres participating

Table 3 | Genetic syndromes associated with thoracic aortic aneurysm and dissection

Genetic syndrome	Prevalence; incidence ^a	Common clinical features	Genes involved	Samples for diagnostic testing	Comments on aortic disease
Marfan syndrome	15/100,000; 25/100,000 ^b	Skeletal features, ectopia lentis, dural ectasia	<i>FBN1</i> ^c	Ghent diagnostic criteria; DNA for sequencing ^d	Surgical repair when the aorta reaches 50 mm unless the patient has a family history of aortic dissection at <50 mm, a rapidly expanding aneurysm or presence of clinically significant aortic valve regurgitation
Loeys–Dietz syndrome	Reported in 52 families	Bifid uvula or cleft palate, arterial tortuosity, hypertelorism, skeletal features similar to those in Marfan syndrome, craniosynostosis, aneurysms and dissections of other arteries	<i>TGFBR2</i> or <i>TGFBR1</i>	DNA for sequencing	Surgical repair recommended at an aortic diameter of >42 mm by TEE (internal diameter) or 44–46 mm by CT and/or MRI (external diameter)
Ehlers–Danlos syndrome type IV or vascular type	1/100,000 ^b ; 1/10,000–25,000	Thin translucent skin, gastrointestinal rupture, rupture of the gravid uterus, rupture of medium-sized and large arteries	<i>COL3A1</i>	DNA for sequencing, dermal fibroblasts for analysis of type III collagen	Surgical repair is complicated by friable tissues; non-invasive imaging is recommended
Turner syndrome	5.5/100,000 (birth prevalence) ^b ; 1/2,000–2,500	Short stature, primary amenorrhoea, bicuspid aortic valve, aortic coarctation, webbed neck, low-set ears, low hairline, broad chest	45, X karyotype	Blood cells for karyotype analysis	Risk of aortic dissection is increased in patients with bicuspid aortic valve, aortic coarctation, hypertension or pregnancy
Arterial tortuosity syndrome	<1/100,000; unknown (102 cases)	Tortuosity, stenosis and aneurysm of large-sized and medium-sized arteries; altered facial features; soft, hyperextensible skin; skeletal features similar to those in Marfan syndrome	<i>SLC2A10</i>	DNA for sequencing	Aortic tortuosity, stenosis and aneurysm; management requires baseline whole-body vascular imaging and follow-up should be individually tailored
Aneurysms–osteoarthritis syndrome	<1/100,000; unknown	Tortuosity, aneurysms and dissections throughout the arterial tree; early-onset joint abnormalities; craniofacial, skin and skeletal features similar to those in Marfan syndrome and Loeys–Dietz syndrome	<i>SMAD3</i>	DNA for sequencing	Aortic aneurysms and dissections; some physicians suggest aggressive surgical management, as is recommended for Loeys–Dietz syndrome

TEE, transoesophageal echocardiography. ^aData on prevalence and incidence are global unless otherwise indicated. ^bData from Europe only (<http://www.orpha.net>). ^cGenetic variants in *TGFBR2* have also been associated with Marfan syndrome, but the clinical phenotype is debated. ^dScreening is recommended for first-degree relatives; all affected family members should undergo regular aortic imaging. Data from REFS^{2,3}.

Table 4 | Aortic diseases associated with BAV

Prevalence (%)	Incidence (%)	Gene involved	Screening	Prevalence of BAV in aortic dissection (%)		BAV type	Percent of patients	Comments on aortic disease
				Type A	Type B			
1.0–2.0	0.5–2.0	NOTCH1	First-degree relatives, using transthoracic echocardiography	2–9	3	LCC–RCC	70	Ascending aortic dilatation is common; aortic root dilatation; aortic coarctation
						RCC–NCC	10–20	Aortic root is rarely affected; dilatation of the ascending aorta
						LCC–NCC	5–10	–

BAV, bicuspid aortic valve; LCC, left coronary cusp; NCC, non-coronary cusp; RCC, right coronary cusp. Data from REF.⁴.

in the IRAD) more frequently have type B AAD than white individuals (52.4% versus 39.3%; $P = 0.001$)⁸⁸. Furthermore, African American patients with AAD are younger (mean age 54.6 ± 12.8 years versus 64.2 ± 15.2 years; $P < 0.001$) and more likely to have a history of cocaine abuse, hypertension and diabetes than white individuals⁸⁸. No significant differences in clinical features, management and outcomes have been observed between African American and white patients with AAD⁸⁸.

The relationship (if any) between BMI and AAD remains a matter of debate. A preliminary analysis from the IRAD showed no significant effect of BMI on overall in-hospital outcomes with AAD⁸⁹. However, patients with a higher BMI presented to hospital with AAD at a younger age and were more likely to have hypertension and/or diabetes⁸⁹.

Risk factors

Conditions associated with the development of AAD overlap with those described for aortic aneurysms (BOX 1).

Systemic hypertension. Among the conditions associated with increased aortic wall stress, systemic hypertension (mostly uncontrolled by drug therapy) is by far the most common treatable pre-morbid risk factor^{2,3,7,58}. Systemic hypertension is present in approximately 75–80% of patients with AAD and is more frequent in those with type B AAD than in those with type A AAD (80.9% versus 74.4%; $P < 0.001$)^{2,3,7,19,85,86,90}. Of note, a history of hypertension remains, along with radiating pain and increasing age, an independent predictor of type A AAD even at aortic diameters of <55 mm (REF.⁸). This observation emphasizes the paramount importance of aggressive blood-pressure control to optimal levels (together with smoking cessation) in the presence or absence of evident effects on aortic structure^{2,3}. Given the high prevalence of asymptomatic hypertension in the general population, screening programmes for hypertension are recommended in all adults aged ≥ 18 years^{58,91}.

Cocaine use. Cocaine use seems to be associated with AAD. Among 3,584 patients enrolled in the IRAD, cocaine use was reported more often in those with type B AAD (2.4% of 1,252 patients) than in those with type A AAD (1.4% of 2,332 patients)⁹². The typical patient with cocaine use was fairly young (mean age 47.7 years for cocaine users versus 62.0 years for non-users in patients with type A AAD; 47.6 years versus 64.0 years, respectively, in patients with type B AAD)⁹². Black ethnicity, male sex and a history of tobacco use were significantly more common in the cocaine-using cohort⁹². The most frequent comorbidity was systemic hypertension, regardless of cocaine use ($>80\%$ of patients in the registry)⁹². In-hospital mortality among patients with type A AAD was lower among those using cocaine than among those not using cocaine (6.1% of 33 patients versus 25.5% of 2,332 patients; $P = 0.0012$), probably owing to the younger age of cocaine users⁹². No significant differences in in-hospital mortality among patients with type B AAD were reported between those taking and not taking cocaine (10.0% of 30 patients versus 10.4% of 1,252 patients; $P = 1.0$)⁹². Although similar all-cause mortality was reported at 5 years in the two groups, freedom from rehospitalization was lower among cocaine users than among cocaine non-users (59.5% versus 81.5%; $P = 0.001$)⁹². These data highlight

Table 5 | Non-syndromic familial thoracic aortic aneurysm and dissection

Gene involved	Contribution (%)	Associated clinical features	Comments on aortic disease
ACTA2	14	Livedo reticularis, iris floccule, patent ductus arteriosus, bicuspid aortic valve	Two of 13 patients with documented aortic dissections <50 mm; patients with thoracic aortic aneurysm and dissection also present with coronary artery disease, stroke and Moyamoya disease
TGFBR2	4	Thin translucent skin, arterial or aortic tortuosity, aneurysm of arteries	Multiple aortic dissections documented at aortic diameter of <50 mm
MYH11	1	Patent ductus arteriosus	Patients with documented aortic dissection at aortic diameter of 45 mm
MYLK	–	Abnormality of connective tissue, cutis marmorata, cystic medial necrosis of the aorta	Aortic dissection with little to no aortic enlargement
PRKG1	–	Erdheim cystic medial necrosis	Aortic aneurysm and acute aortic dissection at relatively young age

Data from REFS^{2,3}.

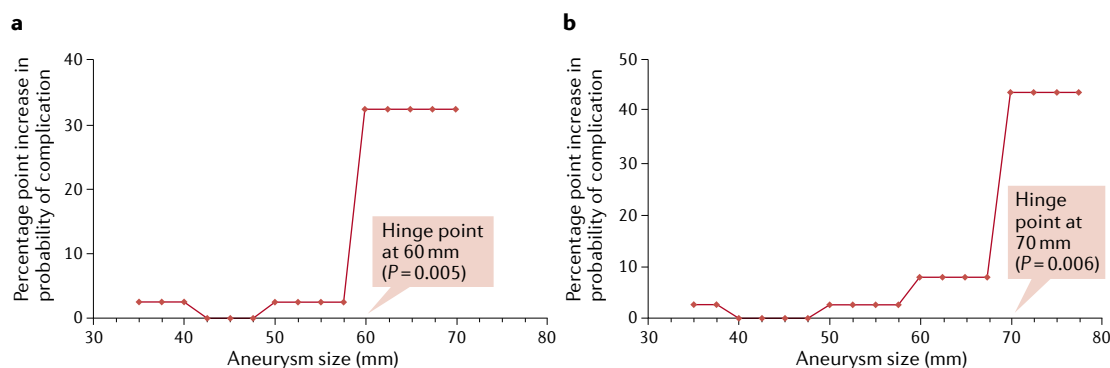


Fig. 3 | Effect of aortic aneurysm size on the risk of complications. Increasing thoracic aortic aneurysm (TAA) size confers an increased risk of dissection or rupture. Ascending TAAs with a diameter of ≥ 60 mm (part **a**) and descending TAAs with a diameter of ≥ 70 mm (part **b**) are widely regarded as being at very high risk of aortic dissection or rupture. However, in addition to the maximum aneurysm diameter, the risk of dissection or rupture is also related to the rate of aneurysm growth per year and the patient's demographic and clinical features, such as age, sex, smoking status, diastolic hypertension and aneurysm-related pain¹¹. Adapted with permission from REF.⁴⁸, Elsevier.

that a history of cocaine use should always be investigated in a young patient with AAD in order to provide specific substance abuse counselling if necessary.

Marfan syndrome. Marfan syndrome is the most frequent heritable (autosomal dominant) connective tissue aortic disorder and is caused by genetic variants in *FBNI*, which encodes fibrillin 1, a connective tissue protein^{93,94}. The estimated incidence of Marfan syndrome ranges between 2 and 3 per 10,000 individuals, in equal proportions among men and women⁹⁴. Marfan syndrome variably affects several organs and systems, including the cardiovascular system, skin, skeletal system, eyes, lungs and dura mater⁹³. Although any anatomical segment of the aorta can be involved, aortic root enlargement is present in the majority of patients (60–80%)⁹³. Prognosis is usually determined by progressive dilatation of the aorta, leading to aortic dissection and/or rupture⁹³, that occurs even at diameters of < 50 mm (REFS^{2,3,93}). Importantly, patients with pathogenic variants in *FBNI* and a maximum aortic diameter of < 50 mm who are receiving appropriate β -blocker therapy and are not practising strenuous sports seem to have low risk of AAD⁹⁵. Further studies are needed to define surgical intervention thresholds in relation to specific pathogenic variants in *FBNI*.

Among 6,424 consecutive patients with AAD enrolled in the IRAD, 258 (4%) had Marfan syndrome⁹⁶. As expected, type A AAD was more frequent than type B AAD, although the difference was not significant (63.6% versus 36.4%; $P = 0.691$)⁹⁶. Patients with Marfan syndrome were younger than patients without Marfan syndrome (aged 38.2 ± 13.2 years versus 63.0 ± 14.0 years; $P < 0.001$) and presented with fewer comorbid conditions (atherosclerosis and hypertension) at the time of AAD⁹⁶. The majority of patients with Marfan syndrome and type A AAD underwent open surgery (88.4%), with an in-hospital mortality of 13.1%⁹⁶. Conversely, 50% of patients with Marfan syndrome and type B AAD received only medical therapy, with an in-hospital mortality of 4.3%⁹⁶. Among the cohort of patients with Marfan syndrome and type B AAD who were managed

surgically (28.7%), no in-hospital deaths were reported⁹⁶. Endovascular treatment, which was implemented in 19.1% of patients with Marfan syndrome and type B AAD, was associated with an in-hospital mortality of 5.6%⁹⁶. These data suggest that when interventions are deemed necessary, open surgery should be considered rather than endovascular therapy². At 5 years in patients with either type A or type B AAD, no significant difference in survival was reported between those with Marfan syndrome and those without Marfan syndrome (80.1% versus 79.8%; $P = 0.712$)⁹⁶. However, patients with Marfan syndrome often underwent reinterventions (estimated freedom from reintervention rate among patients with Marfan syndrome versus those without Marfan syndrome: 44.7% versus 81.5%; $P < 0.001$)⁹⁶. Therefore, subspecialty aortic clinics including follow-up programmes are recommended for patients with Marfan syndrome or other genetic aortopathies^{2,3,7,97}.

Bicuspid aortic valve. BAV disease is the most common congenital cardiac defect (prevalence at birth 1–2%; male-to-female ratio 2:1 to 4:1)^{2,3} (TABLE 4). Most experts recommend screening of first-degree relatives of individuals with BAV². Although BAV can be found as an isolated condition, it is also present in several cardiovascular malformations and genetic syndromes, most frequently in patients with ventricular septal defects (10%), coarctation (50–75%) or Turner syndrome (30%)^{2,3,93}. In particular, BAV is a risk factor for aortic dilatation, aneurysm formation and aortic dissection or rupture². Among the several phenotypes of ascending aneurysm described, the aneurysm most frequently (60–70% of patients) involves the tubular ascending aorta and is independent of valve pathophysiology⁹⁸. The real prevalence of BAV in patients with aortic dissection is not clearly defined, mainly owing to pre-emptive surgical interventions on the ascending aorta^{2,3}. Current data indicate a prevalence of BAV in patients with AAD only slightly higher than that in the general population². Among 3,393 patients with AAD enrolled in the IRAD, 113 (3.3%) had BAV, comprising 93 (82.3%) type A AAD and 20 (17.7%) type B

AAD⁹⁹. The familial tendency for BAV and aortopathy is noteworthy^{2,3,99}.

Iatrogenic dissection. Among 108,083 consecutive cardiac catheterizations (66,354 diagnostic procedures and 41,729 therapeutic procedures), the Registry on Aortic Iatrogenic Dissection (RAID) reported only 74 patients with iatrogenic catheter dissection of the ascending aorta (66.9 ± 10.8 years, 67.6% men)¹⁰⁰. A total of 35 of these patients underwent angioplasty with stenting, three underwent cardiac surgery and 36 were treated conservatively¹⁰⁰. Only two patients died after the aortic dissection from cardiogenic shock. No major dissection-related complications were recorded during follow-up (median 51.2 months)¹⁰⁰. These data indicate that iatrogenic catheter dissection of the ascending aorta is rare and is usually characterized by a favourable short-term and long-term prognosis with a conservative (non-surgical) approach.

Insights into AAD from IRAD

The IRAD, established in 1996, is a voluntary, observational, non-randomized registry involving 51 specialized aortic centres, mostly located in the Western world^{7,101}. Interestingly, trends analysis of data collected over the past two decades (1996–2013) has yielded important observations on predisposing conditions, presentation, management and outcomes of AAD^{85,102}. Of note, data from the IRAD need to be interpreted in the context of the limitations that are intrinsic to the registry design^{7,85,101}. First, results cannot be generalized to low-income and middle-income countries. Second, data are collected partly retrospectively, and no core imaging laboratory is available. Third, treatment is decided by individual physicians rather than by protocol-driven approaches. Finally, the IRAD does not include patients who died before reaching IRAD-participating centres or who were not transferred from community hospitals^{7,85,101,102}.

Demographics, clinical characteristics and diagnosis.

Among 4,428 patients enrolled at 28 IRAD centres between 1996 and 2013, type A AAD was more frequent than type B AAD (67% versus 33%)^{7,85}. Demographic and clinical characteristics did not change over time.

The majority of patients were white men (two-thirds of the study population) in the seventh decade of life, and patients with type B AAD were generally older than those with type A AAD (64 ± 14.1 years versus 62 ± 14.6 years; *P* < 0.001)^{7,85}. Systemic hypertension was by far the most common risk factor and was more prevalent among patients with type B AAD than among those with type A AAD (81% versus 74%)^{7,85}. Severe or worst-ever pain (93% for type A AAD and 94% for type B AAD) and chest pain (83% for type A AAD and 71% for type B AAD) were the most common presenting complaints^{7,85}. Back pain was more frequent in patients with type B than in those with type A AAD (70% versus 43%)^{7,85}. However, clinical manifestations can be diverse and variously overlap. Of note, in a small proportion of patients (<6%), AAD can present without pain^{7,85}. Chest radiography and electrocardiography have a low diagnostic accuracy and can be within normal limits in a substantial number of patients (28% and 39%, respectively)^{7,85}. The use of CT (which has high diagnostic accuracy, is widely available in emergency departments, and is easily and rapidly accessible) as the initial diagnostic imaging modality in type A AAD increased from 46% to 73% (*P* < 0.001) between 1996 and 2013 and consistently increased by 80–85% in type B AAD^{7,85}. Therefore, CT is firmly established as the first-line diagnostic imaging technique in the acute setting, followed by transoesophageal echocardiography (TEE) and, more rarely, MRI or aortography¹⁰³. However, given that all the above imaging techniques yield reliable diagnostic accuracy in AAS, the choice mainly depends on local institutional factors (expertise and availability) as well as patient clinical condition^{2,3,103}. Of note, some patients can require more than one imaging test not only to confirm the diagnosis but also to help to plan the most appropriate therapeutic interventions^{2,3,7,103}.

In real-world clinical practice, substantial time delays still occur from symptom onset to diagnosis and therapy, especially among patients (more often women) with atypical symptoms, those who have undergone previous cardiac surgery and those who are initially referred to a community hospital and then transferred to tertiary referral sites with expertise and experience in aortic disease⁷. Therefore, a timely and accurate diagnosis of

Table 6 | Incidence and prevalence of abdominal aortic aneurysms

Age (years)	Developed countries				Developing countries			
	Incidence		Prevalence		Incidence		Prevalence	
	1990	2010	1990	2010	1990	2010	1990	2010
50–54	44.7	40.6	156.5	142.1	33.6	33.4	118.0	116.6
55–59	81.7	74.0	440.2	397.7	61.3	61.7	332.8	333.6
60–64	125.1	116.5	894.5	827.9	94.9	94.3	685.3	678.2
65–69	157.9	147.6	1,501.9	1,402.7	123.3	121.1	1,165.5	1,146.3
70–74	177.3	158.4	2,171.3	1,943.9	144.8	139.3	1,709.3	1,654.7
75–79	189.3	175.1	2,666.9	2,478.6	163.5	157.6	2,190.1	2,139.3
≥ 80	223.2	203.4	3,404.3	3,157.3	197.9	188.6	2,883.0	2,836.2

All data are per 100,000 of the general population. Adapted with permission from REF.⁶⁰ CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

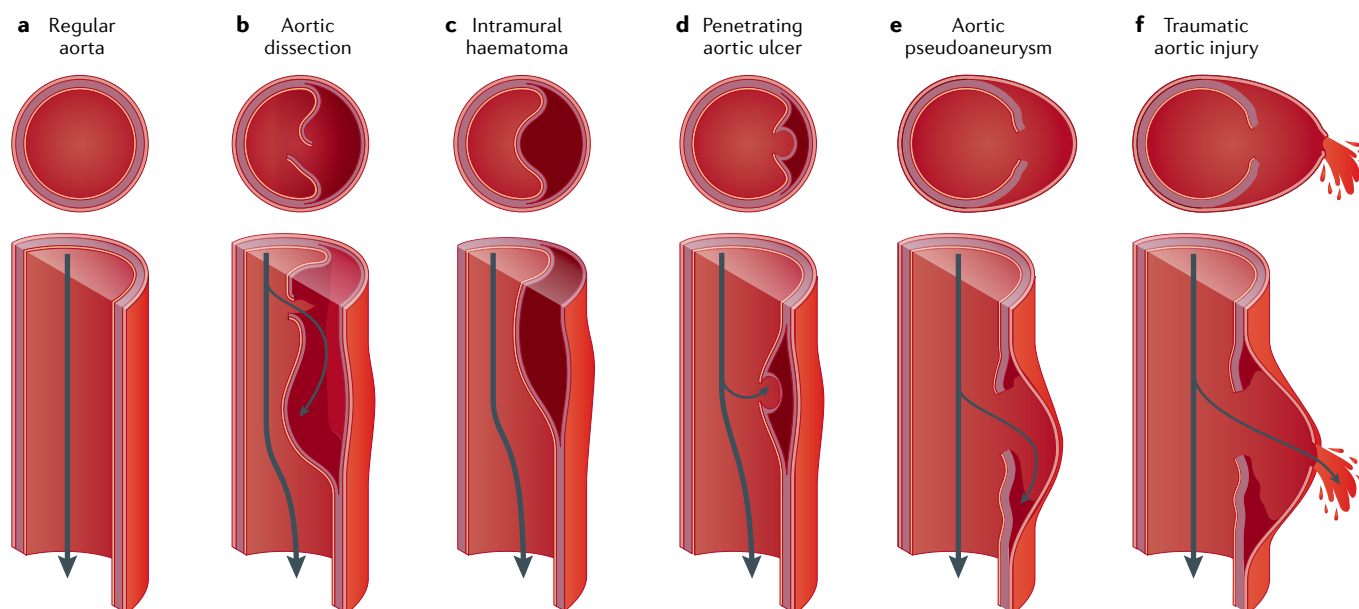


Fig. 4 | **Acute aortic syndromes.** **a** | Normal aorta. **b** | Classic aortic dissection: disruption of the medial layer results in separation of the aortic wall layers and subsequent formation of true and false lumens divided by an intimal flap. **c** | Intramural haematoma can develop in the media of the aortic wall in the absence of a false lumen and intimal tear. **d** | Penetrating aortic ulcer: ulceration of an aortic atherosclerotic plaque, penetrating through the internal elastic lamina into the media. **e** | Pseudoaneurysm: dilatation of the aorta owing to disruption of all the aortic wall layers, contained only by the periaortic connective tissue. **f** | Traumatic aortic injury: rupture of all aortic wall layers caused by a trauma.

AAD remains challenging and requires a high clinical index of suspicion by the care team. In this regard, the ESC guidelines² on aortic diseases have designed a diagnostic multiparametric algorithm based on the clinical aortic dissection detection risk score, which was developed in the 2010 AHA/ACC guidelines for the management of thoracic aortic disease (sensitivity >95%)^{2,3}. The algorithm also includes the measurement of the plasma D-dimer level (to rule out classic AAD within the first 6 h of symptom onset; cut-off level $\geq 500 \mu\text{g/l}$) and the assessment of imaging (TTE plus CT or TEE) markers of AAD^{2,3}. Use of the clinical AAD detection risk score should be encouraged at first medical contact, and patients with a moderate to high risk of AAD should be rapidly transferred to tertiary referral centres, by-passing community hospitals if possible⁴.

Management and in-hospital outcomes. Between 1996 and 2013, surgical management of type A AAD increased from 79% to 90% ($P < 0.001$) in all patients⁸⁵. Endovascular management of complicated type B AAD increased from 7% to 31% ($P < 0.001$)⁸⁵. Complicated type B AAD is currently defined by the presence of one or more of the following: persistent or recurrent pain, uncontrolled hypertension despite full medication, early or rapid aortic expansion, signs of aortic rupture (haemothorax, increasing periaortic and mediastinal haematoma) or malperfusion syndrome (the most frequent complication, present in ~30% of patients, and involving the renal, visceral, spinal and/or lower-extremity vasculature; mesenteric compromise is associated with a high early mortality of >30%)^{2,104}. By contrast, uncomplicated type B AAD

is a clinically stable condition, with none of these complications^{2,104}.

In-hospital mortality for type A AAD decreased significantly from 31% to 22% between 1996 and 2013 ($P < 0.001$), mainly due to decreased surgical mortality (25% to 18%; $P < 0.003$)^{7,85}. In-hospital mortality for type B AAD did not change significantly (12% to 14%)^{7,85} (FIG. 8). Accordingly, a strong interest exists in redefining complicated versus uncomplicated type B AAD, taking into account high-risk imaging features (primary entry tear diameter >10 mm, initial total aortic diameter ≥ 40 mm, false lumen ≥ 22 mm, patent false lumen or partially thrombosed false lumen) indicating unstable disease in apparently clinically stable patients^{104–106}. As a consequence, an increasing number of patients with type B AAD are likely to undergo pre-emptive TEVAR rather than medical therapy alone¹⁰⁷.

Variants of aortic dissection

IMH and PAU are variants on the spectrum of AAS^{2,3} (FIG. 4). Although the two conditions often overlap, IMH (and AAD) primarily affect the media, whereas PAU primarily affects the intima¹⁰⁸. In the majority (60–70%) of patients, IMH and PAU occur in the descending thoracic aorta^{2,3,86}. The clinical course remains uncertain and is highly dependent on anatomical location and anatomic-pathological features of the lesion as well as the patient's risk profile^{2,3}. Current therapeutic interventions are quite similar for IMH and PAU, and usually consist of surgery for type A and medical therapy for uncomplicated type B^{2–4}. In complicated type B, endovascular treatment (TEVAR or EVAR) is preferred (if not contraindicated) to surgical treatment^{2–4,109}.

Intramural haematoma

IMH comprises 5–25% of all cases of AAS (1.2 cases per 100,000 person-years)^{2,3,59,86}. Interestingly, investigators from South Korea and Japan have reported significantly higher rates of IMH than in the IRAD (28.9% versus 5.7% of AAD)¹¹⁰. This difference might be partially explained by the exclusion from the IRAD of patients admitted to primary care centres who are not transferred to IRAD-participating centres⁷. However, the clinical features seem to be similar irrespective of the geographical region of origin. Compared with AAD, patients with IMH tend to be older (mean age approximately one decade older) but present with identical symptoms (predominantly acute chest or back pain) and risk factors^{2,3,59,86}. In type A IMH, aortic regurgitation, malperfusion syndrome and pulse deficits are less likely than in type A AAD, whereas periaortic haematoma and pericardial effusion are more frequent^{7,59,111,112}.

Diagnosis. Unenhanced followed by contrast-enhanced CT is considered the first-line imaging technique to diagnose IMH (sensitivity up to 96%)^{2,3,103}. Crescentic or circular aortic wall thickening without an intimal flap or tear is the diagnostic hallmark of IMH^{2,3,103}.

MRI has similarly high accuracy and can be complementary to CT for detecting small IMHs and for distinguishing between TAA thrombi and IMH, but is generally not readily available or feasible in the acute setting¹⁰³. The capacity of TEE to detect IMH is slightly lower than that of CT or MRI¹⁰³.

Natural history and clinical outcomes. IMH is characterized by a dynamic process, which can progress to AAD (16–47% of patients) and/or aortic rupture (20–45% of patients)^{86,113}. Regression is seen in <10% of patients^{86,113}. In-hospital and long-term outcomes are similar to those of AAD⁷. In-hospital mortality for type A IMH is 26.6% (surgical 24.1% and medical 40.0%) compared with 4.4% for type B IMH (surgical 20.0% and medical 3.8%)⁷. Mortality is higher the closer the haematoma is to the aortic valvular complex, regardless of medical or surgical treatment¹¹².

Of note, a marked difference in the management and outcomes of patients with type A IMH exists in Eastern countries compared with Western countries. First, the majority (80.8%) of patients are initially managed only with medical treatment instead of open surgery, which is recommended by current guidelines in Western

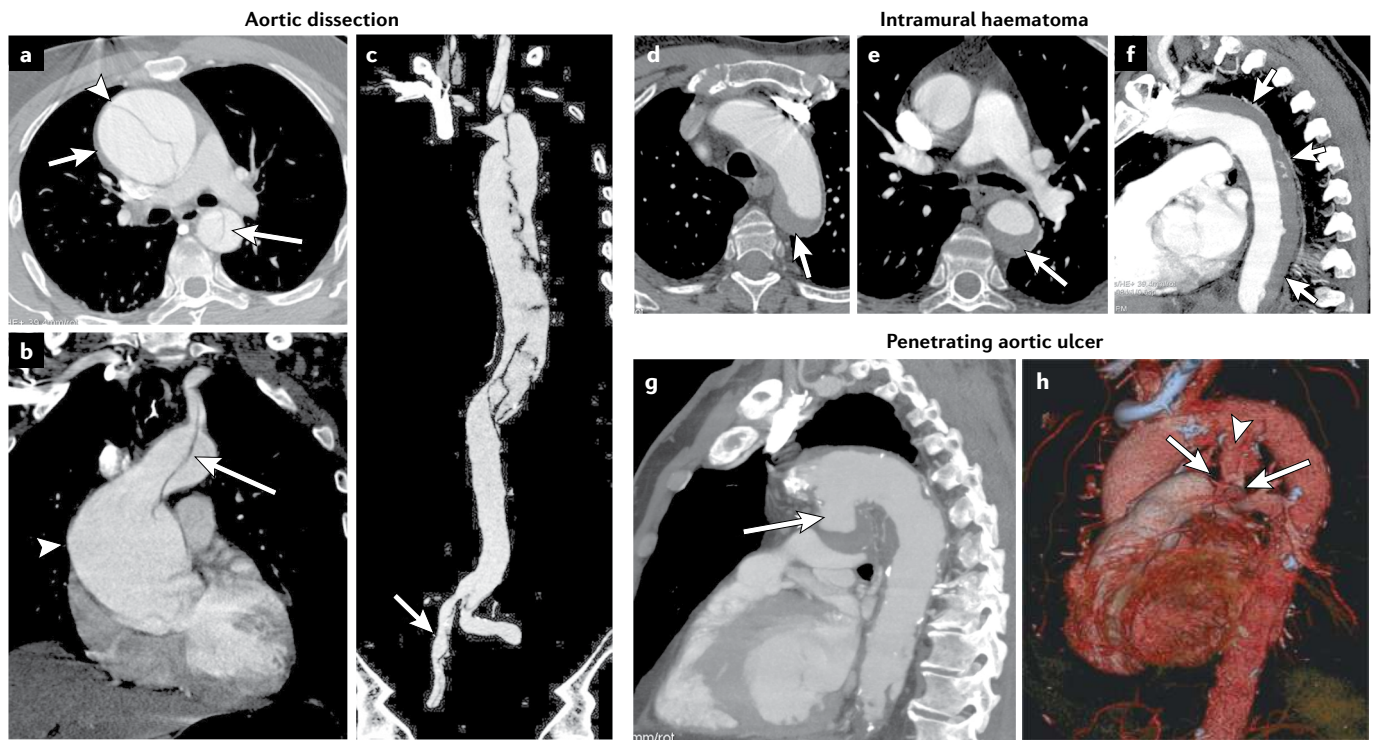


Fig. 5 | Imaging of acute aortic syndromes. a | Aortic dissection. Axial contrast-enhanced CT image showing an ascending thoracic aortic aneurysm (TAA; arrowhead) complicated by a type A dissection (arrows) caused by elastic tissue dystrophy in a patient with Marfan syndrome. **b** | Coronal contrast-enhanced CT reconstruction showing an ascending TAA (arrowhead) with an intimal dissection (arrow) that extends into the anonymous trunk lumen in a patient with Marfan syndrome. **c** | Coronal contrast-enhanced CT reconstruction showing an intimal flap inside the aortic lumen that extends into the common right iliac artery lumen (arrow). **d** | Intramural haematoma. Axial contrast-enhanced CT image showing a thoracic aortic arch haematoma with intramural blood collection (arrow).

e | Axial contrast-enhanced CT image showing a descending thoracic aortic haematoma with intramural semilunar blood collection (arrow). **f** | Sagittal contrast-enhanced CT reconstruction showing a descending thoracic aortic haematoma with intramural blood collection (arrows) with a decreased diameter of the aortic lumen. **g** | Penetrating aortic ulcer. Oblique sagittal contrast-enhanced CT reconstruction showing an aortic arch ulcer (arrow) with out-pouching of contrast medium extending from the aortic lumen into an intramural haematoma. **h** | Volume-rendered, contrast-enhanced CT reconstruction showing an aortic arch ulcer (arrowhead) extending from the aortic lumen into the aortic-pulmonary window (arrows). Images courtesy of L. Romano (A. Cardarelli Hospital, Naples, Italy).

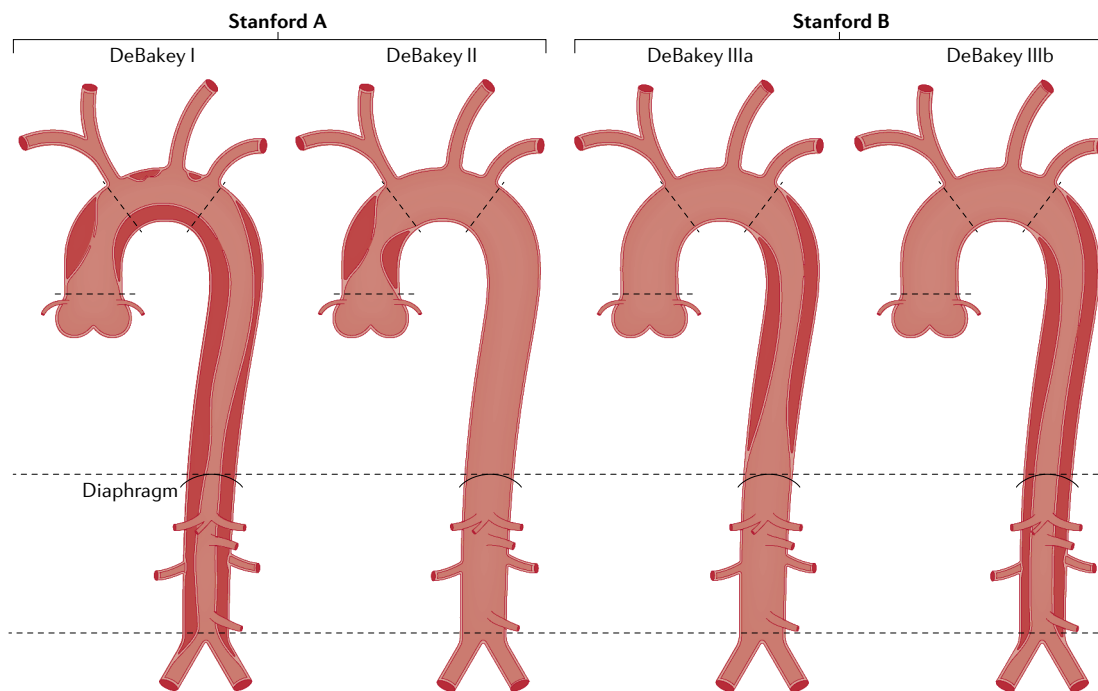


Fig. 6 | **Classification schemes for aortic dissection.** The Stanford system divides aortic dissection into two categories regardless of the site of origin: type A involving the ascending aorta and type B not involving the ascending aorta^{2,3}. The DeBakey system takes into account the origin of the intimal tear and the extent of dissection. Type I dissections involve the ascending aorta, aortic arch and/or the descending aorta. Type II dissections are confined to the ascending aorta. Type III dissections originate distal to the left subclavian artery: type IIIa are limited to the descending thoracic aorta, whereas type IIIb extend below the diaphragm³.

countries². Second, significantly better outcomes have been reported, with overall in-hospital mortality down to 6.6% (medical 5.9% and surgical 9.4%)¹¹⁴. In Eastern countries, clinicians might intercept more cases of mild, uncomplicated IMH at a very early stage of disease because of a higher clinical suspicion at primary centres^{110,114,115}.

Penetrating aortic ulcer

PAU comprises 2–7% of all cases of AAS (2.1 cases per 100,000 person-years)^{2,3,59}. PAU is characterized by ulceration of an aortic atherosclerotic plaque penetrating

through the internal elastic lamina into the media, often coexisting with IMH and diffuse atherosclerosis of the thoracic aorta^{2,3,59}. Often, multiple PAUs are present, ranging from 5 mm to 25 mm in diameter and 4 mm to 30 mm in depth^{2,3,59}. Patients with PAU are usually older individuals (aged >65 years) who smoke and have multiple comorbidities, namely systemic hypertension, coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency and/or vascular disease (atherosclerosis)¹¹⁶. Although the majority of patients present with acute chest or back pain without signs of aortic regurgitation or malperfusion, 25% can be

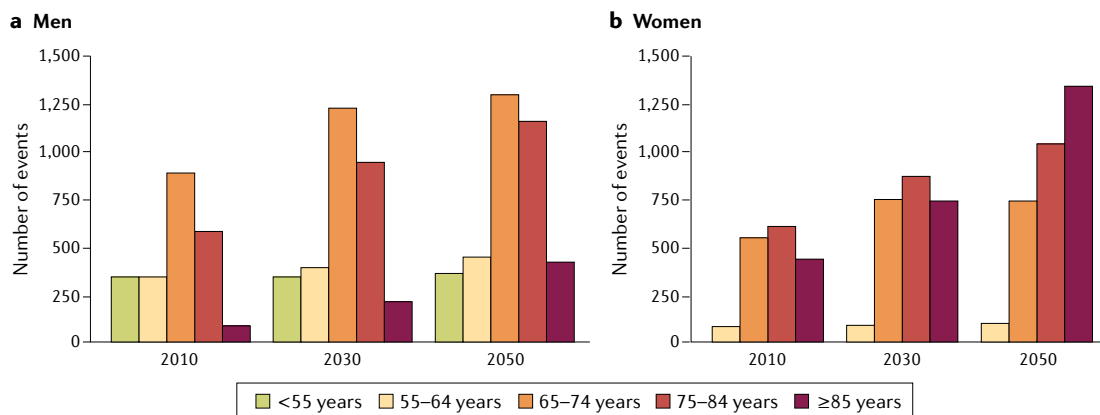
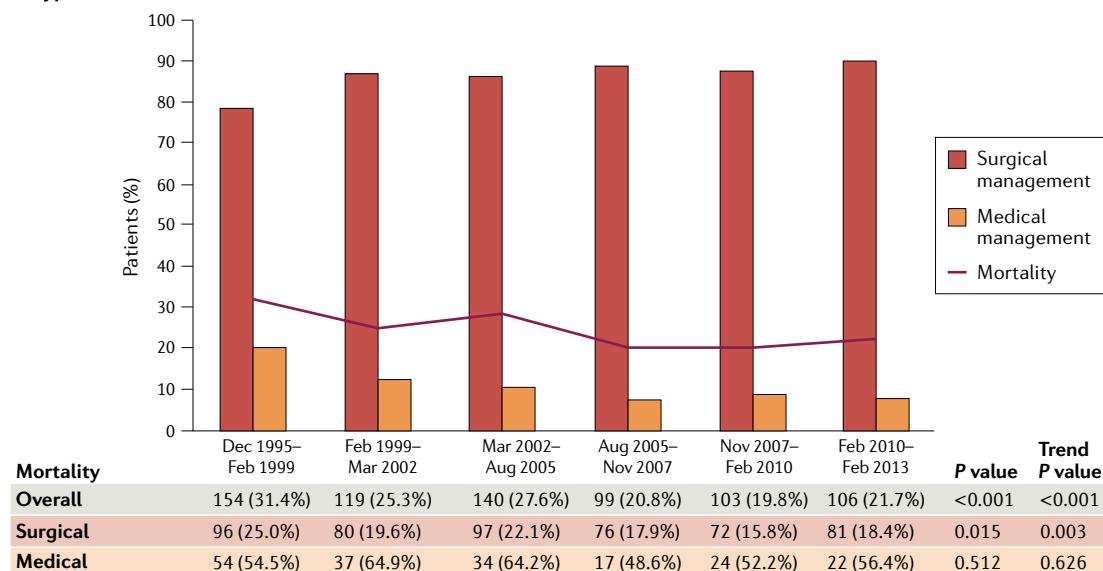


Fig. 7 | **Aortic dissections in the UK.** Estimated number of incident aortic dissection events occurring in the UK population in 2010, 2030 and 2050 stratified by age in men (part a) and women (part b). Adapted with permission from REF.⁵⁷, AME Publishing Company.

a Type A AAD



b Type B AAD

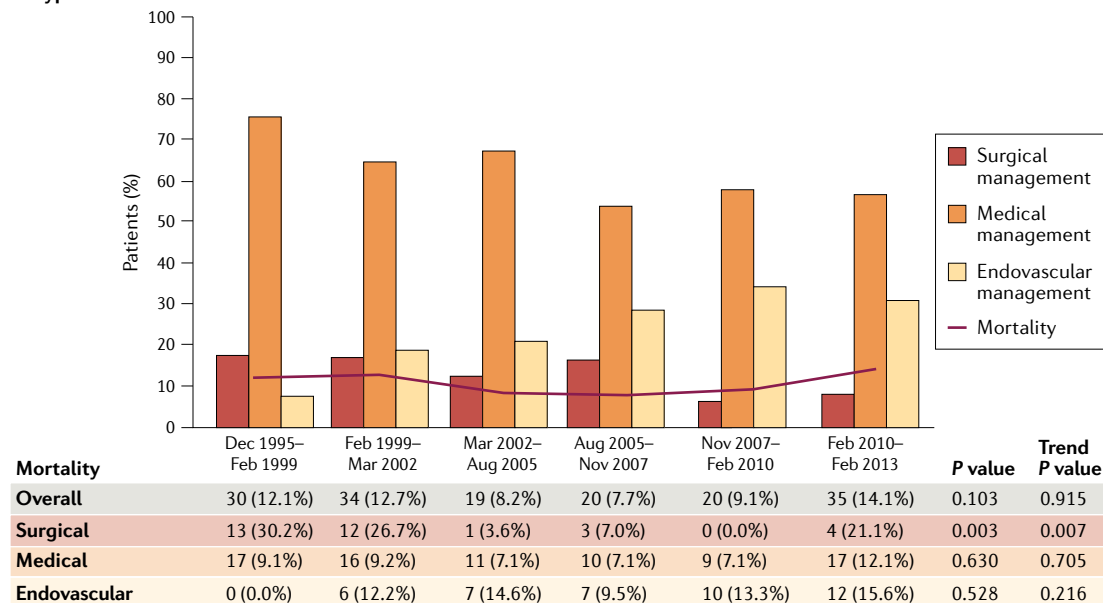


Fig. 8 | Aortic dissection: management and mortality over time in the IRAD. The International Registry of Acute Aortic Dissection (IRAD) analysed trends in mortality among patients with type A or type B acute aortic dissection (AAD) over 17 years (December 1995 to February 2013)^{7,85}. **a** | In-hospital mortality for type A AAD decreased significantly from 31% to 22%, mainly owing to decreased surgical mortality (25% to 18%; $P=0.003$). **b** | In-hospital mortality for type B AAD did not change significantly (12% to 14%). Adapted with permission from REF.⁸⁵, Elsevier.

asymptomatic, and the PAU is identified as an incidental finding during imaging examinations^{2,3,116}.

Diagnosis. Contrast-enhanced CT, including axial and multiplanar reformations, is the first-line imaging modality to diagnose PAUs, which appear as a localized, contrast-like out-pouching (‘ulcer-like’ or ‘crater-like’) of the aortic wall communicating with the lumen^{2,3,103}. MRI is the second-line imaging modality (being less widely available and less suitable than CT, especially in emergency scenarios), and TEE the third-line imaging modality (being less well studied

than either CT or MRI, and being semi-invasive and operator-dependent)¹⁰³.

Natural history and clinical outcomes. The clinical evolution of PAU can vary from longstanding stabilization of the lesion to medial haematoma, adventitial false aneurysm and transmural rupture. Transmural rupture is significantly more frequent with PAU (up to 40% patients) than with type A AAD (7.0%) or type B AAD (3.6%)^{2,3,116}. In patients with acute type B PAU who are treated with open surgery, early and 3-year aortic event mortality of 15.9% and 25.0%, respectively, has been

reported¹⁰⁹. By contrast, significantly lower early and 3-year aortic event mortality (7.2% and 10.4%, respectively) has been reported in patients with acute type B PAU who are treated with TEVAR¹⁰⁹. These data support the strategy of endovascular repair as the first-choice treatment (if suitable anatomy is present) in complicated type B acute aortic PAU^{2,109}.

Traumatic aortic injury

TAI is the partial or complete transection of the aorta and is the second most common cause of death in patients with blunt thoracic trauma (on-site mortality >80%)^{2,3}. TAI often occurs as a result of a high-speed motor vehicle accident or falling from a great height^{2,3}. Rapid deceleration is thought to cause shear stress at less mobile aorta segments, such as the aortic isthmus (90%), aortic root (5%) and/or diaphragmatic hiatus (5%)^{2,3,117,118}. An analysis of data from the Cooperative Crash Injury Study¹¹⁹ (7,067 road traffic accidents in the UK during the period 1992–1999, involving 8,285 vehicles and 14,435 occupants) found that 21% (130/613) of those who were killed had blunt traumatic aortic rupture. Among 132 individuals with blunt traumatic aortic rupture, the at-scene survival was 9% and the overall mortality was 98% (21% owing to frontal impacts and 44% owing to side impacts)¹¹⁹.

Diagnosis and therapeutic interventions. The signs and symptoms of TAI can be non-specific (chest or mid-scapular pain and haemodynamic instability) and are often obscured by the presence of potential associated thoracic or abdominal injuries^{2,3}. Therefore, the diagnosis relies on clinical suspicion followed by prompt and appropriate imaging^{2,3,103} (FIG. 9). CT angiography (accuracy close to 100%) is the current diagnostic technique of choice and can be used to assess the skeletal system and all internal organs rapidly and non-invasively^{2,3,103}. TEE is occasionally an acceptable alternative, taking into account the intrinsic limitations of performing this procedure in unstable patients with multiple traumas^{2,3,103}. A classification scheme has been designed based on anatomopathological aorta lesion severity and relative therapeutic indications¹²⁰:

1. Minimal aortic injury: Society for Vascular Surgery (SVS) grade 1 (intimal tear) and grade 2 (IMH or large intimal flap).
2. Moderate aortic injury: SVS grade 3 (pseudoaneurysm).
3. Severe aortic injury: SVS grade 4 (rupture).

In terms of therapeutic interventions, minimal aortic injury can be managed medically; moderate aortic injury can be managed with semi-elective repair during the first 24–72 h after stabilization of concomitant injuries; and severe injury should be repaired immediately to prevent further extravasation and rapid decline¹²⁰. In patients with moderate or severe injuries, the available data suggest that TEVAR is preferred to surgical repair (in-hospital mortality 7.9% versus 20% (OR 2.94, 95% CI 1.92–4.49, $P < 0.00001$); 1-year mortality 8.7% versus 17% (OR 2.11, 95% CI 0.99–4.52, $P = 0.05$)) if the anatomy is favourable and local expertise is available^{2,120,121}. Although the classification scheme still

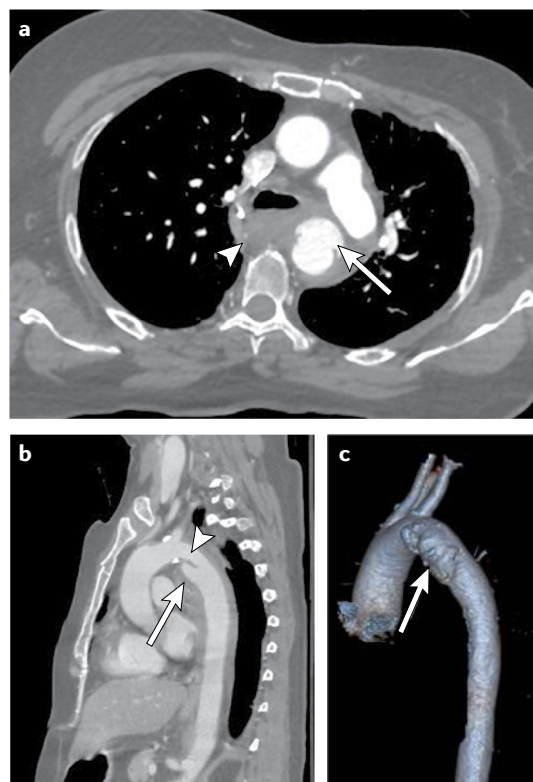


Fig. 9 | Traumatic aortic pseudoaneurysm. **a** | Axial contrast-enhanced CT image showing the irregular and enlarged contour of the proximal descending aorta, with evidence of pseudoaneurysm in the superior aspect of the vessel (arrow) associated with mediastinal haematoma (arrowhead). **b** | Sagittal contrast-enhanced CT reconstruction confirming the pseudoaneurysm (arrow) with intimal flap (arrowhead) at the isthmus level. **c** | 3D surface contrast-enhanced CT reconstruction clearly depicting the traumatic pseudoaneurysm involving the aortic isthmus (arrow). Images courtesy of L. Romano (A. Cardarelli Hospital, Naples, Italy).

needs validation on a large scale, it can be a useful guide for the aortic team in the decision-making process.

Preventive strategies

Primary prevention

As with other forms of cardiovascular disease, healthy lifestyle measures should be adopted from childhood (maintaining a healthy diet, maintaining an ideal BMI and engaging in regular physical activity, together with not more than moderate alcohol consumption and no tobacco exposure) aiming to decrease the probability of developing aortic disease⁴⁰. Of note, stopping smoking is the most cost-effective strategy for the prevention of cardiovascular disease, including aortic disease^{40,63,64,66}. Maximal effort should be made to achieve guideline-directed control of blood pressure (optimal 120/80 mmHg; normal <120–129/80–84 mmHg), plasma LDL cholesterol levels (<3.0 mmol/l (<116 mg/dl) in individuals at low risk of aortic disease; <1.4 mmol/l (<55 mg/dl) or a reduction by $\geq 50\%$ from baseline in individuals at high risk of aortic disease) and blood glucose level ($\text{HbA}_{1c} < 7\%$ or <53 mmol/mol)^{40,122}.

Box 2 | Acute aortic syndromes and aneurysms: long-term follow-up

Clinical and imaging follow-up

Acute aortic syndrome^{2,3}

- 1, 3, 6, 9 and 12 months and yearly thereafter
- First choice: TTE^a and MRI
- Second choice: TTE^a and CT angiography

Thoracic aortic aneurysm¹¹

- Open repair: CT angiography after 6 months then yearly (CT angiography or MRI); after 3 years of follow-up, the interval can be extended to every 2–3 years.
- Thoracic endovascular repair: CT angiography between 1 and 12 months after the procedure, then yearly (CT angiography or MRI); after 3 years of follow-up, the interval can be extended to every 2–3 years.

Abdominal aortic aneurysm^{12,13}

- Open repair: abdominal and pelvic imaging (CT angiography) is recommended every 5 years.
- Endovascular aneurysm repair: abdominal and pelvic imaging (CT angiography and A-US) after 1 month; in the absence of an endoleak or sac enlargement, imaging should be repeated in 12 months (CT angiography or A-US); thereafter, abdominal and pelvic CT angiography should be performed every 5 years.

Cardiovascular risk-factor modifications and healthy lifestyle targets

Blood pressure and heart rate⁹¹

- Blood pressure <120/80 mmHg
- Heart rate <60 bpm
- First-line therapy: β -blockers
- Second-line therapy: angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
- Third-line therapy: calcium-channel blockers (long-acting dihydropyridines)

Plasma LDL-cholesterol level¹²²

- Patients at very high risk: <1.4 mmol/l (<55 mg/dl) or a reduction by $\geq 50\%$ from baseline
- First-line therapy: statins
- Second-line therapy: statins plus ezetimibe
- Third-line therapy: statins plus ezetimibe plus PCSK9 inhibitor

Educational programmes and psychological support^{125–128}

- Optimization of and adherence to medical treatment
- Healthy diet (low in saturated fat, with a focus on whole-grain products, vegetables, fruit and fish)
- BMI 20–25 kg/m²
- Waist circumference <94 cm (men) or <80 cm (women)
- Avoid cocaine and other stimulating drugs, such as methamphetamine
- Drive carefully and wear a seatbelt
- No exposure to tobacco in any form
- Avoid excessive alcohol intake
- Annual influenza vaccination
- Genetic counselling

Exercise training^{125–127}

- Mild to moderate aerobic exercise (3–5 METs) can be performed for ≥ 30 min on most days of the week, for a total of 150 min per week (walking, slow jogging and recreational cycling).
- Avoid strenuous physical activities (isometric exercise, pushing or straining that would require a Valsalva manoeuvre, carrying heavy objects) and contact sports (such as competitive football or ice hockey).
- Common-sense approach to sexual activity: avoid straining and maximal exertion.
- Participation in a cardiac rehabilitation programme is advised (in-hospital, at a community centre and/or home-based).

A-US, abdominal ultrasonography; MET, metabolic equivalent of task; TTE, 2D transthoracic colour-Doppler echocardiography. ^aMultiview cardiovascular ultrasonography: transthoracic, suprasternal and abdominal.

Emerging evidence suggests that statin therapy might reduce AAA growth, rupture and perioperative mortality after elective repair¹²³. Structured population screening programmes (or opportunistic detection) need to be implemented for systemic hypertension and AAA^{2,91}. TAA screening should also be performed among specific high-risk patient cohorts^{2,124}.

Secondary prevention

AAS and aneurysms are life-long conditions that affect the whole aortic system, and affected individuals remain at high risk of long-term major complications (progressive aortic insufficiency, increasing diameters, aneurysm formation and rupture, recurrent dissection, leakage or haemorrhage at surgical anastomoses or stent-grafted sites, and malperfusion) despite successful treatment of an acute index event^{2–4,11–13}. Therefore, patients should undergo clinical and imaging surveillance (an integrated multidisciplinary team approach) regardless of the initial therapeutic strategy (medical, interventional or surgical)^{2–4,11–13,91,122,125–128} (BOX 2). In addition to multiview (transthoracic, suprasternal and abdominal) cardiovascular ultrasonography, MRI or CT examination is warranted for a comprehensive assessment of the aorta and its branches together with the possibility to identify precise landmarks for serial measurements¹⁰³. MRI (if available) is considered the technique of choice (if not contraindicated, as in patients with ferromagnetic and/or magnetically activated implanted devices or claustrophobia), especially in young patients, because this technique does not involve ionizing radiation and does not require iodinated contrast medium^{2,3,103}. Also, guideline-recommended medical therapies need to be implemented to reach optimal blood-pressure levels, heart rate and plasma LDL-cholesterol levels^{91,122}. Of note, setting lifestyle gold standards (risk-factor modification for atherosclerotic disease, adherence to medical treatment, and avoidance of isometric exercise and contact sports) is essential through educational sessions targeted at patients and their family members^{2–4,11–13,91,122,125–128} (BOX 2). Patients should also be encouraged to participate in a tailored cardiovascular rehabilitation programme in hospital, in community centres or at home⁴⁰.

Conclusions

Despite remarkable progress in diagnostic and therapeutic techniques, the burden of aortic diseases remains high^{2,6,19,56,57,60}. Therefore, specific resources need to be allocated to design and implement prevention and screening programmes at the individual and policy levels^{2,4,40}. The development of regional specialized multidisciplinary aortic centres might enable the most appropriate diagnostic and therapeutic pathways, including specialized follow-up clinics. Ongoing clinical registries and trials should shed further light on the optimal timing for pre-emptive endovascular interventions^{7,107}. Finally, advances in genetics, proteomics, and both dynamic and disease-specific imaging offer a substantial hope for more precise diagnosis, prevention and treatment of aortic diseases in the future.

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