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# Marfan Syndrome – Advances in Diagnosis and Management

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Additional information is available at the end of the chapter

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## 1. Introduction

Cardiovascular disease is the leading cause of death in most Western societies and it is increasing steadily in many developing countries. Aortic diseases constitute an emerging share of the burden. New diagnostic imaging modalities, longer life expectancy in general, longer exposure to elevated blood pressure, and the proliferation of modern non-invasive imaging modalities have all contributed to the growing awareness of acute and chronic aortic syndromes. Despite recent progress in recognition of both the epidemiological problem, diagnostic and therapeutic advances, the cardiology community and the medical community in general are far from comfortable in understanding the spectrum of aortic syndromes and defining an optimal pathway to manage aortic diseases.

Aortic aneurysms and dissections are the main disorders that can affect this artery in the thoracic cavity. Thoracic aortic aneurysms are usually asymptomatic, a silent disease, and they may not be diagnosed until a serious complication appears, such as acute aortic dissection or rupture. Those complications have a high morbidity and mortality, and entail a considerable healthcare expenditure. Prophylactic aortic surgery is being applied to prevent these potentially catastrophic aortic complications. It is very important to correctly identify patients at high risk, by establishing periodic monitoring and follow-up with imaging tests to determine the size of the aorta and the rate of aortic growth.

There have been identified many genetic syndromes that may predispose to the development of thoracic aortic aneurysms and type A aortic dissections. The most important is the Marfan syndrome, as almost all patients with this syndrome will develop an ascending aortic aneurysm throughout his life.

## 2. Body

The Marfan syndrome (MFS) is an autosomal dominantly inherited disorder of connective tissue with multisystem involvement. It is caused by mutations in the *FBN1* gene on chromosome 15, which encodes a glycoprotein called fibrillin-1, a component of the extracellular matrix. Over 1700 mutations have been identified in the fibrillin-1 gene associated with MFS, other genes related with the disease have been discovered and other disease-related genes with phenotypes very similar to this clinical syndrome (which need a thorough differential diagnosis) have been also identified. Because connective tissue is found throughout the body, MS can affect many body systems, including the ocular, cardiovascular, skeletal, and pulmonary Systems, as well as the skin and dura mater. The most serious signs and symptoms associated with MS involve the cardiovascular system; the cardiac complications, particularly aortic dilatation, dissection and rupture and involvement of the aortic and mitral valves, lead to a greatly reduced life expectancy.

### 2.1. Diagnostic criteria for Marfan's syndrome

The MFS was described by the first time in 1896 by Antoine-Bernard Marfan, and it was not until 1995 that it was included in the connective tissue diseases classification. In 1986 a group of experts established a set of clinical criteria for the diagnosis of MFS (Berlin nosology). Later, in 1996 [1], it suffered a modification, known as Ghent's nosology (table 1), in order to avoid the overdiagnosis and to facilitate the differentiation with other similar syndromes. These criteria have been used throughout the world for the diagnosis of the SM, with a high specificity, as mutations in the gene *FBN1* had been detected in up to 97 % of the patients who assemble these criteria [2]. Nevertheless, it presents some limitations, such as not consider the dependence on the age for some clinical manifestations, preventing the diagnosis in children, or to include not specific clinical manifestations, or with a poorly established diagnostic value. These facts may involve the overdiagnosis of MFS in patients with ectopia lentis or mitral valve prolapse syndrome; or on the contrary they may restrict the diagnosis in patients with ectopia lentis and aortic dilatation without sufficient skeletal manifestations.

Organ / System	Requirements for the classification of major criteria	Requirements for the affection of organs/systems
Skeletal	At least four of the following ones: 1. <i>Pectus carinatum</i> 2. <i>Pectus excavatum</i> that needs surgery 3. Reduced upper segment / lower segment ratio, or increased armspan / height 4. Thumb and wrist's signs 5. Curvature of the spine (20°) o	At least two findings for major criteria, or one of those and two of the following minor criteria: 1. Moderate severity pectus excavatum 2. Articular hypermobility 3. Marked arch palate, or dental agglomeration

	espondilolistesis 6. Reduced elbow extension (<170°) 7. Medial displacement of the internal ankle causing plain flat feet 8. Protrucio acetabulae	4. Typical facial appearance (dolichocephaly, malar hypoplasia, retrognathia, downward slanting palpebral fissures, enophthalmos)
Ocular	Ectopia lentis	At least two of the following minor criteria: 1. Flattened cornea 2. Increase of the axial length of the eyeball 3. Miosis reduced by iris of ciliary muscle hipoplasia
Cardiovascular	At least one of the following ones: 1. Ascending aortic dilatation, with or without regurgitation, concerning Valsalva sinus 2. Ascending aortic dissection	At least one of the following minor criteria: 1. Mitral valve prolapse, with or without regurgitation 2. Pulmonary artery dilatation, in absence of estenosis or other cause in adults < 40 years 3. Mitral ring calcification in adults < 40 years 4. Aortic dilatation or dissection
Pulmonary	None	At least one of the following minor criteria: 1. Spontaneous pneumothorax 2. Apical bullous
Coverings	None	At least one of the following minor criteria: 1. Skin striae not associated with marked weight changes, pregnancy or repeated stress 2. Recurrent of iincisional hernia
Dura mater	Lumbosacral dural ectasia	None

For the diagnosis of Marfan's syndrome in patients without family history of the disease, there must be involved two organs / systems that assemble major criteria, and at least the affectation of a third organ / system. In patients with positive family history of this syndrome, it is needed a major criteria, with information that suggest the affectation of a second system.

**Table 1.** Diagnostic criteria of Ghent's nosology

In order to solve the limitations of Ghent's nosology, it has been proposed a review of this. A group of international experts in the diagnosis and the management of MFS summoned in Brussels by the National Marfan Foundation, published recently "*The revised Ghent nosology*" [3], based on the review of wide cohorts of patients, experts opinion and the available literature about the application of the classic criteria, the differential diagnosis of the MS and the solidity and limitations of the genetic study.

Among the most important changes, a major value is granted for two cardinal findings of the MFS, the aneurysm/dissection of the root of the aorta and the ectopia lentis, being sufficient the combination of both to establish the diagnosis. The rest of ocular and cardiovascular manifestations, as well as the findings of other organs/systems, contribute to a systemic score that facilitates the diagnosis when the aortic disease is present but not the ectopia lentis (table 2).

A more relevant role is assigned to the genetic study of the gene FBN1 and other related genes (TGFBR1 and TGFBR2). Some of the less specific manifestations lose importance in the diagnostic evaluation.

The new criteria emphasize the need of diagnostic considerations and additional tests if patients assemble sufficient criteria for MS but show unexpected findings, especially because of the possibility of an alternative specific diagnosis. It is emphasized specially in Sphrintzen-Goldberg and of Loeys-Dietz syndromes, and in the vascular form of Ehlers-Danlos's syndrome.

The new diagnostic criteria have been defined for a sporadic index patients, or for a patient with positive family history (table 3).

- **In absence of any family history**, the diagnosis can be established in the following cases:
  1. The presence of aortic root dilatation or dissection ( $Z$  score  $\geq 2$ , adjusted to age and body surface area) and ectopia lentis establish the diagnosis, independently of the presence of other systemic findings, except when these are indicative of other genetic syndromes of aortic aneurysm, as Sphrintzen-Goldberg and of Loeys-Dietz syndromes, and the vascular form of Ehlers-Danlos's syndrome
  2. The presence of dilatation or dissection ( $Z$ -score  $\geq 2$ ) and the identification of a mutation of the FBN1 gene is sufficient to establish the diagnosis of the MS.
  3. In presence of dilatation or dissection ( $Z$ -score  $\geq 2$ ) without ectopia lentis and ignorance of mutations of the FBN1 gene, diagnosis can be established when sufficient systemic findings exist ( $\geq 7$  points); in this case, there must be excluded the possibility of other genetic aortic aneurisma syndromes.
  4. In presence of ectopia lentis without aortic dilatation / dissection, the identification of mutations of the FBN1 gene associated with aortic disease allows the diagnosis of the MS.

Wrist AND thumb sign: 3 (wrist OR thumb sign: 1)
<i>Pectus carinatum deformity</i> : 2 ( <i>pectus excavatum</i> o chest asymmetry: 1)
Hindfoot deformity: 2 (plain flat foot: 1)
Pneumothorax: 2
Dural ectasia: 2
Protrusio acetabulae: 2
Reduced upper segment/lower segment and increased armspan/height: 1
Scoliosis of thoracolumbar kyphosis: 1
Reduced elbow extension 1
3 of 5 facial features: 1 (dolichocephaly, enophthalmos, downward slanting palpebral fissures, malar hypoplasia, retrognathia)
Skin striae: 1
Myopia >3 diopters: 1
Mitral valve prolapse: 1
Maximum total 20 points; <i>score</i> $\geq 7$ indicates systemic affectation.

**Table 2.** Systemic findings score

- **In the presence of family history**, the diagnosis can be established in the presence of ectopia lentis plus a systemic score  $\geq 7$  points, or the presence of aortic dilatation ( $Z \geq 2$  in adults  $\geq 20$  years, or  $Z \geq 3$  in individuals  $< 20$  years).

#### **In absence of family history for Marfan's syndrome**

1. Ao ( $Z \geq 2$ ) and EL = MFS<sup>a</sup>
2. Ao ( $Z \geq 2$ ) and FBN1 mutation = SMF
3. Ao ( $Z \geq 2$ ) and systemic *score* ( $\geq 7$  points) = SMF<sup>a</sup>
4. EL and FBN1 mutation identified in individuals with aortic aneurysm = SMF
  - EL with or without systemic score, without FBN1 mutation, or with FBN1 mutation not related to aortic aneurysm/dissection = ELS
  - Ao ( $Z \geq 2$ ) and systemic score ( $\geq 5$  points) without EL = MASS
  - PVM and Ao ( $Z < 2$ ) and systemic *score* ( $< 5$  points) without EL = SPVM

#### **In the presence of family history**

5. EL and FH of MFS = MFS
6. Systemic score  $\geq 7$  points and FH of MFS = SMF<sup>a</sup>
7. Ao ( $Z \geq 2$  in  $> 20$  years,  $Z \geq 3$  in  $< 20$  years) and FH of MFS = MFS<sup>a</sup>

Ao: aortic diameter in Valsalva sinus (indicated by Z-score) or dissection; FBN1 mutation: mutation in fibrillin 1 gene; EL: ectopia lentis; MASS: phenotype with myopia, mitral valve prolapse, bordering expansion of aortic root ( $Z < 2$ ), skin striae and skeletal findings; PVM: mitral valve prolapse; ELS: ectopia lentis syndrome; MFS: Marfan's syndrome; VMPS: mitral valve prolapse syndrome; Z: Z-score.

<sup>a</sup> Warning: reject Shprintzen-Goldberg, Loeys-Dietz o vascular type Ehlers-Danlos syndromes, study of TGFBR1/2, COL3A1 mutations, and collagen biochemistry.

**Table 3.** The revised Ghent nosology for the Marfan Syndrome

In addition, there are considered two new situations in patients younger than 20-year-old. The first of them, the **“unspecific disorder of the connective tissue”** for the cases with insufficient systemic findings (<7 points) and/or bordering dimensions of the aortic root (Z <3), without mutation of the FBN1 gene. The second one, the **“MFS potential”** for the sporadic or family history cases with mutation of the FBN1 gene and aortic dimensions with Z<3 score.

In adults, three alternatives categories are defined: ecopia lentis syndrome (ELS), mitral valve prolapse syndrome (MVPS) and the phenotype MASS.

Finally, the experts' panel recognizes the difficulty for establishing MFS's diagnosis in certain patients due to the overlapping phenotype of diverse entities.

## 2.2. Hereditary syndromes related to thoracic aorta aneurysms

The thoracic aortic aneurysms (TAA) are a relatively frequent entity, being responsible for approximately 15,000 annual deaths in USA. Up to 20 % of the patients with TAA, a genetic substratum is detected [4].

The familial TAA are classified in syndromics (they appear with phenotypics manifestations to other levels) and non syndromics (they appear as an isolated manifestation but with family aggregation, suggesting a genetic substratum).

The MFS is the most important entity inside the familial syndromics TAA. It is necessary to establish the differential diagnosis between this one and others mixed connective tissue diseases with clinical manifestations and similar phenotypics features. The majority of these diseases (table 4) are monogenics and with a dominant autosomal inheritance.

<b>Familial Syndromic Thoracic Aortic Aneurysm Syndromes</b>	<b>Non fibrilinopathies</b> Loeys-Dietz's syndrome Type IV Ehler-Danlos's syndrome Turner's syndrome Beals's syndrome Noonan's syndrome Alagille's syndrome Autosomal dominant polycystic kidney disease <b>Fibrinilopathies</b> Shprintzen-Goldberg's syndrome Weill-Marchesani's syndrome MASS phenotype
<b>Familial Non Syndromic Thoracic Aortic Aneurysm Syndromes</b>	TAAD1, TAAD2, TAAD3, TAAD4, TAAD5, FAA1 and TAAD associated to ductus arterial persistent Bicuspid aortic valve

**Table 4.** Differential diagnosis of Marfan's syndrome

Among the genetic syndromes that can be accompanied of TAA, we can emphasize:

*MAAS phenotype (mitral valve, aorta, skin, skeletal)*

It is included inside the fibrillinopathies group, that is to say, diseases results from mutations in the FBN1 gene. It is characterized by the presence of myopathy, mitral valve prolapse, aortic dilatation (slight and not progressive) and alterations of the cutaneous and musculoskeletal system. At least two systems must be affected.

*Loeys-Dietz's syndrome*

Autosomal dominant genetic syndrome caused by mutations in the genes encoding transforming growth factor  $\beta$ 1 (TGFB1) or 2 (TGFB2). Two phenotypic variants can be currently distinguished (table 5).

The aortic aneurysms are very frequent, appearing in 98 % of the cases, at early ages, and they are characterized by a high risk of dissection and / or rupture, even with diameters <5 cm. Up to 53 % of the patients may develop aneurysms in other locations. In general way, it is accepted that those patients with more severe craniofacial manifestations present the most aggressive vascular disease.

Patients with this syndrome are recommended to realize a complete imaging study to evaluate the aorta in the moment of the diagnosis and every 6 months, to check the growth rate of the TAA. An annual craniothoracoabdominal magnetic resonance must be fulfilled for the detection of systemics vascular aneurysms.

	<b>Type I Loeys-Dietz syndrome</b>	<b>Type II Loeys-Dietz syndrome</b>
<b>Phenotype</b>	Hypertelorism Craniosynostosis Cleft palate or bifid uvula Arterial tortuosity and aneurysms/dissections	Without other craniofacial anomalies, except bifid uvula Similar to type IV Ehlers-Danlos's syndrome
<b>Mutated genes</b>	TGFB1 and TGFB2	TGFB1 and TGFB2
<b>Prevalence</b>	Unknown	Unknown
<b>Prognosis</b>	37 years of median survival Average age of death at 26 years	37 years of median survival Average age of death at 26 years

**Table 5.** Variants of Loeys-Dietz's syndrome

The surgical repair of the TAA in patients with Loeys-Dietz's syndrome must be realized when the internal diameter overcomes 4,2 cm for transesophageal echocardiogram or the external diameter is major than 4,5 cm in a computerized tomography or magnetic resonance.

### *Ehlers-Danlos's syndrome vascular type or type IV Ehlers-Danlon's syndrome*

It is caused by mutations in the genes encoding the collagenous type 3 (COL3A1) with an autosomal dominant inheritance. It is characterized by vascular and visceral external fragility, which can lead to vascular and visceral spontaneous breaks or with minimal traumatism. The cutaneous or articular hyperlaxity is less marked than in other subtypes. The majority of the deaths are due to vascular breaks.

It is recommended to carry out non-invasive imaging tests because of the high risk of vascular break. It is unknown the usefulness of the aortic surgery in the repair of the not complicated TAA. In case of dissection or rupture, the urgent surgery is indicated, with special attention to the vascular anastomosis because of the trend to the hemorrhage, vascular fragility and the difficulties in the tissue regeneration capacity in this syndrome.

### *Turner's syndrome*

It is a chromosomal abnormality in which the monosomy X is the most common (cariotipe 45, X0). The patients affected with Turner's syndrome present characteristic physical abnormalities such as short stature, webbed necks and sterility. There can be associated different cardiovascular manifestations, as the coarctation of aorta, early ischemic cardiopathy, bicuspid aortic valve and TAA (up to 40 % of the cases). The incidence of aortic dissection in these patients is greater compared with the healthy population, six-times increased risk, with a median age of presentation of 31 years.

It is recommended to realize an initial imaging test to reject bicuspid aortic valve, coarctation of aorta and / or TAA. If the test is normal and there are no risk factors for aortic dissection it is enough to do an imaging test every 5-10 years. In the opposite case, annual controls are advised. In those patients with Turner's syndrome who are planning to get pregnancy, an imaging test must be realized to determine the risk of aortic dissection.

### *Autosomal dominant polycystic kidney disease*

Disease caused by a mutation in the genes PKD1 and PKD2. Its more frequent complication are the hemorrhages subaracnoideas due to the rupture of cerebral aneurysms. It is also associated with an increase in TAA and type-A aortic dissections.

### *Beals's syndrome or congenital contractural arachnodactyly*

It is an autosomal dominantly inherited connective tissue disorder caused by a mutation in FBN2 gene. Although the clinical features can be similar to Marfan syndrome, multiple joint contractures (especially elbow, knee and finger joints), arachnodactyly, severe kyphoscoliosis, abnormal pinnae, muscular hypoplasia and crumpled ears in the absence of significant aortic root dilatation are characteristic of Beals syndrome and rarely found in Marfan syndrome.

Responsible gene	Familiar Non syndromic TAA	%	Aortic dissection
Unknown gene Locus 5q13-14 Gene that codifies for the proteins versican, trombospondina 4 and protein related to the cartilage	TAAD1		
TGFBR2 Gene that codifies the receptor of the transforming growth factor $\beta$ 2 Mutation in arginina 460, locus 3p24-25	TAAD2 The same gene mutated in the syndrome Loeys-Dietz	5 %	Risk of aortic dissection with diameter <5 cm Recommendations similar to those for Loeys-Dietz's syndrome
MYH11 Heavy chain of the 11- $\beta$ miosina, specific for smooth muscle cells. Located in the chromosome 16p	TAAD-persistent arterious ductus	1 %	Risk of aortic dissection with diameter $\leq$ 4,5 cm
ACTA2 Gene that codifies for the region alfa2 of the actina of the aortic smooth muscle. Locus 10q22-24	TAAD4	15 %	Risk of type A aortic dissection with diameter <5,0 cm and at early ages of life Risk of type B aortic dissection with < 21 years old
TGFBR1 Gene that codifies the receptor of the transforming growth factor $\beta$ 1 Locus 9q33-34	TAAD5 The same gene mutated in Loeys-Dietz's syndrome and Furlong's syndrome		
FAA1 Locus 11q23-24	FAA1		
FBN1 Gene that codifies the fibrilina 1 Locus 15q21.1 It can present mosaicism in somatic and germinate cells	The same gene mutated in Shprintzen-Goldberg's syndrome, Weill-Marchesani's syndrome and the phenotype MASS (fibrilinopathies)		

**Table 6.** Familial non syndromic thoracic aortic aneurysm syndromes (*see text*)

The majority of the familial TAA and aortic dissections are produced in patients who cannot be fitted in any of the syndromes described before. The studies of family aggregation suggest that between 11 and 19 % of the patients with TAA or dissections present a first degree relative with this antecedent.

In general, the presentation of aortic complications (rupture and/or dissection) in patients with familial non syndromic TAA occur at earlier ages in comparison with the sporadic aneurysms (median age of 56,8 years opposite to 64,3 years), though without reaching the precociousness of the syndromic TAA. The aortic dilatation can concern both the tubular portion of the ascending aorta and sinus of Valsalva. The age of appearance and the growth rate are very changeable, even inside the components of a same family.

From a genetic point of view, the familial non syndromic TAA are very heterogeneous, having been located up to 7 different loci, that can explain only 20% of the cases: TAAD1, TAAD2, TAAD3, TAAD4, TAAD5, FAA1 and TAAD-partner to persistent arterial ductus (table 6). The way of inheritance is autosomal dominant with incomplete penetrance, minor in the female sex.

In patients with familial non syndromic TAA it is necessary to realize an individualized genetic advice to the relatives. It is necessary to realize a genetic analysis to the first degree relatives in case of a known mutation in the index case. In the first degree relatives with a negative genetic study, it is recommended an unique imaging test to reject aortic pathology. In case of presenting any of the genetic mutations described mutations, periodic reviews must be made every 2 years approximately.

### 2.3. Genetics of Marfan's syndrome

Marfan syndrome results from mutations in the fibrillin-1 (FBN1) gene located on chromosome 15q21.1 and, occasionally, by mutations in *TGFβR1* or *TGFβR2* genes (transforming growth factor-β receptor 1 and 2) located on chromosome 9 and on chromosome 3p24.2-p25, respectively [5]. More than 500 fibrillin gene mutations have been identified. Almost all of these mutations are unique to an affected individual or family. Different fibrillin mutations are responsible for genetic heterogeneity. Phenotypic variability in the presence of the same fibrillin mutation suggests the importance of other, yet-to-be-identified factors that affect the phenotype.

#### *Fibrillin-1 (FBN1) gene*

The fibrillin-1 gene consists of 65 exons and it is located in the chromosome 15q-21.1. It encodes for the glycoprotein fibrillin, which is a major building block of microfibrils that constitute the structural components of the suspensory ligament of the lens and serve as substrates for elastin in the aorta and other connective tissues.

The FBN1 gene is characterized for having several rich sequences in cysteine, comparable to the factor of epidermal growth (EGF). 47 exons codify a complete domain EGF and 43 of these include the sequence consensus for the union to the calcium *Asp/Asn-x-Asp/Asn-*

*Glu/Gln-xm-Asp/Asn\*-xn-Tyr/Phe* (where x represents any amino acid, \* it represents possible beta-hydroxylation of this residue and "m" y "n" represent a variable number of residues). Each of the EGF-similar contains six residues highly preserved of cysteine that form three disulfide bonds between C1 and C3, between C2 and C4 and between C5 and C6, resulting in a structure of  $\beta$  strand what is involved in the union to the calcium. Calcium plays a very important role in the stability of the domain and awards a major resistance to the proteolytic degradation.

Nowadays, several strategies can be used in the genetic study of the FBN1 gene, being the reference the direct sequentiation of the exons and the border intron regions. Another method is the high-performance denaturing liquid chromatography liquid, with later confirmation for direct sequentiation. When a mutation is not identified and there is a high clinical suspicion of the presence of the disease, there can be looked big deletion/duplication, impossible to detect for the previous methods, using MLPA (multiplex ligation-dependent probe amplification). Finally, the analysis of genetic linkage can be used to determine if an individual has inherited an allele of the FBN1 gene that is associated with the syndrome in several members of the family, nevertheless its cost and efficiency are limited compared by the sequencing technique.

In order to consider the identified mutation as responsible, the following criteria must be evaluated:

1. If the mutation has been described before, familial cosegregation must be demonstrated, that is to say, that in a family with MFS, the ones with the mutation must be affected and those without the mutation must be healthy.
2. If the mutation has not been described before, it is necessary to consider the following premises:
  - a. Certain mutations have a high probability of being pathogenic:
    - *Nonsense mutation*, that creates a premature stop codon
    - Insertion/deletion that concerns a number of bases that is not multiple of three, and consistently alters the reading, usually creating a premature stop codon
    - Mutation that affects the *splicing* of the sequence of reference or that alters to level of the cDNA/mRNA ("splice site mutations"); mechanism that forms a part of the mRNA maturation consisting of the elimination of the introns so that a codificant and without interruptions sequence is obtained, and it can be translated into protein.
    - *Missense* mutation that creates or replaces cysteine
    - *Missense* mutation that concerns a preserved residue of the consensus EGF sequence.
  - b. The mutation must concern a preserved residue in the evolution. It is considered that the amino acids that have not suffered changes along the evolutionary scale are important for the function of the same one.
  - c. For the demonstration of the pathogenic of a mutation, bioninformatic models can be used so that they can predict if the change that induces the mutation can carry deleterious effects or not in the protein.

- d. The familial cosegregation must be demonstrated if possible, and the absence of the mutation in at least 40 chromosomes of the same etnia, that is to say, at least in 200 subjects.
- e. The pathogenicity is high probably in the identified mutations by genetic linkage.

The sensibility to find a mutation in a patient with MFS is high, varying between 76 and 93% in recent studies. It depends on several factors, as the age, the familial history or the method used for the genetic study.

Marfan syndrome is known as an autosomal dominant connective tissue disorder. Hereby, the risk that a son of an affected father has the disease is 50%. Approximately, 75% of the patients with MFS has one of his parents affected, and only in 25% the affected one presents a de novo mutation.

The penetration of the mutations in FBN1 is in general high, being considered to be near to 100%. It has been communicated exceptional cases of incomplete penetration. It is necessary to consider that many of the manifestations appear with the age.

Those patients with severe and progressive forms of the disease (called "The neonatal Marfan Syndrome") usually have mutations in the central part of the gene, between exons 24 and 32 of FBN1. Affected individuals are generally diagnosed at birth or shortly thereafter. Congestive heart failure associated with mitral and tricuspid regurgitation is the main cause of death, whereas aortic dissection is uncommon; survival beyond 24 months is rare. As a general rule, the mutations that produce insertions or deletions with change or displacement of the frame of reading or *splice site mutations*, are usually associated to severer forms of the disease. The patients with mutations that alter the terminal-C-propeptide procesate have been related to predominantly skeletal affectations of the disease. It is evident that it is necessary to compile information about the clinical consequences and the phenotype associated with different mutations, since mutations with the same mechanism can have very different clinical consequences, as it is demonstrated in other genetic pathologies.

The diagnosis of the MFS can be realized without needing a genetic study. Nevertheless, it has a great importance in the following suppositions:

1. It is of great relevancy in patients who do not fulfill clinical criteria, especially in patients with ectopia lentis and patients with cardiovascular suggestive features combined with skeletal findings or in sporadic cases in young subjects.
2. It is very useful in relatives of affected patients, especially children, to know if they have inherited the mutation of their parents and so they will need periodic controls.
3. It must be realized in patients in whom the genetic diagnosis can influence their way of life, as in high competitive sports, for the initiation of the treatment or programming of clinical follow-up.
4. It can be useful for prenatal diagnosis, analyzing DNA extracted from foetal cells obtained of the chorionic villus between 10 and 12 weeks' gestation. It might be done whenever a causal mutation had been identified in the relative, with pathogenicity

clearly demonstrated, and avoiding the pollution by mother DNA of the studied sample, in the cases in which the mother is affected.

5. In the preimplantational diagnosis in in-vitro fertilization treatments. The use for the prenatal and preimplantational diagnosis is controversial in many countries, with ethical and legal aspects that must be have in mind.

#### *Transforming growth factor- $\beta$ receptor 1 and 2 (TGFB $\beta$ 1 and 2)*

There have been found mutations in these genes in some of the MFS diagnosed patients or thos with MFS's suspicion. These patients present a more aggressive form of the vascular disease, with dissections and ruptures at earlier ages and with smaller diameters. Initially they were identified by MFS's type 2, leaving the type 1 for mutations in the FBN1 gene. Later, these patients with marfanoid phenotype, aggressive vascular disease and other morphologic features (hyperterolism, bifid uvula, ...) were grouped in Loeys-Dietz's syndrome. Thus, we can find it with both nomenclatures.

#### **2.4. Use of biomarkers in Marfan's syndrome**

According to the definition of the National Intitutes of Health, a biomarker is “a characteristic that can be quantified and evaluated in an objective way as an indicator of normal biological processes, pathogenic processes or pharmacological answers to a therapeutic intervention” [6]. The employment of biomarkers facilitates the identification of patients at risk, and they are usually molecules that can be identified by a blood analysis.

Nowadays we don't have many specific bibliography about circulatory biomarkers for the thoracic aortic aneurysm. The not circulatory biomarker that is in use with more frequency is the diameter of the aneurysm.

Below we will detail the biomarkers that could have importance in the clinical management of the thoracic aortic aneurysms, as in Marfan syndrome:

##### *D-dimer*

It has been demonstrated that the concentrations of D-dimer allow to detect the Stanford type A acute aortic dissection. The concentration of the D-dimer obtained during the hospital admission is correlated by the survival of these patients. Thus, elevations in the concentration of D-dimer in patients who come to Emergency Room for thoracic pain it should be realized a tomography computerized to reject acute aortic dissection as well as acute pulmonary embolism.

##### *Cellular biomarkers*

There have been identified two types of cells that are associated with the evolution of an aneurysm, the CD 28 T-lymphocytes and the natural citolytic lymphocytes or natural

killer. It has been demonstrated in studies the presence of population of natural killer lymphocytes in greater number in patients with abdominal aortic aneurysm compared with healthy subjects. The CD 28 T-lymphocytes appear in diverse inflammatory disorders, and express in a more frequent form with the age. It has been observed in patients with aneurysms greater quantity of this cellular type in peripheral blood compared to healthy controls. In addition, on a contradictory way, highest rates are found in patients with smaller aneurysms in comparison with patients with big aneurysms, appearing the hypothesis about the intervention of Cd 28 T-lymphocytes in the genesis of the aneurysms.

### *Biomarkers in plasma and serum*

Several circulating biomarkers have been identified with the aneurysms, in relation to their appearance, diameter or expansion. These can be classify in inflammation biomarkers, indicators of tissue turnover, and others as homocysteine, serum amyloid A, osteopontin, osteoprotegerin and the concentrations of plasmin / antiplasmin complex.

Inflammation biomarkers have been the more widely studied. At present, the formation of the aortic aneurysm is understood as an inflammatory process. Many studies relate diverse inflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor- $\alpha$ , interferon  $\gamma$  and cold-reactive proteins) to the formation, expansion or rupture of the aneurysm. Its disadvantage is the lack of specificity, being able to rise their concentrations in other inflammatory processes, reason why their clinical utility as aortic aneurysm biomarker is limited.

Special mention is deserved to the matrix metalloproteinases (MMPs). Their main function is the degradation of the extracellular matrix. The MMPs are active in many pathological processes, either in trivial ones as periodontitis or others more serious as heart failure. In experimental models with animals, there has been demonstrated that MMP's inhibition, by genetic deletion directed or by pharmacological intervention, determines a minor progression of the abdominal aortic aneurysms. In patients with abdominal aortic aneurysm, the circulating concentrations of MMP-9 presented a direct correlation with the concentrations of MMP-9 in the aortic wall. It has been observed an increase in the concentration of MMP-1 and MMP-9 in the thoracic aortic walls with aneurysms or dissections in comparison with healthy controls. It has also been observed an increase of the quotient MMP-9/TIMP-1 (tissue inhibitor of metalloproteinases-1), favoring the proteolysis of the aortic wall. Other studies have documented a correlation of MMP's activity, especially MMP-9, with the genesis and evolution of the thoracic aortic aneurysms.

### *Molecular biomarkers*

It has been studied the RNA of circulating leukocytes and there have been identified characteristics of expression that relate to the appearance of thoracic aneurysms, with an accuracy up to 78%. In the same line, there has been identified a hyperexpression of certain

genes in patients with thoracic and abdominal aortic aneurysms. Among these genes, we must emphasize those who codify the intracellular adhesion molecule-1, v-yes-1 oncogene, mitogen activated protein kinase and the MMP-9.

In short, it does not exist a perfect biomaker for a pathological process. In case of the thoracic aortic aneurysms, the best described biomarker and with wide diffusion in the clinical practice is the diameter of the same one. Big advances have been achieved in circulating biomarkers, though further study is required to be able to generalize it to the daily clinical practice.

## 2.5. Diagnosis of the aortic affection in the MFS

In a summarized form, the management of the aortic pathology in the MFS is based on the clinical study and imaging techniques to detect and to quantify the progression of the aortic expansion [7].

The initial clinical evaluation of every patient with MFS's suspicion must include anamnesis and a complete clinical examination. The diagnosis of certainty can be reached in almost 90% of the cases through the Ghent's nosology, being able to be completed by the genetic study as we have described before. To complete the information about diagnostic criteria (table 1) we will carry out an imaging test that allows to evaluate the ascending aorta and the cardiac valves.

The transthoracic echocardiogram (TTE) represents the main technique for the diagnosis of the cardiovascular affection in the initial evaluation of patients with MFS, allowing to explore the aortic root, the proximal ascending aorta and the aortic arch. The maximum diameters of the aortic annulus, Valsalva sinus, sinotubular junction and of the ascending aorta must be measured perpendicularly to the longitudinal axis of the aorta. The obtained information will be compared in nomogramas with the expected values according to the age, the sex and the corporal surface. The severity of the aortic affection relates to the degree and the extension of the dilatation, being most important when it spreads from the root over the ascending aorta up to the aortic arch. The second TTE will be carried out at 6 months of the diagnosis to determine the speed of growth. If the diameter remains stable, the ultrasonic study can be realized annually, but if accelerated expansion is detected or when it comes closer to 45mm, the evaluation will have to be more frequent (table 7).

In spite of the fact that the transthoracic echocardiogram is the most used technique to monitor the size of the aortic root, its precision depends on the operator. The computerized tomography (CT) or the magnetic resonance (MRI) are more precise and must be used if the echocardiogram does not give a suitable image of the aorta. It is advisable to know that the echocardiographic measures, being realized between internal edges, can be up to 4mm lower than the obtained ones with MRI or CT, in which the thickness of the wall joins.

**Anamnesis, physical examination, echocardiogram:****At the beginning and at the 6 months<sup>a</sup>****Later: every year, if the growth rate is stable and without complications<sup>a</sup>****CT or MRI:**

If there is aortic dilatation or dissection.

After the surgery, before the discharge, at 6 months, and then annually.

The evaluation will be more frequent as the aortic root approaches 45mm or if it is registered an accelerated rate of growth (> 5 mm / year)

a Class I recommendation, level of evidence C.

b It is considered of utility to correct the aortic diameters in accordance with the age and the corporal size (class IIa, level of evidence C).

**Table 7.** Cardiovascular follow-up in Marfan's syndrome

## 2.6. Pharmacological treatment in the prevention of the cardiovascular complications of the MFS

The pharmacological treatment in the prevention of the cardiovascular pathology in patients with MFS is based on the employment of  $\beta$ -adrenergic blocking agents and renin-angiotensin system antagonists [8].

### *Beta blockers*

Many studies have demonstrated that the employment of betablockers can slow down the aortic rate expansion and delay the moment of appearance of the aortic complications of the MFS, as the aortic regurgitation, the aortic dissection, the need of surgery, the congestive heart failure or the death, specially if they are used in the initial phases of the disease, as they can reduce the hemodynamic stress of the thoracic aorta wall.

These benefits are in all the groups of age, being more important in patients with not severe aortic dilatation.

Nowadays the clinical guidelines recommend the employment of betablockers at the right dose in all patients with MFS who tolerate them, independently from the degree of aortic dilatation.

Given that the aortic growth rate changes along the life, presenting a prepuberal peak, it is recommended the beginning of the treatment with betablockers in the infancy, and to support it forever, even in patients who have received aortic prophylactic surgery.

The effects of the pharmacological treatment must have a periodic review to assure an optimal management of the cardiac frequency and the arterial pressure of the patient (table 8).

<b>Betablockers</b>	<p><b>Use always in MFS, except in cases of intolerance<sup>a</sup></b>  <b>Atenolol: more used (long half-life and cardioselective)</b>  <b>Dose: to titrate up to CF at rest &lt;60 lpm and &lt;100 lpm in exercise, if the AP allows it.</b>  <b>To monitor the efficiency and the doses in periodic visits</b></p>
<b>Calcium channel blockers</b>	Verapamil: second line treatment in patients who do not tolerate betablockers
<b>ACE inhibitors</b>	Associated to betablockers when additional treatment is needed to control the AP, specially those with chronic dissection
<b>AT1R-II</b>	AT1 blockers (losartan) <i>associated to betablockers</i> ; in small not randomized studies, major efficiency in delaying the aortic rate growth <sup>b</sup> . AT1 blockers, <i>associated to betablockers</i> ; alternative use to ACEi when additional medication is needed for AP's control
	<p>a Class I recommendation, level of evidence B.  b Class IIa recommendation, level of evidence B.</p>

**Table 8.** Pharmacological treatment in the MFS

### *Renin-angiotensin-aldosterone system antagonists*

The influence of the renin-angiotensin-aldosterone system in the aortic wall degeneration of the MFS seems to be increasingly important. The angiotensin II (ATII) stimulates the expression of metalloproteases and promotes the apoptosis of the smooth muscle cells in the aortic wall. The experimental models have demonstrated that the deficiency of *FBN1* increases the TGF- $\beta$  active, causing the detention of the cellular differentiation cycle, an increase of the apoptosis and deposit of extracellular matrix. The employment of renin-angiotensin system antagonists by means of angiotensin-converting-enzyme inhibitors (ECAs) or with angiotensin II receptor antagonists (ARAI), produces beneficial effects at different levels. The ECAs contribute, apart from the control of the AP, to the decrease of the inflexibility of the aortic wall. The selective block of the type 1 receptor (AT1) of the angiotensin II might reduce the deleterious effects of the TGF- $\beta$ , independently of the effects on the control of the AP. Though in animal models, losartan has demonstrated to stop and even to revert MFS manifestations, including the aortic aneurysm and its complications, we are waiting for the results of controlled clinical trials in human beings that are in process.

It is important to insist that the medical treatment, based fundamentally on betablockers, which is possible to associate to the renin-angiotensin system block, gets delaying the aortic expansion, but no medicament, up to the moment, has demonstrated either to avoid the development of aortic dissection or to avoid the need for surgery in human beings.

### *Physical activity*

To reduce the hemodynamic stress in the MFS, the restriction of the physical activity complements the pharmacological therapy. The intense isometric exercise is contraindicated

due to the marked increases in the peripheral AP and the stress of the proximal aortic wall. Also competitive sports, contact sports and those that with marked changes in the atmospheric pressure are contraindicated, to prevent the arterial traumatism and the pneumothorax. Since the dynamic exercise is associated with minor aortic stress, for the decrease of the peripheral vascular resistance and of the diastolic AP, in patients without high risk, the practice of aerobic activity of moderate intensity is considered to be sure (table 9).

## 2.7. Prophylactic surgery of the proximal aorta

In the MFS, the prophylactic surgery of the aortic root and the ascending aorta is recommended, because of the high mortality of the emergency aortic replacement and because both, the type A aortic dissection and the aortic rupture, are the complications with major impact in the survival. Though technically more complex, the aortic valve conservation techniques, remodeling or reimplantation, are usually the ones preferred than the valvulated tubes, whenever they offer good results.

Provided that the dissection and mortality risk are proportional to the size of the proximal aorta, the guidelines recommend elective surgery in adults when the *external* diameter is  $\geq 50$ mm. The surgery also must be considered in patients with diameter  $< 50$ mm if they present additional risk factors: rapid growth of the aortic diameter ( $> 5$ mm/year), familial history of aortic dissection or rupture, or the presence of significant aortic regurgitation (table 10).

With regard to the *timing* of the elective surgery, some considerations must be done. According to the value of the threshold of the diameter, a more or less important proportion of patients will present complications without reaching this value or will surrender unjustifiably to the surgical risk of an elective procedure still being removed from complications. It turns out important to incorporate another information, as the growth rate, and indexing the diameters by body surface. The corporal surface, used in many nomograms on having contemplated the weight, can artificially modify the surgical risk. The current trend is to correct according to the stature, in order that in subjects of minor stature, specially women, but at risk of complication, surgery could be indicated even if their diameters were more near to 45 than to 50mm. In the clinical practice, the surgical indication starts being considered when the aorta is expanded ( $\geq 2$  deviations over the average,  $Z$ -score  $\geq 2$ ) or when its diameter comes closer to 45mm (before if the stature is lower than 170cm). The surgical results are determinant to indicate prophylactic surgery, preferably preserving the valve and with very low mortality, necessarily lower than 5%.

In *children and teenagers* with MFS, the establishment of a relation with the diameter of the aorta is more difficult than in adults, since the complications are infrequent before 12 years of age. The elective aortic surgery in this population, up to 18 years, is recommended when the aortic diameter exceeds 50mm, when there is a rapid aortic growth ( $> 10$ mm/year), when aortic regurgitation appears, or when there is simultaneous affection of the mitral valve. As for the *timing*, it is necessary to weigh the risk of dissection and the delay of the surgical moment to avoid prosthetic *mismatch*, since the children will continue growing. The

paediatric nomograms have been re-calculated to improve their correspondence with those of adults. The normalization for sex, age and corporal surface seems to be suitable, though it will be necessary to define better which is the dilatation of risk in which the benefits of the prophylactic surgery unequivocally overcome the risks.

Type of patient	Recommendation
Every patient with SM: Any degree of aortic root dilatation	To avoid contact sports of contact and those with risk of corporal impact
Low risk: all the following ones: Without aortic root dilatation: <ul style="list-style-type: none"> <li>• Adults, root &lt;40 mm</li> <li>• Children and teenagers: root Z-score &lt;2</li> </ul> Mitral regurgitation less than moderate Without familial history of dissection or sudden death	Static and dynamic activity of low and moderate intensity <sup>a</sup>
Risk: any of the following ones: Aortic root dilatation <ul style="list-style-type: none"> <li>• Adults, root ≥40 mm</li> <li>• Children and teenagers: root Z-score ≥2</li> </ul> Moderate or severe mitral regurgitation Previous surgery of aortic root Chronic dissection Familial history of dissection or sudden death	Alone advisable dynamic activity of low intensity

Treatment with betablockers is considered to be a standard for all patients.

a Maximum heart rate during activity <100 lpm (adults) and up to 110 lpm (children) with betablockers.

b If there is usual sport practice, it is suitable to follow-up the growth rate of the aortic root by a transthoracic echocardiogram each six months.

The presence of significant aortic regurgitation with aortic root dilatation makes inadvisable any type of sports practice.

**Table 9.** Recommendations for the physical activity in Marfan's syndrome

In what concerns the aspects of the *surgical techniques*, the Bono and Bentall procedure has been considered the *gold standard* for the treatment of these patients. It consists in replacing the root and the aortic valve with a composite graft by a dacron vascular graft (rectum or with morphology that imitates to Valsalva's sinus) and a prosthetic valve; the coronary arteries have to be reimplemented into the vascular graft. Diverse technical variations (inclusion vs interposition, *button technique*, Cabrol modification or Svensson) have emerged over the years trying to reduce the early complications (bleeding, coronary occlusion) and the late ones (anastomotic pseudoaneurysms) of the same one, being the most used nowadays the Bono-Bentall by interposition with anastomosis of the coronary arteries in tablets (*button technique*). In young patients, mechanical prosthetic valves are the most used,

whereas in those of major age or with contraindications for anticoagulation, biological valves are usually used.

**Class I recommendations, level of evidence C**

**External diameter of proximal aorta  $\geq 50$  mm**

**External diameter  $<50$ mm with any of the following risk factors:**

- **Familial history of dissection or aortic rupture**
- **Rapid progression of the aortic diameter ( $> 5$  mm/year)**
- **Significant aortic regurgitation (moderate or major)**

**Class IIa recommendations, level of evidence C**

In women with MFS who wish to get pregnancy, it looks reasonable the aortic root and ascending aorta replacement when the diameter is  $> 40$  mm

Aortic surgery will be recommended when the quotient of the proximal aortic maximum area (in  $\text{cm}^2$ ) divided by the stature in meters is superior to 10, since the smallest patients and up to 15% of the MFS patients have aortic dissection with diameters  $<50$  mm

**Table 10.** Criteria for the elective surgery of the aorta proximal in adults with MFS

The immediate and long-term results of this technique are very good, and the rates of the long-term survival are similar to those of the general population. Nevertheless, the results deteriorate considerably when the surgery is realized in an emergent form in the context of an aortic dissection. The long-term morbidity of these patients is in relation with the fact of being carriers of a valve prosthesis. This is the reason why in the last years some techniques have emerged to try to preserve the native aortic valve, which is re-implanted to the dacron vascular graft. They are the valve preserving techniques or *valve-sparing*, basically with two variants, the *reimplantation technique* or David procedure and the *remodeling technique* or Yacoub's surgery. In both cases, the aortic root is cut just above the aortic valve annulus and the coronary ostia; the diseased portion of aorta is removed and a collagen-coated polyester graft is used. In the modified David procedure, the sutures are placed just below the aortic valve, around the left ventricular outflow tract, and these sutures are then tied around a Hegar's dilator to shape the bottom portion of the aort graft similar to a natural aortic root. Next, the valve is resuspended within the graft, the aortic valve may be repaired or remodeled, and small holes are produced in the aorta graft for the coronary ostia, which are re-attached through the small holes.

In the Yacoub technique, the graft of dacron stands out imitating Valsalva's bosoms and the graft is sutured to the remnants of aortic fabric that stay close to the insertion of the veils.

David's technique is the one that more followers has inside the surgical community since theoretically it stabilizes better the valvular ring, though there are surgeons who praise the use of Yacoub's technique associated with maneuvers of stabilization to annul (anuloplastias

with suture or with external rings), since this skill preserves better the functionality of the aortic root.

Those valve sparing methods can be realized either if the aortic valve is competent in the moment of the intervention or when it is not, though in the latter case, specially if the regurgitación is very ancient, it maybe not possible to preserve the valve. This owes to the intense elongation that the leaflets can present, with very thin and friable tissue even with big fenestrations, on having been submitted to a great mechanical tension for a long time.

The immediate results of these procedures are similar to those of Bentall's surgery, though they are technically challenging, so they are used only in reference centres [9]. The long-term results also are excellent, remaining the patients free of significant degrees of aortic valve regurgitation and reoperation greater to 90% at 10 years [10].

Given these good long-term results, in many centers the valve sparing surgeries have turned into the new *gold standard* for the patients with Marfan syndrome.

## 2.8. Elective surgery of the descending aorta

Though the elective surgery of the descending aorta is nowadays a safe procedure, the risk of paraplegia is still present (that should be lower than 5%) depending on the group experience, on the extension of the aortic segment to be replaced and on the spinal cord protection. Since the operative risk increases in the emergency cases (dissection or rupture), and given the limitation for the use of stents in these patients, it is recommended the prophylactic replacement of the aortic segment when the diameter is > 55mm (class I recommendation, level of evidence C).

## 2.9. Treatment of the acute aortic complications

The treatment of the acute aortic complications in patients with MFS includes the management of the type A and B ascending aortic dissection (table 11).

### *Type A ascending aortic dissection*

Given that the unpredictable nature of the aortic dissection in the MFS, it is necessary to educate the patients on the symptoms of the acute aortic dissection. As in the general population, the type A aortic dissection in the MFS is a emergency surgery emergency in which there must be replaced the sinus and the sufficient extension of the ascending aorta.

### *Type B descending aortic dissection*

The type B aortic dissection represents approximately 10% of the acute aortic dissections in the MFS. Like in other patients, the medical management is initially recommended, except

complications or lack of response, in which case, the surgery must be considered. The routine accomplishment of CT or MRI is recommended if the descending aorta is large or if it has been dissected after the repair of a type A dissection. In the type B chronic aortic dissection it is recommended the open surgery when, in the absence of high comorbidity, the aorta diameter is >55mm.

<b>Type A ascending aortic dissection</b>	<b>Emergency surgery<sup>a</sup></b>
<b>Type B descending aortic dissection</b>	Initial management: medical treatment <sup>a</sup>
<b>Type B acute aortic dissection</b>	Surgery indicated if <sup>b</sup> : <ul style="list-style-type: none"> <li>• Mesenteric ischaemia, limbs or branches of the abdominal aorta</li> <li>• Progression of the dissection</li> <li>• Accelerated rate of the aortic diameter</li> <li>• Inability to control the symptoms (pain...) or PA</li> </ul>
<b>Type B chronic aortic dissection</b>	In the absence of a elevated comorbidity, open surgery if the diameter > 55 mm <sup>a</sup>
<b>Endovascular therapy</b>	The stents of the descending aorta are not indicated in patients with MFS, except in those cases with conditions prohibiting the conventional open surgery

a Class I recommendation, level of evidence B.

b Later management: betablockers, additional medication if it is necessary for the control of the arterial pressure, and follow-up with MRI or CT according to the symptoms, the diameter and the aortic growth rate.

**Table 11.** Treatment of the aortic complications in Marfan's syndrome

## 2.10. Therapy endovascular with stents

Though the experience with endoprosthesis in the type B acute or chronic aortic dissection in the MFS is limited, it has been observed that in spite of the correct implantation of the stent, with total thrombosis of the false light, the aorta continues expanding. This is the reason for which it is not recommended to use aortic stents in the MFS, except high risk for the conventional surgery. The pseudoaneurysms after aortic replacement can be an exception when it is possible to fix to the previous graft the stent to seal the point of entry of the false aneurysm as an alternative to the surgical reintervention (table 12).

<b>Before discharge postsurgery</b>	<b>CT or RMI<sup>a</sup>: complete aorta</b>
<b>At 6 months</b>	CT or RMI: to value diameters <ul style="list-style-type: none"> <li>• Stable: annual</li> <li>• Progression: every 6 months</li> </ul>
<b>Annually</b>	Throughout life, except unstabilization
<b>Appearance of complications</b>	CT or RMI at 1,3, 6 and 12 months If later stable: annual

Class IIa recommendation, level of evidence C.

a The aorta must be valued in its entirety, not only the ascending portion, since a great proportion (almost a third) of the aortic events that compromise the distal aorta happen during the follow-up of these patients.

**Table 12.** Follow-up after aortic surgery in Marfan's syndrome

### 2.11. Recommendations after the aortic intervention in the MFS

After the aortic repair, the grafts, relatively rigid, transmit tension towards contiguous territories, as the coronary arteries, the aortic arch and principal trunks, and the descending aorta, predisposing to the late development of aneurysms and dissection. These patients must support the treatment with betablockers and they must be followed by means of imaging techniques throughout life, restricting the irradiation for CT when possible (table 12).

### 2.12. Surgery of the valvular mitral prolapse in the SM

The mitral and tricuspid affectations constitute the most frequent cardiac finding in the MFS, though the tricuspid rarely has repercussion. The alterations of the mitral connective tissue carry to the growth in a myxoid aspect, with high content of air in its interior, though the histology and the morphology of the mitral valve in patients with MFS are different from the classic myxoid valve disease. In the MFS the leaflets, though thicker than normal, they are longer and thinner than the myxoid ones and with minor cellularity.

Patients with MFS present more frequently affectation of both leaflets or the anterior one, which, together with the laxity of the valvular tissue, makes more frequent the prevalence of mitral prolapse in patients with MFS compared with the healthy population (50-80% opposite to 2,4%). In these patients the prolapse can produce moderate mitral regurgitation or major up to 25 % of the cases. It is also typical the trend to the early calcification of the mitral ring, which constitutes a minor diagnostic criteria.

In the most serious forms of the MFS, which begin in the first years of life, the mitral affectation can cause cardiac heart failure and pulmonary hypertension, with very

unfavorable surgical results in younger than 2 years old, being an important reason for mortality in children with MFS. In teenagers and adults the surgical repair of the severe mitral severe regurgitation is associated with a high events free survival.

The mitral isolated surgery is infrequent, and in the majority of the occasions we carry out combined conservative procedures on the aorta and the mitral valves to avoid the anticoagulation therapy.

The extensive calcification of the mitral ring is the main contraindication for the mitral repair in the MFS. It is important to insist that not repair severe mitral regurgitation, concerns adversely the aortic hemodynamic stress and the ventricular function in the MFS.

In a similar way to the case of the aortic valve, the classic method used in patients with severe mitral regurgitation is the valve replacement, usually with mechanical prosthesis. Nevertheless, and given the high morbidity that these can produce over the years because of the thromboembolic and infectious events, the conservative mitral valve techniques are the gold standard of the mitral surgery, with long-term results similar to the ones obtained in patients without Marfan's syndrome.

Before this type of valves, the surgeon must use the whole available technical equipment and devices, being in an extensively use the PTFE's neocordae, and always associating annuloplasty rings, preferably rigidly or semi rigid. In occasions, it is used the double orifice technique, described by Alfieri, less demanding technically, though the anatomical repair methods are the ones preferred.

The immediate and long-term results are very good, with events free survival and reintervention free survival of 95 % at 10 years, specially when the early surgery is indicated.

### **2.13. Other cardiovascular manifestations of the SM**

The expansion of the trunk of the pulmonary artery is less frequent than the aortic one, and rarely it causes dissection. In the MFS it is possible to have alterations in the atrioventricular conduction and in the ventricular repolarization (long QT, ST alterations and U waves), that might be associated with ventricular arrhythmias, but it is not clear if these changes are secondary to a primary myocardiopathie or to ventricular dilatation owed to the evolved regurgitations.

## **3. Conclusion**

The diagnosis of Marfan syndrome is inevitably complex, due to the high variability of presentation of affected individuals, the dependence of the age in many clinical manifestations, the absence of gold standards diagnostic tests, and the wide differential diagnosis. The new Marfan syndrome diagnostic criteria are intended to facilitate a

correct and early identification by professionals and improve the prognosis of these patients.

In last decades there have been significant changes in the prognosis of the Marfan syndrome. Cardiovascular management of these patients is based on three pillars aimed to increase hope and quality of life: stratification of risk, medical treatment and prophylactic aortic surgery.

Imaging techniques contribute to establish the risk of these patients and select better cases and the most appropriate time for the indication of elective surgery.

All patients should be treated early, at least with beta-blockers. Meanwhile, it will continue to evaluate new therapies aimed at stopping or even reversing the pathological changes associated with the disease.

More and more patients with Marfan syndrome will achieve more advanced stages of life, and this will mean new challenges. It will be tested the acquired knowledge and teamwork from specialized multidisciplinary units will be essential.

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