BMJ Best Practice

Marfan syndrome

The right clinical information, right where it's needed

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Summary

- An uncommon, autosomal dominant inherited disorder of connective tissue characterised by loss of elastic tissue, resulting in musculoskeletal deformities, lens subluxation, aortic dissection, and root aneurysms.
- Multidisciplinary team of consultants confirm diagnosis and manage treatment.
- Dilation of aorta progressive if diameter is approximately >4.5 cm, but dilation may be delayed by beta-blockers, angiotensin-II receptor antagonists, or verapamil. Risk of aortic dissection beyond this size or with pregnancy.
- Standard of elective surgical care for aortic dilation is modified David's reimplantation operation with preservation of aortic valve leaflets and replacement of the aortic root.
- Acute aortic dissection requires immediate surgical repair and has reduced long-term survival.
- Other manifestations of Marfan syndrome (e.g., lens subluxation and/or cataract, glaucoma, retinal detachment, dural ectasia, scoliosis, and pulmonary complications) require treatment from appropriate medical or surgical consultants.

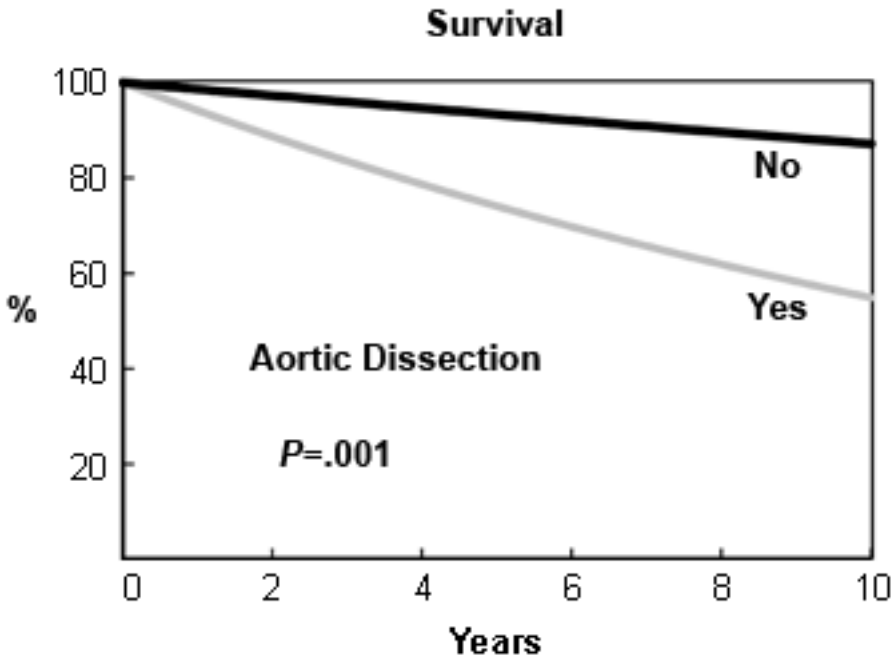
BASICS

Definition

This autosomal dominant inherited disorder of connective tissue, characterised by loss of elastic tissue, affects numerous body systems, including the musculoskeletal, cardiovascular, neurological, and respiratory systems, and the skin and eyes.[1] The essential simplified criteria for diagnosis are 3 out of the 4 following findings: relevant family history, specific musculoskeletal abnormalities, ocular lens subluxation, and aortic dilation/dissection.[2] Skin striae, dural ectasia, hernias, pneumothorax, and emphysematous bullae on CXR may also be noted.

Epidemiology

Prevalence is thought to be similar throughout the world and regardless of sex or ethnicity.[3] The incidence in the European population is estimated to be 3 in 10,000.[4] The incidence in the US population is not accurately known, but is estimated to be 1 in 10,000.[5] The average life expectancy used to be only 32 years but, due to early surgery, it is now approaching that of the general population. Once aortic dissection occurs, survival is considerably reduced to between 50% and 70% at 5 years.[6] [7]



Impact of aortic dissection on patient survival

From the collection of LG Svensson, E Mendrinos, C Pournaras

Aetiology

Caused by mutations in the fibrillin-1 gene in 99% of classical Marfan syndrome patients.[8] In 75% of patients, the gene is passed on from a parent and is autosomal dominant, although the appearance of family members and degree of pathological features may vary. In 25% of patients the mutation occurs spontaneously and may be associated with older paternal age.

The first fibrillin-1 gene mutation was identified in 1990.[9] However, subsequently, over 3000 different mutations have been identified.[10]

Pathophysiology

Mutations in the fibrillin-1 gene result in the production of an abnormal fibrillin protein, leading to abnormalities in the mechanical stability and elastic properties of connective tissue.[11] Up-regulation of C-terminal fragment of filamin-A in dilated aortic media of Marfan syndrome has been found.[12] This is due to cleavage by the protease calpain. Therefore, increased calpain activity may help to explain histological alterations in the dilated aorta.

More recently, research suggests that transforming growth factor-beta is implicated in the failure of normal elastic tissue formation.[13] [14]

Early experience from surgical treatment and histological studies has found that patients suffer from a loss of elastic tissue in the aortic wall (medial degeneration). Frequently, particularly in association with aortic dissection, a loss of smooth muscle cells (medial necrosis) is also noted. In addition, a diagnosis of cystic medial necrosis may be made, the so-called cysts being fluid collections of mucin and ground substance. These abnormalities lead to a weakening of the aortic wall with subsequent aortic dilation and potentially aortic dissection, aneurysms, and rupture. They also lead to a reduction of the structural integrity of the skin, ligaments, eye lenses, lung airways, and the spinal dura.[13]

Classification

Type according to family history

Familial: 75% of cases; inherited as an autosomal dominant trait.

Sporadic: 25% of cases; the mutation occurs spontaneously and may be associated with older paternal age.

Screening

Genetic screening for fibrillin-1 gene mutations may be used for screening of other family members, including antenatal diagnosis and pre-implantation genetic diagnosis.[28]

Secondary prevention

Any patient who has prosthetic material, either valve or graft, will require antibiotic prophylaxis for invasive procedures.[37]

Patients with mechanical valves will need lifelong warfarin therapy.

Children require repeated refraction measurements to prevent amblyopia.

Case history

Case history #1

In a routine medical examination, a young man is noted to be tall with a slight scoliosis and pectus excavatum. He had been told that he was over the 95% percentile for height as a child. The examining physician suspects the patient has Marfan syndrome, and auscultation reveals a heart murmur. Echocardiography shows an enlarged aortic root, aortic valve regurgitation, and mitral valve prolapse.

Case history #2

A man in his 40s presents in the emergency department with sudden-onset chest pain. He is noticed to be tall. The CT scan of his chest reveals acute aortic dissection requiring immediate surgical repair.

Other presentations

Acute aortic dissection not infrequently causes sudden-onset left shoulder or abdominal pain. However, pain may be absent altogether, especially in patients on corticosteroids. Clinical presentations related to musculoskeletal problems (e.g., scoliosis), hernias, or ophthalmic refractive errors are less common. The main ocular symptoms are blurred vision and monocular diplopia caused by progressive lens subluxation and resulting severe astigmatism.

Step-by-step diagnostic approach

History and physical examination (including slit-lamp ophthalmic examination with pupil dilation) in conjunction with imaging of the aortic root and the ascending, descending, and abdominal aorta (echo, CT, MRI) are usually sufficient for diagnosis.[1]

Use of diagnostic criteria

There are two main sets of diagnostic criteria in use, and there is debate among doctors over which is the most appropriate. However, it is likely that they will be superseded by a further revision in the near future.

The essential simplified criteria for diagnosis are 3 of the 4 following findings: relevant family history; specific musculoskeletal abnormalities (including high arched palate, scoliosis, pectus excavatum, flat feet, arachnodactyly with positive thumb sign, dolichostenomelia with increased arm span, and high level of pubic bone); ocular lens subluxation; and aortic dilation/dissection.[2]

These criteria were revised in 1996 into a list of features categorised as major and minor criteria.[15] These revised diagnostic criteria require people with a negative family history to have 2 major criteria and 1 minor criterion. People with a positive family history (parent, sibling, or child) or documented genetic mutation in the family and in the patient, fibrillin-1, require 1 major plus 1 minor criterion (see diagnostic criteria section).
[Fig-2]

Identification of risk factors

Risk factors include the presence of a family history of Marfan syndrome, or of aortic dissection or aneurysm. There is also a weak association with high parental age.

Other historical considerations

There may be a family history of myopia, astigmatism, strabismus, amblyopia, premature cataract or other lens abnormalities, glaucoma, retinal detachment, dental extraction or braces for dental crowding, hernias, or spontaneous pneumothorax. Patients may have a history of joint pain or low back ache.[1]

Physical examination

Tall stature, wide arm span, high level of pubic bone, high arched palate, arachnodactyly, positive wrist and thumb sign,[16] pectus excavatum, pectus carinatum, scoliosis, striae (other than from pregnancy/weight change), flat feet, thick spectacles for myopia, hernias, aortic or mitral valve murmur may be present. Spontaneous pneumothorax or emphysematous bullae may present as dyspnoea. Skeletal abnormality may result in other pulmonary complications also presenting as dyspnoea.

There may be signs of heart failure due to valve disease or cardiomyopathy.[17]

Complete ophthalmic examination, including fundus examination with pupil dilation, is recommended in all patients. There may be signs of lens subluxation or dislocation, cataract, glaucoma, or retinal detachment.

It is possible that the patient may present with signs and symptoms of acute aortic dissection or rupture. This presentation is covered in the complications section.
[Fig-2]

Initial investigations

Echocardiography, thorax CT, and thorax MRI are used initially for aortic root imaging. Abdominal ultrasound, CT, and MRI are used for visualisation of the descending aorta. CXR is performed to exclude the presence of a pneumothorax, and may reveal emphysematous bullae.

Subsequent investigations

Blood screening for mutations in the fibrillin-1 (FBN1) gene confirms the diagnosis if in doubt. Once detected, the mutation can be used to screen other relatives, and used for antenatal diagnosis and pre-implantation genetic diagnosis. This test is more specific than MRI for dural ectasia, which can also be found in Ehlers-Danlos syndrome.

Lower spine CT scan or MRI can be performed to exclude dural ectasia. This is a widening of the dural membrane surrounding the spinal cord and is a recognised complication of Marfan syndrome. MRI is particularly useful for follow-up investigations to avoid accumulative radiation, assessing aortic size and extent of any dural ectasia.

Plasma homocysteine levels help in unclear cases to differentiate homocystinuria. A skin biopsy is indicated only if Ehlers-Danlos syndrome is suspected.

Risk factors

Strong

FHx of Marfan syndrome

- Inherited as an autosomal dominant condition in 75% of cases.
- 50% risk of a child having Marfan syndrome if one parent is affected.

FHx of aortic dissection or aneurysm

- Regular monitoring is recommended for family members at risk.

Weak

high parental age

- Associated with spontaneous gene mutations, including those resulting in Marfan syndrome.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Risk factors include the presence of a family history of Marfan syndrome, or of aortic dissection or aneurysm. There is also a weak association with high parental age.

tall stature (common)

- Typically associated with dolichostenomelia (unusually long limbs).

wide arm span (common)

- Arm span-to-height ratio >1.05.

high level of pubic bone (common)

- Pubic bone-to-height ratio >0.5.

high arched palate (common)

- May lead to dental crowding.

arachnodactyly (common)

- Long, slender fingers are a characteristic finding, confirmed by positive thumb and wrist signs.

positive wrist sign (common)

- Distal phalanges of the first and fifth digits of the hand overlap when wrapped around the other wrist.

positive thumb sign (common)

- When the patient bends the thumb toward the palm of the hand and covers it with the fingers, the tip of the thumb protrudes beyond the palm of the clenched hand.
  [Fig-2]

pectus excavatum (funnel chest) (common)

- Sternum sunk inwards.

pectus carinatum (pigeon breast) (common)

- Sternum pushed outwards.

scoliosis (common)

- Most commonly develops in childhood and adolescence with rapid growth.
- Can affect any part of the spine and varies in severity and need for treatment.

flat feet (pes planus) (common)

- Due to ligament laxity.

dislocated/subluxed eye lens (common)

- Systematic investigation required if this diagnosis is considered.
- Between 50% and 80% of patients have some degree of lens subluxation, which is usually bilateral and symmetrical.
- The direction of dislocation/subluxation is typically but not always superotemporal, whereas dislocation into the vitreous cavity or the anterior chamber is rare.
- Other less frequent lens abnormalities are microspherakia and lens coloboma.[18]

myopia and/or astigmatism (common)

- Refraction and ocular motility are performed as part of a thorough ophthalmic assessment with full pupil dilation.
- Most people with Marfan syndrome are myopic and astigmatic.
- Anisometropia, amblyopia, or strabismus may occur.
- Children require screening for amblyopia.

retinal abnormalities (common)

- Fundus examination is an important part of a thorough ophthalmic examination.
- Retinal abnormalities include myopic posterior staphyloma, lattice degeneration, white-without-pressure, retinal pigmentary changes, atrophic holes or retinal tears, choroidal and scleral thinning.
- The most serious complication is retinal detachment, which may be bilateral.[18]

joint hypermobility (common)

- Incidence of joint dislocation (apart from the patella) similar to that in the general population.

aortic valve murmur (common)

- Present in about one third of adults.

mitral valve murmur (common)

- Approximately one third of people have a non-ejection systolic click and about 10% have a regurgitation murmur.

hx of treatment for dental crowding (common)

- Dental extraction or braces for dental crowding is a common requirement in people with Marfan syndrome, due to narrow jaw and high arched palate.

hx of myopia and/or astigmatism (common)

- There may also be a history of other eye problems including strabismus, lens dislocation, cataract, glaucoma, or retinal detachment.

reduced elbow extension (uncommon)

- Extension of <170 degrees is 1 of the major skeletal features.[15]

Other diagnostic factors

glaucoma (common)

- Primary open-angle glaucoma is the most prevalent form of glaucoma in these patients.
- Secondary open-angle glaucoma may occur following chronic iritis.
- Primary angle closure glaucoma has not been described in Marfan syndrome.
- Pupillary block is rare and can be produced by an anterior lens dislocation.
- Secondary angle closure may occur and is associated with congenital abnormalities of the irido-corneal angle.[18]

hx of spontaneous pneumothorax (common)

- Affects approximately 10% of patients, usually pubertal males.
- May be recurrent.

striae (common)

- Unrelated to pregnancy/weight change (usually on shoulder, lumbar area to mid-back, thighs, and around knees).

low back ache (common)

- Suggestive of spondylolisthesis or dural ectasia.

joint pain (common)

- Suggestive of arthritis.
- Hips: due to protrusio acetabulae (adults).
- Other joints: due to hypermobility, especially the knees, ankles, and wrists.

inguinal/abdominal/incisional hernias (common)

- May be recurrent.

dyspnoea (uncommon)

- Restrictive lung disease may be due to skeletal deformity.
- May also be related to development of emphysematous bullae, spontaneous pneumothorax, fibrosis, or asthma.

signs of heart failure (uncommon)

- Due to heart valve disease or cardiomyopathy.

Diagnostic tests

1st test to order

Test	Result
echocardiography • If aortic dissection is found, there may potentially be rupture or leak. • Mitral valve regurgitation and/or calcification may occur.	**aortic regurgitation; aortic root dilation or ascending aortic dissection; mitral valve prolapse**
CT scan, thorax • If aortic dissection is found, there may potentially be rupture or leak. • Mitral valve regurgitation and/or calcification may occur.	**aortic root dilation or ascending aortic dissection; aortic regurgitation; mitral valve prolapse**
slit-lamp eye examination with intra-ocular pressure measurement • As part of a thorough ophthalmic assessment with full pupil dilation.	**visualisation of subluxed/dislocated lens or other lens abnormalities (e.g., microspherakia, lens coloboma or lens opacities); elevated intra-ocular pressure; other anterior segment findings (e.g., megalocornea or cornea plana, corneal endothelial guttata, iris coloboma, eccentric and poorly pharmacologically dilated pupils)**
ultrasound, abdomen • Useful for visualisation of the descending aorta.	**aortic dissection of descending aorta or abdominal aneurysm**
CXR • Helpful to exclude spontaneous pneumothorax and reveal pulmonary changes.	**pneumothorax, apical blebs; enlargement of the aortic and cardiac silhouette in thoracic dissection**
MRI, thorax • Particularly useful for follow-up to avoid accumulative radiation.	**aortic root dilation or ascending aortic dissection, potentially with rupture or leak; aortic regurgitation; mitral valve prolapse/regurgitation/calcification**
CT scan, abdomen • Used to examine the descending and abdominal aorta.	**aortic dissection of descending aorta or abdominal aneurysm**

Test	Result
MRI, abdomen • Used to examine the descending and abdominal aorta.	**aortic dissection of descending aorta or abdominal aneurysm**

Other tests to consider

Test	Result
CT scan, lower spine • May be used to exclude dural ectasia.	**dural ectasia: widening or ballooning of dural sac**
blood screening for fibrillin-1 (FBN1) gene mutation • Positive for mutation in 99% of classical Marfan syndrome patients.[8] • Interpretation of results must be done in correlation with information gathered from accurate clinical examination.	**mutations in FBN-1 gene**
MRI, lower spine • Patient should stand upright during investigation.	**dural ectasia: widening or ballooning of dural sac**
skin biopsy • Only indicated if Ehlers-Danlos syndrome is suspected and requires exclusion.	**no changes consistent with Ehlers-Danlos syndrome**
plasma homocysteine • Indicated if diagnosis is not clear and homocystinuria is suspected, especially in a child with dislocated lenses and suspected mental disability.	**levels not elevated**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Aortic dissection not associated with Marfan syndrome	• No eye or musculoskeletal findings. • Relevant family history in familial dissections.	• Mutation screening for thoracic aortic aneurysm and dissection genes including TGFBR1/TGFBR2,[19] ACTA2,[20] MYH11,[21] SMAD3,[22] and TGFB2.[23] [24]
Bicuspid aortic valve	• No eye or musculoskeletal findings, although occasionally occurs with Marfan syndrome.	• Echo, thorax CT, or thorax MRI will show abnormal bicuspid aortic valve.
Ehlers-Danlos syndrome	• Joint hypermobility more common presentation. • Type IV variety, which most commonly affects the aorta, is characterised by thin skin and bleeding disorders with increased bruising.	• Skin biopsy for abnormal collagen and DNA testing for gene mutation.

Condition	Differentiating signs / symptoms	Differentiating tests
Erdheim's deformity	• Flask-like root dilation of the aortic root as in Marfan syndrome, but no eye or musculoskeletal findings or family history.	• No differentiating tests.
Homocystinuria	• Signs and symptoms very similar. • Generalised osteoporosis and disorders of mental development more likely in homocystinuria.	• Plasma homocysteine levels are elevated.
Loeys-Dietz syndrome	• No associated lens dislocation. • Aortic dissection occurs at much smaller diameter.[25] • Bifid uvula or cleft palate. • Arterial tortuosity. • Hypertelorism.	• Mutation screening for TGFBR1/TGFBR2 genes.
XXY (Klinefelter) syndrome	• No associated lens dislocation or aortic aneurysm. • Mental deficiency. • Hypogonadism.	• Karyotype reveals extra X chromosome.
Marfanoid hypermobility syndrome	• X-linked. • No eye or heart involvement.	• No gene identified.

Diagnostic criteria

Diagnostic criteria proposed by the International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986[2]

The presence of 3 of 4 major criteria:

- Family history
- Lens subluxation (ectopia lentis)
- Musculoskeletal findings
- Aortic dilation or dissection.

Revised diagnostic criteria for the Marfan syndrome[15]

Simplified as:

Negative family history: 2 major criteria and 1 minor criterion

Positive family history (parent, sibling, or child) or documented genetic mutation in family and in patient, fibrillin-1 gene: 1 major plus 1 minor criterion.

Major criteria:

- Aortic dilation or dissection
- Lens subluxation
- Dural ectasia
- Finding of 4 of the following musculoskeletal features: pectus excavatum, arm span/height ratio >1.05, scoliosis, reduced elbow extension (<170 degrees), wrist sign and thumb sign, pes planus (flat feet), and protrusio acetabulae.

Minor criteria:

- Hypermobility
- High arched palate
- Facial appearance
- Flat cornea
- Increased axial orbit size
- Mitral valve prolapse with regurgitation
- Increased pulmonary artery size
- Calcified mitral valve <40 years
- Aortic dissection of descending aorta or abdominal aneurysm <50 years
- Pneumothorax
- Apical blebs
- Striae
- Incisional hernia.

Revised Ghent Nosology for the Marfan syndrome[16]

An international expert panel has established a revised Ghent nosology that puts more weight on the cardiovascular manifestations (in particular, aortic root aneurysm) and ectopia lentis, which are the cardinal clinical features. The presence of these 2 features are sufficient for the unequivocal diagnosis of Marfan syndrome. In the absence of either of these, the presence of a bona fide fibrillin-1 (FBN1) mutation or a combination of systemic manifestations is required. These criteria may delay a definitive diagnosis of Marfan syndrome, but will decrease the risk of premature diagnosis or misdiagnosis and facilitate worldwide discussion of risk and management guidelines.[26] [27] Dural ectasia is no longer a major finding as it is non-specific and also found in Ehlers-Danlos syndrome.

Step-by-step treatment approach

No curative treatment exists, so management aims to prevent cardiac,[29] ophthalmic, and musculoskeletal complications, and will vary with individual symptoms.

Aortic dilation

Aortic dilation, dissection, and rupture all occur in people with Marfan syndrome. Aortic dissection and rupture are considered as complications of the syndrome, whereas aortic dilation is considered part of the syndrome.

In patients with aortic dilation, if the aortic root area/body height ratio is <10 or the aortic diameter is approximately <4.5 cm (<4.0 cm in women at reproductive age), beta-blocker (or the calcium channel blocker verapamil) therapy is instituted to prevent further aortic dilation. Beta-blockers have been shown to reduce the rate of aortic growth and reduce the risk of complications such as aortic dissection and rupture.[30] However, 20% of children with Marfan syndrome have asthma, and in these children beta-blockers are contraindicated. Losartan or another angiotensin-II receptor antagonist may be used instead.[31] Trials of losartan are demonstrating equal efficacy in preventing aortic root dilation.[32]

Elective surgery is recommended once aortic diameter measures 4.5 cm to 5 cm (earlier in symptomatic patients with chest pain) or if aortic root area over body height ratio is >10.[31] [33] Surgery is indicated earlier (at aortic diameter >4.2 cm) in women of reproductive age. In women who are pregnant, there is a significant risk of dissection when the aortic root is ≥4.2 cm.[34] The measurement of the aortic root/body height ratio is taken into account and if this ratio is >10, elective surgery is likely, but the decision of exactly when to operate may vary between surgeons.

Modified David's reimplantation with replacement of the aortic root and sparing of the aortic valve has a 91% to 97% freedom from reoperation at 10 years if performed at a centre with sufficient experience and a low postoperative death rate after elective procedure <1%.[35] [36] A second-line surgical option is replacement of the aortic root with a composite Dacron graft and mechanical valve, but this is now only indicated outside the centres performing modified David's aortic valve reimplantation. Lastly, the root remodelling operation has been found to have worse results than the David's reimplantation operation.

Following surgery for severe aortic dilation, lifelong therapy with beta-blockers (or verapamil or losartan if beta-blockers are contraindicated/not tolerated) is indicated. Patients with mechanical valves will need lifelong warfarin therapy, and any patient who has prosthetic material, either valve or graft, will require antibiotic prophylaxis for dental work and any future invasive procedures.[37]

Early evidence, emerging from evaluation of robust clinical trial results, suggests that angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists can slow the progression of aortic dilation in Marfan syndrome.[32] The use of losartan (an angiotensin-II receptor antagonist) alone and in combination with beta-blockers has shown positive results in delaying the progression of aortic dilation in preliminary clinical trials.[38] [39] [40] Although the results of these early trials are promising, losartan is still being evaluated in randomised placebo-controlled trials. One large trial has compared losartan with the beta-blocker atenolol in children and young adults with Marfan syndrome.[41] The trial found losartan and atenolol to be equally effective at reducing aortic root dilation over 3 years. Discussion continues as to the relative merits of atenolol and losartan.[42] [43] [44] [45] Some physicians recommend using both as complementary medications.[46] Evidence is emerging that the patient's response to losartan depends

on the type of fibrillin-1 (FBN1) mutation.[47] More large trials are needed to establish the role of losartan in the management of Marfan syndrome.

Musculoskeletal findings and dural ectasia

Scoliosis and kyphoscoliosis are frequently seen in growing teenagers. Curves of 20 to 40 degrees will require orthopaedic bracing, and for larger curves, surgical correction with Harrington rods and spinal fusion is required. Telescopic rods are becoming increasingly popular for young children.[48] Spondylolisthesis <30 degrees is also treated with bracing, whereas a larger slippage will require surgical realignment.

Pectus excavatum and carinatum are usually corrected surgically only if there is cardiopulmonary compromise. Surgery is not indicated for cosmetic reasons because of potential risks, unless serious psychological problems occur with body image. Experimental work with pressure bracing for pectus carinatum and suction for excavatum is promising.[49]

Arthritic pain is managed medically, but advanced arthritis in adults due to protrusio acetabulae may necessitate hip replacement. Mild painkillers and orthopaedic arch supports and footwear may be given in cases of painful flat feet, with foot surgery only rarely becoming necessary.

Dural ectasia is mostly asymptomatic and will only rarely need treatment, such as analgesics for lower back pain or neurosurgery should neurological symptoms occur (e.g., pain or numbness in legs).

Ophthalmogy findings

Refractive errors are corrected with spectacles/contact lenses or may need surgery. Dislocation of the lens is treated either with a combination of spectacles/contact lenses and 1% atropine drops or with surgery. Cataracts are treated by surgical removal of the lens and contact lenses if tolerated by the patient, or intra-ocular lens implantation in the posterior or anterior chamber.[50] Glaucoma requires either medicine or surgery, or a combination of both (see glaucoma topics for more detail concerning specific treatment).

Retinal tears or retinal detachment need immediate attention. Argon laser photocoagulation or transconjunctival cryocoagulation is required for retinal tears, whereas surgical repair is needed in cases of retinal detachment.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)		
Patient group	**Tx line**	**Treatment**
aortic dilation meeting the indications for surgery	**1st**	**modified David's reimplantation with replacement of the aortic root and sparing of the aortic valve**

Acute (summary)

	plus	endocarditis prophylaxis prior to high-risk procedures
	2nd	replacement of the aortic root with a composite Dacron graft and mechanical valve
	plus	lifelong postoperative anticoagulation
	plus	endocarditis prophylaxis prior to high-risk procedures
	3rd	root remodelling operation
	plus	endocarditis prophylaxis prior to high-risk procedures
retinal tear or detachment	1st	argon laser photocoagulation, transconjunctival cryocoagulation, or surgical repair

Ongoing (summary)

Patient group	Tx line	Treatment
aortic dilation not meeting indications for surgery or following aortic surgery	1st	beta-blocker
	2nd	angiotensin-II receptor antagonist
	3rd	verapamil
myopia	1st	corrective lens
	2nd	surgery
▪ optical correction possible, no anterior lens dislocation, no dislocation into vitreous cavity	1st	spectacles/contact lenses with or without atropine drops
▪ optical correction not possible, anterior lens dislocation with secondary glaucoma or dislocation into vitreous cavity	1st	trial of contact lenses
▪ optical correction not possible, anterior	2nd	surgery

Ongoing (summary)		
lens dislocation with secondary glaucoma or dislocation into vitreous cavity		
retinal detachment	1st	surgical re-attachment
cataract	1st	surgical removal of lens and intra-ocular lens implantation
scoliosis/kyphoscoliosis	1st	orthopaedic bracing
	2nd	surgery
severe pectus excavatum/ carinatum with evidence of cardiopulmonary compromise	1st	surgery
arthropathy and/or spondylolisthesis	1st	physiotherapy and analgesics
	2nd	surgery

Treatment options

Acute

Patient group	Tx line	Treatment
aortic dilation meeting the indications for surgery	**1st**	**modified David's reimplantation with replacement of the aortic root and sparing of the aortic valve** » Elective surgery is recommended once aortic diameter measures 4.5 cm to 5 cm (earlier in symptomatic patients with chest pain) or if aortic root area over body height ratio is >10.[31] [33] Surgery is indicated earlier (at aortic diameter >4.2 cm) in women of reproductive age who wish to become pregnant. In women who are pregnant, there is a risk of dissection when the aortic root is ≥4.2 cm.[34] The measurement of the aortic root/body height ratio is taken into account and if this ratio is >10, elective surgery is likely, but the decision of exactly when to operate may vary between surgeons. Surgery has a 91% to 97% freedom from reoperation at 10 years if performed at a centre with sufficient experience and a low postoperative death rate after elective procedure less than 1%.[35] [36]
	plus	**endocarditis prophylaxis prior to high-risk procedures** » Guidelines recommend that any patient who has prosthetic material, either valve or graft, will require antibiotic prophylaxis for invasive procedures directed against viridans group streptococci.[37] » Administered in a single dose 30 to 60 minutes prior to all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa; invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa; procedures on infected skin/skin structures/musculoskeletal tissue. » Cephalosporins should not be used in people with a history of anaphylaxis, angio-oedema, or urticaria with penicillins or ampicillin.
	2nd	**replacement of the aortic root with a composite Dacron graft and mechanical valve** » This procedure is now only indicated outside the centres performing modified David's aortic valve reimplantation, as it carries a higher

Acute

Patient group	Tx line	Treatment
		risk of postoperative complications, such as graft infection, endocarditis or stroke, valve thrombosis, and bleeding from a lifetime of anticoagulation with warfarin.
	plus	**lifelong postoperative anticoagulation**
		» Patients with mechanical valves will need lifelong warfarin therapy.
		» Factors that increase risk of major bleeding with warfarin include high-intensity anticoagulation (INR >4.0), age more than 65 years, highly variable INR, history of GI bleed, hypertension, cerebrovascular disease, serious heart disease, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy.
		Primary options
		» warfarin: children: consult specialist for guidance on dose; adults: 5-10 mg orally once daily initially, adjust according to INR (target: 2.5 to 3.5)
	plus	**endocarditis prophylaxis prior to high-risk procedures**
		» Guidelines recommend that any patient who has prosthetic material, either valve or graft, will require antibiotic prophylaxis for invasive procedures directed against viridans group streptococci.[37]
		» Administered in a single dose 30 to 60 minutes prior to all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa; invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa; procedures on infected skin/skin structures/musculoskeletal tissue.
		» Cephalosporins should not be used in people with a history of anaphylaxis, angio-oedema, or urticaria with penicillins or ampicillin.
	3rd	**root remodelling operation**
		» This procedure has also been shown to have worse results than the David's reimplantation operation.
	plus	**endocarditis prophylaxis prior to high-risk procedures**

Acute

Patient group	Tx line	Treatment
		» Guidelines recommend that any patient who has prosthetic material, either valve or graft, will require antibiotic prophylaxis for invasive procedures directed against viridans group streptococci.[37] » Administered in a single dose 30 to 60 minutes prior to all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa; invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa; procedures on infected skin/skin structures/musculoskeletal tissue. » Cephalosporins should not be used in people with a history of anaphylaxis, angio-oedema, or urticaria with penicillins or ampicillin.
retinal tear or detachment	**1st**	**argon laser photocoagulation, transconjunctival cryocoagulation, or surgical repair** » Retinal tears can be repaired by argon laser photocoagulation and/or transconjunctival cryocoagulation. Retinal detachment requires surgery. The surgical options scleral buckling, vitrectomy, or both depend on the complexity of the detachment, the status of the lens, and the severity of dislocation. » Currently available vitreoretinal techniques result in successful reattachment of the retina in >80% of the eyes.[51] [52]

Ongoing

Patient group	Tx line	Treatment
aortic dilation not meeting indications for surgery or following aortic surgery	**1st**	**beta-blocker** » Treatment with beta-blockers has been shown to reduce the rate of aortic growth and reduce the risk of complications such as aortic dissection and rupture.[30] » Metoprolol is most commonly used; however, atenolol or bisoprolol may also be used as alternative options.

Ongoing

Patient group	Tx line	Treatment
		» In adult patients with an aortic diameter <4.5 cm this may prevent further significant dilation for many years. » Special considerations and dose adjustments are required for children. Atenolol is usually the beta-blocker of choice in paediatric patients. » While titrating dose to effect, avoid systolic BP <100 mmHg and heart rate much <60 beats per minute. **Primary options** » metoprolol: adults: 25 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 200 mg/day **OR** **Secondary options** » atenolol: children: consult specialist for guidance on dose; adults: 25-100 mg orally once daily **OR** **Secondary options** » bisoprolol: adults: 1.25 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
	2nd	**angiotensin-II receptor antagonist** » There is some early evidence to suggest that ACE inhibitors and angiotensin-II receptor antagonists (e.g., losartan, irbesartan, candesartan) can slow the progression of aortic dilation in Marfan syndrome, and these treatments require further evaluation.[30] The use of losartan alone and in combination with beta-blockers has shown positive results in delaying the progression of aortic dilation in preliminary clinical trials.[38] [39] [40] Although the results of these early trials are promising, losartan is still being evaluated in randomised placebo-controlled trials. One large trial has compared losartan with the beta-blocker atenolol in children and young adults with Marfan syndrome.[41] The trial found losartan and atenolol to be equally effective at reducing aortic root dilation over 3 years. Discussion continues as to the relative merits of atenolol and losartan.[42] [43] [44] [45] Some physicians recommend using both as complementary medications.[46]

Ongoing

Patient group	Tx line	Treatment
		» Evidence is emerging that the patient's response to losartan depends on the type of fibrillin-1 (FBN1) mutation.[47] More large trials are needed to establish the role of losartan in the management of Marfan syndrome. **Primary options** » losartan: children: consult specialist for guidance on dose; adults: 50-100 mg orally once daily **OR** **Primary options** » irbesartan: children: consult specialist for guidance on dose; adults: 75-300 mg orally once daily **OR** **Primary options** » candesartan: children: consult specialist for guidance on dose; adults: 4-32 mg orally once daily
	3rd	**verapamil** » Given if beta-blockers or angiotensin-II receptor antagonists are contraindicated or not tolerated. » While titrating dose to effect, avoid systolic BP <100 mmHg and heart rate much <60 beats per minute. **Primary options** » verapamil: adults: 40-80 mg orally (immediate-release) three times daily
myopia	1st	**corrective lens** » Treatment may be achieved by concave spherical correction with spectacles or contact lenses. If present, astigmatism should also be corrected.
	2nd	**surgery** » Surgery (clear lens extraction and intra-ocular lens implantation) may be performed when spectacles or contact lenses are insufficient and/or not tolerated.[53]

Ongoing

Patient group	Tx line	Treatment
optical correction possible, no anterior lens dislocation, no dislocation into vitreous cavity	1st	**spectacles/contact lenses with or without atropine drops** » Lens subluxation/dislocation may cause visual symptoms that vary in severity depending on the degree of lens displacement. » If the subluxation is mild, the patient sees through the phakic portion of the pupil. Optical correction with spectacles or contact lenses is indicated as first-line treatment when possible. » If the subluxation is large enough, the patient sees through the aphakic portion of the pupil. » Pupil dilation with atropine, and optical correction with contact lenses, is indicated when possible. **Primary options** » atropine ophthalmic: children: (0.5%) 1-2 drops into the affected eye(s) twice daily; adults: (1%) 1-2 drops into the affected eye(s) twice daily
optical correction not possible, anterior lens dislocation with secondary glaucoma or dislocation into vitreous cavity	1st	**trial of contact lenses** » Contact lenses can be tried before or after lens removal and, if tolerated, may be sufficient to correct vision without implantation of an intra-ocular lens.[50]
optical correction not possible, anterior lens dislocation with secondary glaucoma or dislocation into vitreous cavity	2nd	**surgery** » Lens extraction and intra-ocular lens implantation is indicated if the edge of the lens bisects the pupil and optical correction is impossible. » Anterior dislocation of the lens with secondary glaucoma is an indication for lens extraction and primary or secondary intra-ocular lens implantation. Pars plana vitreolensectomy is another therapeutic option in this case.[54] Pars plana vitrectomy is also indicated when there is lens dislocation into the vitreous cavity. » When an intra-ocular lens implantation is required, posterior chamber lenses are recommended because they reduce the complications of lens decentration. These lenses are sutured in place by scleral and/or iris fixation.[18] [55] Lenses may be placed in the anterior chamber.[50]

Ongoing

Patient group	Tx line	Treatment
retinal detachment	**1st**	**surgical re-attachment** » Retinal detachment occurs rarely in Marfan syndrome as a primary ocular event, but occurs more often as a result of vitreolensectomy.[51] [52] [54]
cataract	**1st**	**surgical removal of lens and intra-ocular lens implantation** » Complications related to cataract surgery are higher in patients with Marfan syndrome compared with the general population, due to zonular weakness. The risk of posterior capsule rupture with vitreous loss and intra-ocular lens luxation into the vitreous is thus increased. The use of capsular tension rings intra-operatively reduces these complications.
scoliosis/kyphoscoliosis	**1st**	**orthopaedic bracing** » Scoliosis and kyphoscoliosis are frequently seen in growing teenagers. Curves of 20 to 40 degrees require orthopaedic bracing, to be worn for about 23 hours a day.
	2nd	**surgery** » Scoliosis and kyphoscoliosis are frequently seen in growing teenagers. Curves of more than 40 degrees will require surgical correction with Harrington rods and spinal fusion, or telescopic magnetic growth rods, which are becoming increasingly popular for young children.[48] [56]
severe pectus excavatum/ carinatum with evidence of cardiopulmonary compromise	**1st**	**surgery** » Requires surgical correction if impairing breathing. Deformed sternum and ribs are straightened using a metal bar.[57] Surgery is not usually indicated for cosmetic reasons because of potential risks. If open heart surgery is required, this should be performed prior to sternal correction if possible.

Ongoing

Patient group	Tx line	Treatment
arthropathy and/or spondylolisthesis	**1st**	**physiotherapy and analgesics** » Spondylolisthesis or dural ectasia may result in low back pain. Mild arthritic pain is managed medically and with physiotherapy. Spondylolisthesis <30 degrees may also be treated with bracing, whereas a larger slippage will need surgery. » Mild painkillers (e.g., acetaminophen, ibuprofen) and orthopaedic footwear may be given in cases of painful flat feet, with foot surgery only rarely becoming necessary. » Non-steroidal anti-inflammatory drugs (NSAIDs) can be taken concurrently with warfarin, if both are taken regularly, and warfarin dose is adjusted to maintain INR. » Omeprazole can be added to NSAID therapy to prevent NSAID-induced ulcers; however, it can prolong the elimination of warfarin and increase INR. **Primary options** » paracetamol: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day **OR** **Primary options** » ibuprofen: children: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; adults: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day **-or-** » naproxen: adults: 250-500 mg orally twice daily when required, maximum 1250 mg/day Dose expressed as naproxen base. **-or-** » diclofenac: adults: 50 mg orally (immediate-release) three times daily when required, maximum 150 mg/day **-or-** » indometacin: adults: 25-50 mg orally (immediate-release) two to three times daily when required, maximum 200 mg/day **--AND--** » omeprazole: children: consult specialist for guidance on dose; adults: 10-20 mg orally once daily

Ongoing

Patient group	Tx line	Treatment
	2nd	**surgery** » Rarely required. Refer to an orthopaedic consultant for advice and treatment. Spondylolisthesis >30 degrees will need surgical realignment. Advanced arthritis in adults due to protrusio acetabulae may necessitate hip replacement.

Emerging

External stent to support aorta

The experimental procedure involves a mesh tube, custom made using computer-aided design, wrapped around the root of the aorta. Long-term follow-up is under way to evaluate the procedure, which is available only in a few specialised centres.[33] [58] [59]

FOLLOW UP

Recommendations

Monitoring

Patients with an aortic diameter <4.5 cm or aortic root area/body height ratio <10, treated with beta-blockers or verapamil, have a repeat echo and CT of thorax after 3 to 6 months, and then the trend is noted at yearly intervals. MRI of the thorax is preferred for follow-up evaluation to prevent accumulative radiation.

After elective surgery and stable aortic size, a yearly echo and MRI (every 2 to 3 years) of the thorax are performed to check the condition of the remaining aorta.

After acute dissection or surgical repair of chronic dissection, an initial check-up should be scheduled every 3 months, then every 1 to 2 years, and include echo and MRI/CT scan of the thorax.

Patients with Marfan syndrome also need routine eye care for optical correction of refractive errors, periodic monitoring of intra-ocular pressure, and anterior segment examination with a slit-lamp to assess the eye for lens location and opacities. Fundus examination with pupil dilation is routinely performed in all cases, with particular attention to peripheral retinal changes, tears, or detachment.

Specific attention and more frequent monitoring (once every trimester) is required in pregnant women or women planning pregnancy. These patients should also receive genetic counselling about their 50% risk of passing on their condition to their children. Based on a known causative fibrillin-1 mutation in either parent, pre-pregnancy counselling should include advice regarding options of antenatal diagnosis by chorionic villus biopsy at 11 weeks' gestation, or pre-implantation genetic diagnosis to ensure an unaffected fetus.[28] [66]

Patient instructions

The recommendations concerning which sports are safe in these often young patients can be difficult. Generally, the common factor that is associated with the precipitation of acute aortic dissection is rapid upper chest movement while straining. This may include: netball, basketball, tennis, golf, baseball, football, swinging an axe or spade, weightlifting, and suddenly lifting something heavy. Sports that appear safe are cycling, jogging, and gentle swimming. Contraindicated sports include heavy weightlifting and long-distance running, involving prolonged exertion at peak capacity. After surgery, restrictions are not as strong but straining is still discouraged.

Patients are instructed to seek immediate ocular examination if they develop ophthalmological symptoms such as the perception of floaters (myodesopsia), flashing lights (photopsia), glare, or visual-field defect.

Complications

Complications	Timeframe	Likelihood
coronary ostial aneurysm following aortic repair	**long term**	**low**
Risk dependent on method used to reattach the coronary artery button.		
acute aortic dissection/rupture	**variable**	**high**

Complications	Timeframe	Likelihood
May present with: severe, stabbing, sudden-onset chest pain; absent pulses; confusion; tachycardia; loss of consciousness; signs of abdominal ischaemia; differing BP in different arms, wide pulse pressure due to aortic regurgitation, or distant heart sounds secondary to tamponade. Pain is frequently associated with rapid upper chest movement while straining (e.g., swinging an axe or spade), golf, basketball, baseball, tennis, or lifting something heavy. Left shoulder or abdominal pain is not infrequent. Pain may be absent, especially in patients on corticosteroids. Requires immediate surgery, once confirmed by echo and CT scan/MRI of the thorax. Exceptions are previous cardiac surgery, dissection more than a few days old, history of CAD, and anticoagulation therapy. Cardiac catheterisation is recommended in patients with previous cardiac surgery and those with possible CAD. Acute dissection beyond the left subclavian artery is initially treated medically, unless there is evidence of distal ischaemia. Following surgery for aortic dissection, lifelong therapy with beta-blockers (or verapamil if beta-blockers are contraindicated/not tolerated) is indicated.		
chronic aortic dissection	**variable**	**high**
Usually seen after previous cardiac surgery. Patients require extensive work-up for surgery. Most require initial aortic arch replacement beyond a previous ascending aortic graft insertion using the so-called elephant trunk procedure.[62] A second-stage elephant trunk procedure is required 2 to 4 months postoperatively. In many patients, the entire aorta is replaced because of the dissected weakened aorta becoming aneurysmal. Following surgery for aortic dissection, lifelong therapy with beta-blockers (or verapamil if beta-blockers are contraindicated/not tolerated) is indicated.		
continued aortic dilation	**variable**	**medium**
The weakened aortic wall is still too stressed by pulsatile flow. If dilation is beyond 2 mm every 6 months or aortic root area/body height ratio of 10 despite drug treatment, surgical referral is recommended.		
symptomatic aortic regurgitation	**variable**	**medium**
Occurs with aortic root dilation.		

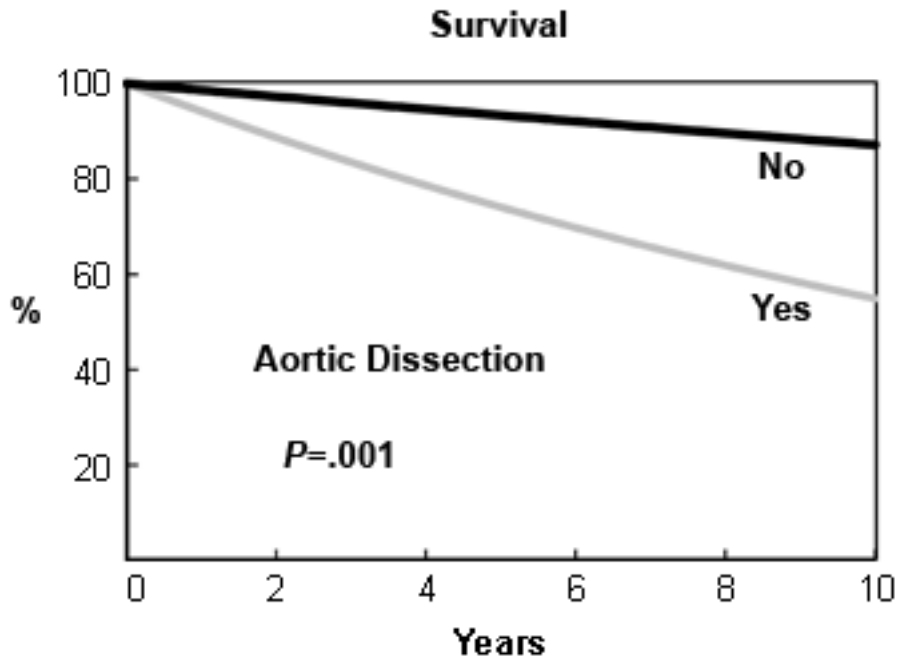
FOLLOW UP

Complications	Timeframe	Likelihood
spontaneous pneumothorax	**variable**	**medium**
May be recurrent. Preventative surgery is recommended after 1 to 3 episodes, depending on severity.[64] [65]		
severe mitral regurgitation	**variable**	**low**
Mitral valve prolapse often progresses to severe mitral valve regurgitation, especially in females. Surgery is indicated when regurgitation either becomes severe (grade 4+) or symptomatic, or if there is evidence of haemodynamic compromise.[63]		
infective endocarditis	**variable**	**low**
Low risk in David's reimplantation; high risk in composite valve graft procedure.		
heart failure	**variable**	**low**
Heart valve disease or intrinsic cardiomyopathy may occur and require referral to a cardiologist.		
symptomatic inguinal/abdominal/incisional hernia	**variable**	**low**
May be recurrent.		

Prognosis

The most important factors in treatment of Marfan syndrome are the diagnosis of the condition, careful long-term follow-up for aortic expansion, referral for surgery when the aortic root area/body height ratio reaches 10 or aortic root diameter in the sinus of Valsalva reaches 4.5 cm to 5.0 cm, and emergency surgery for acute dissection. Long-term survival is excellent with beta-blocker control and surgery when indicated. Acute dissection results in a reduced survival even if successfully treated.[6] [7] However, early diagnosis followed by modern medical and surgical management has definitely improved quality and length of life.[60]

Aortic surgery during pregnancy has increased the chance of preservation of lives of both mother and baby.[61]



Impact of aortic dissection on patient survival
From the collection of LG Svensson, E Mendrinos, C Pournaras

Diagnostic guidelines

North America

Evaluation of the adolescent or adult with some features of Marfan syndrome

Published by: American College of Medical Genetics and Genomics **Last published:** 2012

Summary: This guideline provides an approach to the diagnosis of patients with features suggestive of Marfan syndrome.

Oceania

Recent developments in the diagnosis of Marfan syndrome and related disorders

Published by: Medical Journal of Australia **Last published:** 2012

Summary: This article looks at the clinical criteria for diagnosing Marfan syndrome, comparing the original criteria published in 1966 and the differences in the revised criteria published in 2010. The article also reviews other developments in the understanding of Marfan syndrome, such as DNA testing and potential therapies.

Treatment guidelines

Europe

2017 ESC/EACTS guidelines for the management of valvular heart disease

Published by: European Society of Cardiology **Last published:** 2017

Summary: Includes specific recommendations on management of valvular heart disease in patients with Marfan syndrome.

ESC guidelines on the management of cardiovascular diseases during pregnancy

Published by: European Society of Cardiology **Last published:** 2011

Summary: Includes recommendations on management of pregnancy in Marfan syndrome.

ESC guidelines for the management of grown-up congenital heart disease

Published by: European Society of Cardiology **Last published:** 2010

Summary: Includes brief outline recommendations on the management of heart disease in Marfan syndrome and guidance on the transfer from paediatric to adult cardiology services.

North America

Prevention of infective endocarditis

Published by: American Heart Association **Last published:** 2007

Summary: Endocarditis prophylaxis is indicated prior to high-risk procedures in patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair.

Oceania

Update on the diagnosis and management of inherited aortopathies, including Marfan syndrome

Published by: The Cardiac Society of Australia and New Zealand **Last published:** 2016

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Images

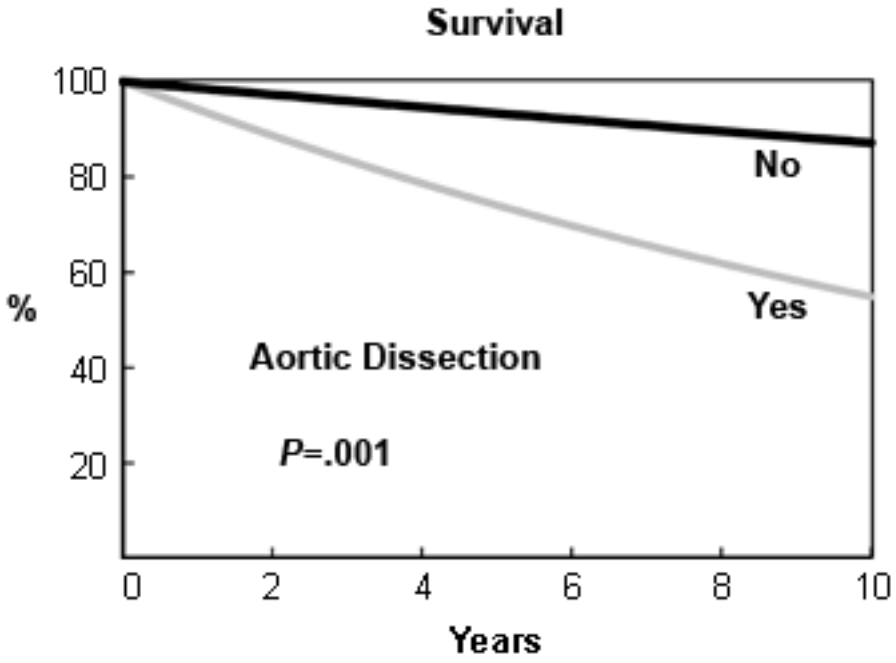

Figure 1: Impact of aortic dissection on patient survival

From the collection of LG Svensson, E Mendrinos, C Pournaras

Figure 2: Positive thumb sign

From the collection of LG Svensson, E Mendrinos, C Pournaras

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