

## ARTICLE



# Marfan syndrome diagnosis and management

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Not supported by any research grant.

## ABSTRACT

Marfan syndrome is the most common inherited multisystem disorder of connective tissue. This autosomal dominant condition has an incidence of 2-3 per 10,000 individuals. Although genetic diagnostic techniques are available, the diagnosis is primarily made using the Ghent diagnostic criteria. Early identification and appropriate management improves the prognosis of patients with Marfan syndrome who are prone to the life-threatening cardiovascular complications of aortic dissection and rupture. Beta-blockers have been demonstrated to slow aortic growth and thus delay the time to aortic surgery. Operative intervention has markedly changed the prognosis of patients with Marfan syndrome and can be safely performed on an elective basis.

The advance in the understanding of the cause of Marfan syndrome, as well as early recognition of the disorder and subsequent institution of medical and surgical therapy has resulted in dramatic improvement in the prognosis of this patient population over the past few decades.

## INTRODUCTION

Marfan syndrome is the most common inherited multisystem disorder of connective tissue. This autosomal dominant condition has a reported incidence of 2-3 per 10,000 individuals without gender, racial, or ethnic predilection. Early identification and appropriate management improves the prognosis of patients with Marfan syndrome who are prone to life-threatening cardiovascular complications.

## GENETICS

Marfan syndrome is caused by a mutation of the fibrillin-1 gene located on chromosome 15.<sup>(1)</sup> Fibrillin-1 protein is an extracellular matrix glycoprotein, which is an important component of the connective tissue elastic microfibrils and is essential to normal fibrinogenesis. Fragmentation and disorganization of the elastic fibers in the aortic media is a histological marker of Marfan syndrome, so-called medial degeneration. Those histological changes make the aorta stiffer and less distensible than the normal aorta. More recently, endothelial dysfunction has also been demonstrated in the Marfan aorta.

The penetrance of the fibrillin mutation is high and the phenotypic expression is variable. To date, more than 500 different mutations involving

the fibrillin-1 gene have been identified, but no correlation between the specific type of fibrillin-1 mutation and the clinical phenotype has been recognized.<sup>(2,3)</sup> In approximately 75% of cases, an individual inherits the disorder from an affected parent. The remaining 25% of cases result from de novo mutation. There is little prognostic information provided by the detection of a mutation beyond the available information provided from the patient's own family history. Therefore, genetic testing is mainly used for adjunctive clinical diagnosis in selected cases.

Approximately 10% of mutations that cause classic Marfan syndrome are missed by conventional screening methods. Limitations to genetic testing include:

1. The mutation in fibrillin-1 gene can cause conditions other than Marfan-like disorder.
2. None of the current methods used to find mutations in fibrillin-1 gene identify all mutations that cause Marfan syndrome.
3. Family members with the same mutation causing Marfan syndrome can show wide variation in clinical manifestations.

The diagnosis of Marfan syndrome depends primarily on clinical features which have been codified into the Ghent diagnostic nosology (Table 1).<sup>(4)</sup>

## DIAGNOSIS

The diagnosis of Marfan syndrome requires a careful history, including information about any family members who may have the disorder or had unexplained early or sudden death. The goal is to determine whether the diagnosis can be established clinically. The modified Ghent criteria, proposed in 1996, allow a uniform approach to the diagnosis of Marfan syndrome.<sup>(4)</sup> A comprehensive multidisciplinary approach involving cardiac, orthopedic, ophthalmologic, as well as genetic consultations and testing are warranted in order to confirm or exclude the diagnosis. In the absence of any family history of Marfan syndrome, the diagnosis is made by identifying major criteria in two different organ systems and involvement of a third system or in the presence of fibrillin-1 mutation and major criteria in one system and involvement in a second organ system (Table 1). In the presence of a family history of Marfan syndrome in a first-degree relative who meets major criteria independently, the diagnosis of Marfan syndrome can be made in the presence of one major criterion in one organ system and involvement of a second organ system.

## Cardiovascular manifestations

The importance of the cardiovascular involvement from Marfan syndrome was initially outlined by McKusick et al.<sup>(5)</sup> Cardiovascular complications are now recognized to be the major cause of morbidity and mortality in patients with Marfan syndrome. Thus it is important to consider the diagnosis and perform cardiovascular imaging studies in all patients with possible Marfan syndrome, and serial imaging in all patients with confirmed

Table 1. Summary of the major and minor suggested Ghent criteria used to establish the diagnosis of Marfan syndrome.

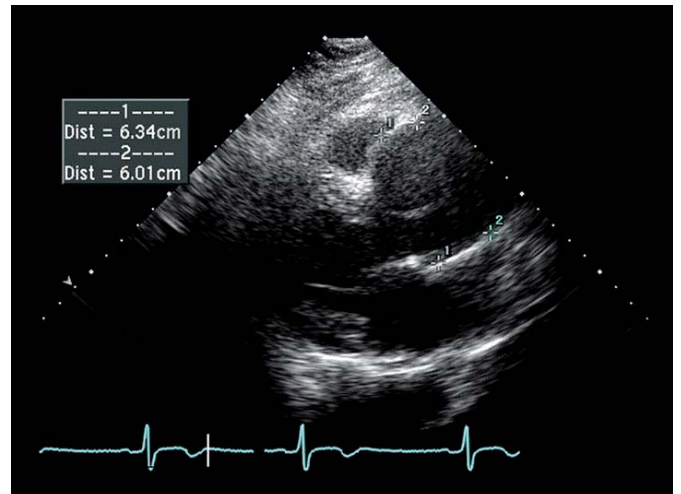
Skeletal	Major (at least four of the following constitutes a major criterion)	Minor
	<ul style="list-style-type: none"> <li>Pectus carinatum</li> <li>Pectus excavatum requiring surgery</li> <li>Reduced upper to lower segment ratio OR arm span to height ratio &gt;1.05</li> <li>Wrist and thumb signs</li> <li>Scoliosis of &gt;20° or spondylolisthesis</li> <li>Reduced extension at the elbows (&lt;170°)</li> <li>Medial displacement of the medial malleolus causing pes planus</li> <li>Protrusio acetabuli of any degree</li> </ul>	<ul style="list-style-type: none"> <li>Pectus excavatum</li> <li>Joint hypermobility</li> <li>Highly arched palate with crowding of teeth</li> <li>Facial appearance: dolichocephaly (long narrow skull) <ul style="list-style-type: none"> <li>malar hypoplasia ( flattening)</li> <li>enophthalmos ( sunken eyes)</li> <li>retrognathia ( recessed lower mandible)</li> <li>down-slanting palpebral fissures</li> </ul> </li> </ul>
	<i>For involvement of the skeletal system, at least two features contributing to major criteria, or one major and two minor criteria must be present.</i>	
Ocular	Major	Minor
	<ul style="list-style-type: none"> <li>Ectopia lentis</li> </ul>	<ul style="list-style-type: none"> <li>Flat cornea</li> <li>Increased axial length of globe (&lt;23.5 mm)</li> <li>Hypoplastic iris OR hypoplastic ciliary muscle causing decreased miosis</li> </ul>
	<i>For involvement of the ocular system, at least two of the minor criteria must be present.</i>	
Cardiovascular	Major (either of the following constitutes a major criterion)	Minor
	<ul style="list-style-type: none"> <li>Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva</li> <li>Dissection of the ascending aorta</li> </ul>	<ul style="list-style-type: none"> <li>Mitral valve prolapse with or without mitral valve regurgitation</li> <li>Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis below the age of 40 years</li> <li>Calcification of the mitral annulus below the age of 40 years</li> <li>Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years</li> </ul>
	<i>For involvement of the cardiovascular system, only one of the minor criteria must be present.</i>	
Pulmonary System	Major	Minor
	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>Spontaneous pneumothorax</li> <li>Apical blebs</li> </ul>
	<i>For involvement of the pulmonary system, only one of the minor criteria must be present.</i>	
Skin and Integument	Major	Minor
	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>Striae atrophicae (stretch marks) not related to marked weight gain, pregnancy or repetitive stress</li> <li>Recurrent or incisional herniae</li> </ul>
	<i>For involvement of the skin and integument, only one of the minor criteria must be present.</i>	
Dura	Major	Minor
	<ul style="list-style-type: none"> <li>Lumbosacral dural ectasia by CT or MRI</li> </ul>	<ul style="list-style-type: none"> <li>None</li> </ul>
Family/Genetic History	Major (one of the following constitutes a major criterion)	Minor
	<ul style="list-style-type: none"> <li>First-degree relative who independently meets the diagnostic criterion:</li> <li>Presence of mutation in FBNI</li> <li>Presence of a haplotype around FBNI inherited by descent and unequivocally associated with diagnosed Marfan syndrome in the family</li> </ul>	<ul style="list-style-type: none"> <li>None</li> </ul>



**FIGURE 1:** Pathology specimen demonstrating heart and aorta following fatal aortic dissection. The red arrow shows the external aortic tear into the pericardial sac. The dissection channel is large and filled with clotted blood. The true lumen has been narrowed substantially. (Courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine.)



**FIGURE 2:** Descending aortic dissection demonstrated on magnetic resonance imaging of the chest with gadolinium. The dissection starts distal to the left subclavian artery and extends to the aortic bifurcation.



**FIGURE 3:** Two-dimensional echocardiogram, parasternal long axis image, demonstrates dilatation of the ascending aorta at the level of the aortic sinuses. The leading edge to leading edge method is used for ascending aortic measurement.

The cardiovascular manifestations of Marfan syndrome include:

1. Dilatation of the ascending aorta, characteristically at the sinuses of Valsalva with associated increased risk of aortic valve regurgitation, as well as aortic dissection (Fig. 1).
2. Mitral valve prolapse with or without mitral valve regurgitation.
3. Mitral anular calcification noted in patients younger than age 40 years.
4. Pulmonary artery dilatation in the absence of pulmonary valve stenosis.
5. Dilatation or dissection of the descending thoracic aorta in a patient younger than age 50 years (Fig. 2).

Aortic sinus enlargement leading to aortic aneurysm is progressive and is present in 50% to 60% of adults and in 50% of children with Marfan syndrome and can be readily detected by echocardiography (Fig. 3).

Recent data suggest that Marfan syndrome is present in 50% of aortic dissection patients presenting under age 40 years and accounts for only 2% of dissections in older patients. <sup>(6) (7)</sup>

Risk factors for aortic dissection in Marfan syndrome include:

1. aortic diameter of more than 5 centimeters,
2. aortic dilatation extending beyond the sinuses of Valsalva,
3. rapid rate of aortic dilatation (more than 5% per year or more than 2 millimeters per year in adults), and
4. family history of aortic dissection.

Aortic diameter should be measured by transthoracic echocardiogram at multiple levels and related to normal values based on age and body surface area reported by Roman and Devereux (Fig. 4).<sup>(8)</sup> The maximum aortic dimension in Marfan syndrome is usually located at the sinuses of Valsalva.

Mitral valve prolapse with or without mitral valve regurgitation can be seen in 60% to 80% of patients with Marfan syndrome undergoing an echocardiographic examination. However, only an estimated 25% of Marfan patients with mitral valve prolapse have progressive mitral valve regurgitation that requires operative intervention. Tricuspid valve prolapse with and without regurgitation also occurs in Marfan syndrome.

### Skeletal manifestations

The most common skeletal manifestations of Marfan syndrome can be easily assessed by a full skeletal examination that includes measurements of height, arm span to height ratio, upper to lower segment ratio, and hand and foot examinations, as well as evaluation for scoliosis, pectus deformity, high arched palate, medial rotation of the medial malleolus causing pes planus (flat feet), joint hypermobility, reduced elbow extension, and arachnodactyly.

Occasionally hip x-ray and lumbosacral MRI or CT may be helpful to document the presence of protrusio acetabula or dural ectasia respectively. Imaging studies are usually performed for symptoms or occasionally when these findings are required to fulfill the Ghent diagnostic criteria for the Marfan syndrome.

### Ocular manifestations

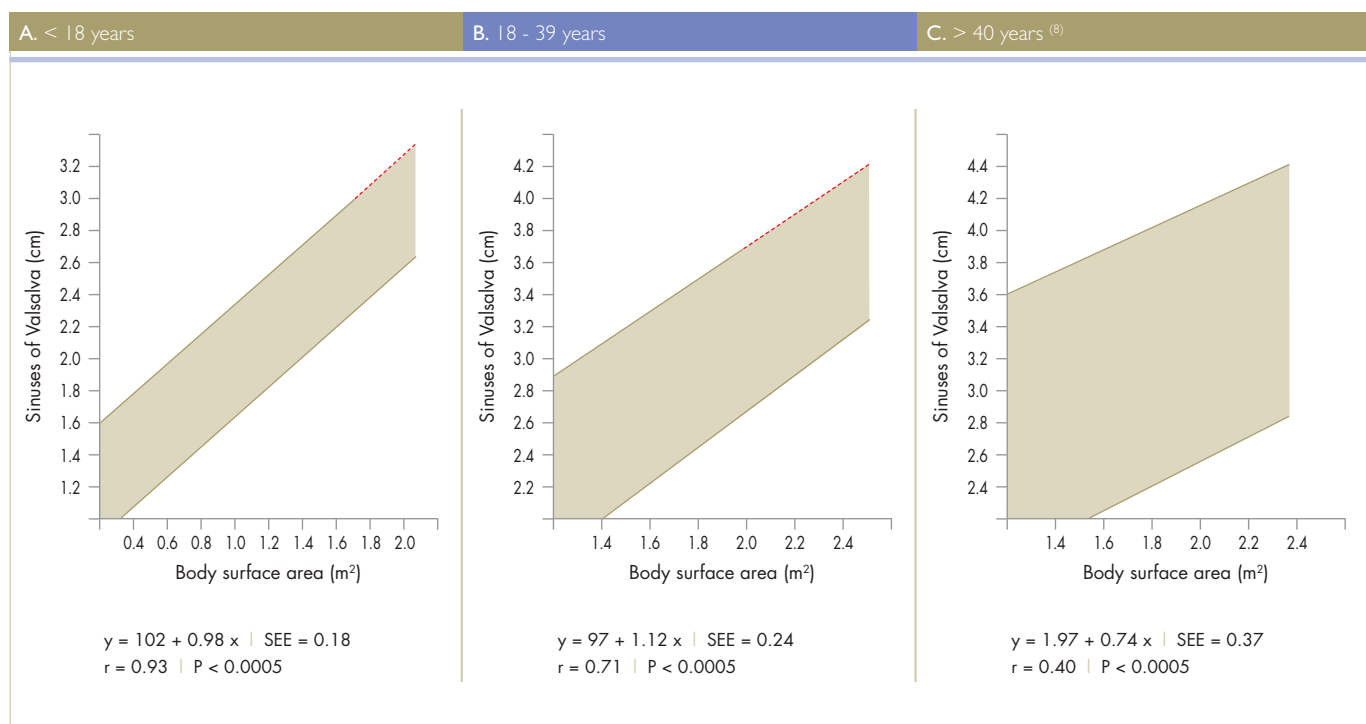
Lens dislocation is the only ocular manifestation that is considered a major criterion and is present in 60% of patients with Marfan syndrome. This is best assessed with a slit-lamp examination with pupillary dilatation performed by an ophthalmologist. Lens dislocation usually occurs early in life but annual ophthalmologic evaluation is recommended due to the recognized risk of early severe myopia, retinal detachment, glaucoma, and cataract formation in Marfan patients. The other manifestations of Marfan syndrome are summarized in Table 1.

Children with suspected Marfan syndrome who do not meet the Ghent diagnostic criteria should have repeat evaluation in preschool, before puberty, and at age 18, since some of the clinical manifestations of Marfan syndrome become evident with age. Serial aortic imaging follow-up is recommended when the aorta is enlarged, irrespective of diagnostic criteria.

### Differential diagnosis

The differential diagnosis of Marfan syndrome includes:

1. **Homocystinuria** which shares several skeletal and ocular features of Marfan syndrome, in addition to mitral valve prolapse. Homocystinuria is an autosomal recessive disorder that is characterized by an elevated urinary homocysteine excretion and can be diagnosed by measuring total homocysteine.
2. **MASS phenotype** includes mitral valve prolapse, aortic enlargement, and nonspecific skin and skeletal features.
3. **Ehlers-Danlos syndrome type IV** includes skin laxity, scars, and easy bruising and a propensity toward arterial dilatation and dissection.



**FIGURE 4:** 95% normal confidence limits for aortic root diameter at the sinuses of Valsalva in relation to body surface area as described by Roman et al for three age groups

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4. **Stickler syndrome** where retinal detachment and not ectopia lentis is a common feature, additional features include cleft palate and hearing loss.
5. **Congenital contractural arachnodactyly or Beals syndrome** is an autosomal-dominant disorder manifest by joint contractures, scoliosis, and crumpled ear malformation in addition to a marfanoid appearance.
6. **Familial thoracic aortic aneurysm or aortopathy.** These individuals do not show any other systemic manifestation of Marfan syndrome but have familial tendency to arterial dilatation and dissection.
7. **Congenital bicuspid aortic valve disease with associated aortopathy,** where the dilatation of the ascending aorta is often in its mid-section rather than at the aortic sinuses. The bicuspid aortic valve may function normally.
8. **Loeys-Dietz syndrome,** which includes hypertelorism and the presence of a broad or bifid uvula, in addition to vascular involvement characterized by arterial tortuosity and aneurysms with an increased risk of dissection throughout the arterial tree, often at small arterial sizes <sup>(9)</sup>.

## **MEDICAL MANAGEMENT**

The management of patients with Marfan syndrome should involve a multidisciplinary approach and treatment should be tailored to individual manifestations. Early diagnosis and treatment are beneficial. Marfan patients of all ages should undergo at least annual evaluation with clinical history, examination, and echocardiogram or another aortic imaging study. Genetic counseling should be provided initially to aid in the diagnosis and should also be provided to potential parents. Phenotypic variability, pregnancy counseling, and the availability of prenatal and presymptomatic diagnostic testing should be discussed. <sup>(10)</sup>

The histologic abnormalities noted in the Marfan aorta reduce its distensibility and compliance; as a result, the aorta becomes stiffer and demonstrates excessive dilation with age. Since beta blockade can increase aortic distensibility and reduce aortic stiffness, in addition to lowering the heart rate and left ventricular ejection force, these medications have been the treatment of choice and should be considered in all patients with Marfan syndrome. A randomized trial of propranolol treatment in adolescents and young adults with Marfan syndrome has demonstrated a reduced rate of aortic dilatation and fewer aortic complications in the treatment group. <sup>(11)</sup> A total of 70 patients with Marfan syndrome were treated with propranolol, mean dose to 112 milligrams a day. At an average follow-up of ten years, the mean slope of regression line for aortic root dimensions was significantly lower in the propranolol group compared to the control group. In another study involving 44 patients with Marfan syndrome followed up for almost four years, those who were taking a beta blocker or calcium channel blocker if intolerant to beta blocker; showed a slower absolute aortic growth rate of 0.9 vs. 1.8 mm/year after adjustment for age and body size. <sup>(12)</sup> Those who responded to beta blockade tended to have a smaller aortic diameter (less than 4.0 centimeters) suggesting that

a reduction in the rate of aortic dilatation with beta blockade is greatest in young patients with a small aorta. Therefore, beta blockade should be considered in all patients with Marfan syndrome, including children, and those with aortic root diameter of less than 4 cm, unless contraindicated. The beta-blocker dose should be adjusted to maintain a resting heart rate of 60-70 beats per minute or heart rate of 100 beats per minute after submaximal exercise.

Recent data demonstrated dramatic alteration in vascular abnormalities in the aortas of Marfan mice treated with angiotensin converting enzyme inhibitor. <sup>(13)</sup> A multicenter prospective comparison of beta blocker and angiotensin receptor blocker is planned in young, unoperated Marfan patients. Until data support therapy in humans, angiotensin receptor blocker therapy should be considered second line after beta blocker; but should be considered in patients with hypertension or beta blocker intolerance. In the presence of aortic or mitral regurgitation, endocarditis prophylaxis is recommended.

One of the major concerns in Marfan syndrome is the increased risk of aortic dissection, which is inherent to the histologic abnormalities of the Marfan aorta. Patients with Marfan syndrome should be counseled to seek urgent medical evaluation for any acute chest, back, or abdominal pain, syncope, sudden change in vision or sense of impending doom.

Treatment with beta blockers, though beneficial in most Marfan patients, does not protect against aortic dissection. In one study, 20% of patients with Marfan syndrome treated with beta blockers or calcium channel blockers had major cardiovascular complications requiring surgery over a four-year period. <sup>(12)</sup> Patients should also be educated to avoid smoking and monitor their blood pressure due to the recognized vascular complications related to nicotine use and hypertension. The goal blood pressure per JNC-7 <sup>(14)</sup> is less than 120/80 mm Hg.

Patients with Marfan syndrome should avoid isometric exercise, competitive and contact sports, or exercising to the point of exhaustion. <sup>(15)</sup> As a general principle, participation in recreational exercise categorized as low to moderate intensity is appropriate for patients with Marfan syndrome, unless they have had prior aortic root and/or valve replacement. Weight lifting, body building, and competitive sports such as ice hockey, full-court basketball, surfing, and scuba diving should be avoided. Impact sports may also cause ocular complications in patients with Marfan syndrome. For other activities thought to be of intermediate risk, such as singles tennis, soccer, touch football, baseball and skiing, individual assessment is suggested. <sup>(16)</sup>

Serial aortic imaging is critical in the management of all patients with Marfan syndrome. It is suggested that the aortic root diameter be plotted serially against body surface area. <sup>(6)</sup> In adults, a yearly echocardiogram measurement of the aortic root diameter is recommended, as long as the diameter is less than 4.5 cm and no major change in aortic dimension has been noted recently. Twice-yearly aortic surveillance is recommended when the aortic



root diameter is more than 4.5 cm, or the patient has not had prior documented aortic enlargement. Alternatively, CT or MRI of the chest could be performed. These imaging techniques provide a complete assessment of the thoracic aorta, including the descending segment that might not be optimally visualized by echocardiography. These imaging modalities complement each other. Periodic CT or MR imaging of the descending thoracic and abdominal aorta is recommended in all patients with Marfan syndrome, especially prior to aortic root replacement, due to the recognized risk of aneurysm formation in other parts of the aorta.

Annual ophthalmologic examination, including screening and treatment for myopia, retinal detachment, glaucoma, and cataracts, is recommended for all patients with Marfan syndrome.

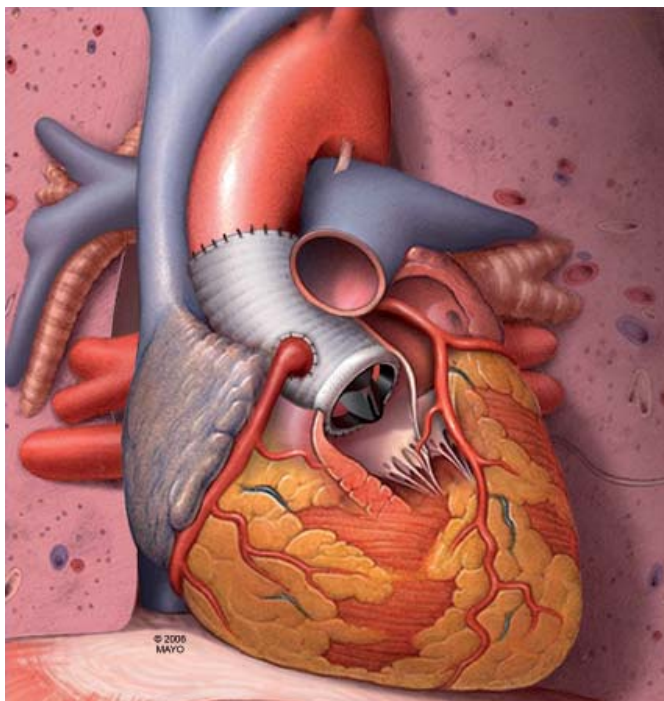
### SURGICAL MANAGEMENT

There is general agreement, based on a number of comparative studies, that overall outcome is better in Marfan patients treated with early aortic root surgery, in addition to continuing beta blockade. (17,18) Prophylactic surgery is recommended when the diameter of the aortic sinuses of Valsalva reaches 5.0 cm. (19) Other factors such as family history of aortic dissection, severe aortic valve regurgitation with associated symptoms or progressive ventricular dilatation or dysfunction, the possibility of a valve-sparing operation, and the rate of aortic dilatation (aortic root growth >2 mm/yr), may indicate the need for surgery at a smaller aortic sinus dimension. An increase in aortic dimension of more than 1.0 centimeter per year is regarded as rapid progression in a child, whereas in the adult an

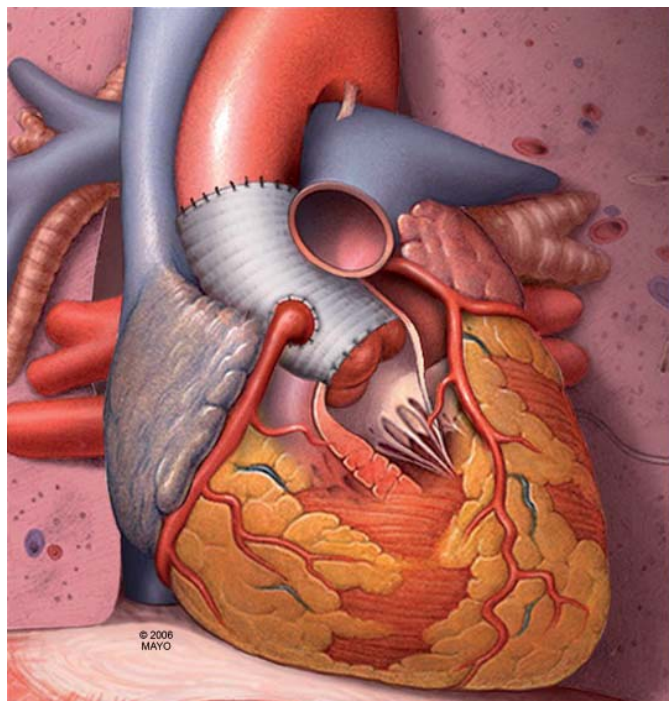
increase of ≥5% per year or an increase of more than 2 mm per year is considered significant, emphasizing the need for regular aortic root surveillance.

The original operation developed for Marfan patients was the Bentall composite graft. This includes aortic root and valve replacement with either a biological or mechanical valve and requires coronary artery reimplantation (Fig. 5). The composite aortic graft is associated with a low operative mortality, especially when done electively, and a 5-, 10-, and 20-year survival of 88%, 81%, and 75%, respectively. The Bentall procedure is the operation of choice in patients with severe aortic valve regurgitation and is often preferred in the setting of emergent operation for aortic dissection.

In the absence of important aortic valve regurgitation, a valve-sparing aortic root replacement can be considered (Fig. 6). The degree of the aortic valve regurgitation, due to root dilatation, is a major determinant of the kind of surgical intervention offered when aortic root replacement is required. There are various types of valve-sparing operation. The mortality risk of the valve-sparing operations is low with a 5-yr survival rate of 96±3%. Mild or no aortic regurgitation may be present in up to 75% of patients, for as long as 10 years. The risk of requiring aortic valve replacement for severe aortic valve regurgitation is estimated to be 10% at ten years. Aortic valve-sparing operation is an indication for early surgery and therefore an aortic root diameter of <50 millimeters with preserved aortic valve function is an indication to consider surgical repair. In addition, the valve-sparing operation or the use of a biological prosthesis is recommended for a woman who



**FIGURE 5:** Schematic of the Bentall operation. In this procedure the proximal aorta is replaced with a valved conduit, the coronary arteries are reimplanted. This schematic demonstrates a mechanical prosthesis. Biological prostheses can also be used.



**FIGURE 6:** Schematic of the valve sparing aortic root replacement. The ascending aorta is replaced with a graft, the native aortic valve is preserved, and the coronary arteries are reimplanted.

wishes to become pregnant and for other patients with relative contraindication for long-term anticoagulation.<sup>(20)</sup>

Mitral valve repair for severe mitral regurgitation with associated symptoms or progressive left ventricular dilatation or dysfunction carries a very low operative risk (<1%).<sup>(21)</sup>

## **POSTOPERATIVE CARDIOVASCULAR CARE**

Marfan patients require long-term medical treatment and lifelong surveillance, even after aortic root surgery, representing a major commitment for patient and doctor. Beta blockers should be continued indefinitely unless not tolerated. Long-term aspirin and endocarditis prophylaxis are recommended in all patients. Long-term anticoagulation with warfarin is recommended for patients with mechanical prostheses or in presence of atrial fibrillation. At least annual cardiovascular and ophthalmologic evaluation with a clinical history, examination, and transthoracic echocardiogram is recommended with periodic imaging of the descending thoracic and abdominal aorta. As Marfan patients age, reoperation is often needed if they develop vascular complications elsewhere in the arterial system, reemphasizing the importance of continuing beta-blocker therapy. Mitral valve replacement or repair may be required in up to 10% of those requiring aortic root surgeries. As a group, it is believed that more than 60% of patients with Marfan syndrome require multiple operations during their lifetime and therefore lifelong comprehensive multidisciplinary follow-up is recommended.

Periodic imaging of the entire aorta is recommended indefinitely following initial aortic repair and monitoring can be accomplished with MRI or CT angiography. The rate of change of the aortic diameter should influence follow-up intervals.

Indications for replacement of an enlarged segment of the aorta should include:

1. Rapid increase in aortic size of more than 5 to 10 millimeters per year;
2. Ascending aortic diameter of >50 millimeters,
3. Affected segment diameter twofold greater than the adjacent segment,  
or
4. Symptoms related to aortic dilatation.

An uncommon late complication of both composite and valve-sparing operation is the development of coronary ostial aneurysms. These aneurysms develop at the site of reimplantation as a result of the perioperative stretch of the weakened wall of the coronary ostium.

## **PREGNANCY IN MARFAN SYNDROME**

Pregnancy in Marfan syndrome is possible. There are, however, two major issues that need to be discussed with the patient and family, including the risk of cardiovascular complications in the affected mother and the 50% risk

of transmission of Marfan syndrome to the fetus. Due to the autosomal dominant nature of the disorder, each offspring of an affected Marfan parent has a 50% chance of inheriting the genetic mutation. Genetic counseling should be offered to all patients with Marfan syndrome. Mutation detection or linkage can be used for prenatal diagnosis if the parents wish.

The risk of aortic dissection in pregnancy is increased and may be caused by the inhibition of collagen and elastin deposition in the aorta by estrogen and the hyperdynamic hypervolemic circulatory state of pregnancy. Previous reports of pregnancies involving patients with Marfan syndrome have demonstrated a complication rate of approximately 11%, mostly related to aortic rupture and endocarditis. The overall risk of death during pregnancy is around 1%. The risk of aortic root complication is increased when the aortic root diameter is more than 4 centimeters at the start of pregnancy and the risk is further increased when the aorta dilates rapidly during pregnancy.<sup>(22)</sup> The risk of further dilatation of the aorta during pregnancy is lowest in the first trimester and greatest in the third trimester, as well as during labor and in the first few weeks post partum. In those who become pregnant, beta blocker therapy should be continued throughout pregnancy and patients should have serial follow-up echocardiograms to assess the change in the size of the aorta during pregnancy. Surgery should be considered during pregnancy in patients with progressive aortic dilatation or before the aortic root diameter reaches 55 millimeters. A planned cesarean delivery is generally the preferred mode of delivery in patients with the Marfan syndrome and enlargement. Assisted vaginal delivery can be considered when the aortic root diameter is less than 4 centimeters, the aorta has not demonstrated change during pregnancy, and there is no associated severe cardiovascular disease. Antibiotic prophylaxis administered around the time of delivery is appropriate for those patients with significant valvular regurgitation or prior root and valve replacement surgery. Postpartum uterine hemorrhage should be anticipated as a complication of Marfan syndrome and has been reported in nearly 40% of women.<sup>(23)</sup>

## **PROGNOSIS**

The life expectancy of untreated patients with Marfan syndrome is significantly reduced, with an early study reporting the lifespan to be about 32 years. However, with beta blocker therapy and elective surgical repair, the median cumulative probability of survival has increased gradually to 72 years.<sup>(24)</sup>

## **SUMMARY**

A marked advance in the understanding of the cause of Marfan syndrome, as well as early recognition of the disorder and subsequent institution of medical and surgical therapy, has resulted in dramatic improvement in the prognosis of this patient population over the past few decades. We anticipate that further medical advances, focused primarily on the genetic basis of Marfan syndrome, will allow continued therapeutic improvements with associated prognostic implications in years to come.

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