Marfan syndrome: Getting to the root of the problem
Franken, Romy

Citation for published version (APA):

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Adapted from:
Marfan syndrome: progress report

Prog Pediatr Cardiol. 2012;12:9-14

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Abstract

Marfan syndrome is a multi-systemic connective tissue disorder, with primary involvement of the cardiovascular, ocular and skeletal systems. This autosomal heritable disease is mainly attributable to a defect in the \textit{FBN1} gene. Until 2010, the clinical diagnosis of Marfan syndrome was based on the Ghent criteria of 1996. Recently, the Ghent criteria have been revised. The revised guidelines of 2010 place more emphasis on aortic root dilation, ectopia lentis and \textit{FBN1} mutation testing in the diagnostic assessment of Marfan syndrome. Although the revised Ghent criteria of 2010 are easier to apply, they do raise some remarks as compared to the guidelines of 1996.

In addition to adjustments in the diagnosis of Marfan syndrome, there is progress in the understanding of the pathophysiology in Marfan syndrome, leading to new treatment strategies. Losartan, an angiotensin II receptor type 1 blocker, has been shown to inhibit transforming growth factor beta signal transduction and thereby prevents aortic root aneurysms in a mouse model of Marfan syndrome. This article will provide a critical appraisal of the revised Ghent nosology in 2010 and will highlight the future perspectives regarding the treatment of Marfan syndrome.
Chapter 1: Marfan syndrome: progress report

Introduction

Diagnosis

Marfan syndrome (MFS) is a multi-systemic autosomal dominant disorder of the connective tissue with a prevalence of 1 per 5000 individuals.\(^1\) MFS is mainly caused by mutations of the fibrillin-1 gene (FBN1) encoding for the extracellular matrix protein fibrillin-1. Patients with MFS may present with aortic dilation, ectopia lentis, dural ectasia and skeletal features.\(^2\)\(^-\)\(^8\) Aortic dilations are present in the vast majority of the patients with MFS and are the most important cause for morbidity and mortality in MFS (Figure 1).\(^9\)\(^-\)\(^12\) The diagnosis MFS is based on the Ghent criteria of 1996 in which the features have been divided into major and minor clinical criteria based on their frequency in MFS, in other conditions and in the general population (Table 1).\(^13\) In the revised Ghent criteria more weight has been given to aortic root dilation, FBN1 testing and ectopia lentis (Table 2).\(^14\) In this article we will discuss the historical evolution of MFS and provide a critical appraisal of the revised Ghent nosology of 2010.

Treatment

Treatment of MFS consists mainly of prophylactic surgical replacement of aortic root aneurysms (or other dilated parts of the aorta). This procedure has resulted in an increased life expectancy in MFS.\(^15\) Before the aortic aneurysm reaches dimensions which will justify surgical prophylactic intervention, beta-blocking agents are standardly used to lower aneurysm expansion rate.\(^16\) Recently, new possibilities for medical therapies have emerged from animal experiments. MFS has recently been associated with an increased Transforming Growth Factor (TGF)-\(\beta\) signalling.\(^17\)\(^,\)\(^18\) TGF-\(\beta\) is a cytokine with diverse cellular functions, including cell proliferation and differentiation. It is involved in cancer pathogenesis, immunity, tissue fibrosis and many other processes.\(^19\) In addition to the role of fibrillin-1 as a structural component of the ECM, it regulates TGF-\(\beta\) activation through interactions with TGF-\(\beta\) precursors, keeping it in its inactive form. Due to defect or deficient fibrillin-1, increased sequestration and activation of TGF-\(\beta\) occurs, causing most of the disease features in a well-established mouse-model of MFS. Many disease
manifestations, including aortic root dilation, mitral valve prolapse, developmental emphysema and skeletal muscle myopathy were attenuated after TGF-β inhibition using TGF-β neutralizing antibodies in MFS mice. Interestingly, similar protection was achieved using the angiotensin II type I receptor (AT1R) blocker losartan. This article will highlight the future perspectives regarding the treatment of MFS.

**Table 1. The Ghent criteria for diagnosis of Marfan syndrome**

<table>
<thead>
<tr>
<th>Criteria for diagnosis of Marfan syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For the index case without family/genetic history:</strong></td>
</tr>
<tr>
<td>• major criteria in at least 2 different organ systems and involvement of a third organ system</td>
</tr>
<tr>
<td><strong>For the index case with family/genetic history:</strong></td>
</tr>
<tr>
<td>• one major criterion in an organ system and involvement of a second organ system</td>
</tr>
<tr>
<td><strong>For a relative of an index case:</strong></td>
</tr>
<tr>
<td>• presence of a major criterion in the family history and</td>
</tr>
<tr>
<td>• one major criterion in an organ system and involvement of a second organ system</td>
</tr>
</tbody>
</table>

**Cardiovascular system**

*Major criterion (either of the following)*

• Dilatation of the ascending aorta and involving at least the sinuses of Valsalva
• Dissection of the ascending aorta

*Minor criteria (for involvement only one minor criteria must be present)*

• Mitral valve prolapse
• Dilatation of the main pulmonary artery < 40 years age, in the absence of an obvious cause
• Calcification of the mitral annulus younger than age 40 years
• Dilatation or dissection of the descending thoracic or abdominal aorta younger than age 50 years

**Skeletal system**

*Major criteria (at least four of the following features) (for involvement: two of the following features)*

• Pectus carinatum
• Pectus excavatum, needing surgery
• Reduced upper-segment to lower-segment ratio or arm span to height ratio >1.05
• Wrist and thumb signs
• Scoliosis of >20° or spondylolisthesis
• Reduced extension at the elbows (<170°)
• Medial displacement of the medial malleolus, causing pes planus
• Protrusio acetabulae of any degree (ascertained on radiographs)

*Minor criteria (for involvement one major criteria and two of the following features must be present)*

• Pectus excavatum of moderate severity
• Joint hypermobility
• Highly arched palate with crowding of teeth
• Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

**Ocular system**

*Major criterion*

• Ectopia lentis

*Minor criteria (for involvement at least two of the following features must be present)*
Chapter 1: Marfan syndrome: progress report

Table 1. The Ghent criteria for diagnosis of Marfan syndrome (continued)

Criteria for diagnosis of Marfan syndrome

- Abnormally flat cornea
- Increased axial length of globe
- Hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis

Pulmonary system

Minor criteria (for involvement only one of the following features must be present)

- Spontaneous pneumothorax
- Apical blebs

Skin and integument

Minor criterion (for involvement only one of the following features must be present)

- Striae atrophicae (stretch marks) without marked weight gain, pregnancy, or repetitive stress
- Recurrent or incisional herniae

Dura

Major criterion

- Lumbosacral dural ectasia

Family/genetic history

Major criteria (any one of the following)

- Having a parent, child, or sibling who meets these diagnostic criteria independently
- Presence of a mutation in \( FBN1 \), which is known to cause Marfan’s syndrome
- Presence of a haplotype around \( FBN1 \), inherited by descent, known to be associated with unequivocally diagnosed Marfan’s syndrome in the family

Progress in diagnosis of Marfan syndrome

History

The Marfan syndrome owes its name to Professor Antoine-Bernard Marfan, who described a five-year-old girl with long slender digits and other skeletal abnormalities in the Bulletin of the Medical Society of Paris in 1896. Ironically, most experts now agree that the child originally presented by dr. Marfan was probably not affected by the Marfan syndrome, but by ‘contractural arachnodactily’, a form of connective tissue disease caused by \( FBN2 \) mutations. After this initial delineation, other aspects of the MFS were recognised by Victor McKusick. He described a range of pleiotropic and phenotypic variability in MFS, including cardiovascular aspects, ectopia lentis, skeletal pectus excavatum and kyphoscoliosis. To ensure accurate communication between health care providers, researchers and patients, the Berlin nosology were predefined as clinical criteria for MFS in 1986. However, a pitfall of this nosology was overdiagnosis of patients with a positive family history of MFS. These patients were sometimes only affected by non-specific connective tissue findings themselves, without carrying the mutation present in more typically affected family members. Therefore, in 1996 the Ghent nosology was reported as new diagnostic criteria to ensure stringent guidelines for the diagnosis of MFS in unequivocally affected individuals and to separate mild connective tissue conditions.
disorders from MFS. The Ghent criteria made use of a classification for the different clinical features, which were divided into major criteria with high diagnostic specificity and minor criteria in which an organ system is involved (Table 1). The presence of a major criterion in two different systems and a minor criterion in a third system were required to make the diagnosis of MFS. The prevalence of a \textit{FBN1} mutation in patients fulfilling the criteria for MFS currently is 91-95\%. Nevertheless, the sensitivity of the Ghent nosology was relatively low as most features of MFS are age dependent, which often postpones the diagnosis of MFS in children with a positive family history. Another concern regarding the sensitivity of the Ghent nosology in diagnosing MFS were the highly variable and diverse features, which are present as well in the general population and in other connective tissue disorders.

The revised Ghent nosology

An international panel of experts in the diagnosis and management of MFS aimed to improve the diagnostic criteria by following several guiding principles: maximal evidence based decision-making, practical patient centric implications, a focus on features that distinguish MFS from other disorders and definition of thresholds for diagnosis of MFS.

Purpose of the revised criteria

One of the aims of the panel for the new criteria was to prevent overdiagnosis of MFS in the absence of evidence for aortic aneurysm, in order to protect patients for restriction of career aspirations, insurance benefits and psychosocial stigmatization. Therefore, one of the main revisions of the revised Ghent nosology was the requirement of aortic root dilation in a personal and/or family history. In absence of aortic root dilation, identification of a pathogenic \textit{FBN1} mutation is required in order to establish the diagnosis MFS. Presence of aortic root dilation according to Z-score and ectopia lentis is now sufficient for establishing the diagnosis of MFS in individual patients. All other clinical features contribute to a ‘systemic score’ (Table 2), which guides diagnosis when ectopia lentis or aortic disease is absent. Less specific manifestations of MFS have been removed or made less influential in the diagnostic evaluation. Even the major criterion ‘dural ectasia’ from the old Ghent criteria has been included in the systemic score in the revised criteria. Dural ectasia are now given 2 points out of 20, whereas more than 7 points is needed to indicate systemic involvement.

Furthermore, a more prominent role is provided for molecular genetic screening of the \textit{FBN1} gene and other relevant genes. The diagnosis of MFS should be avoided if a patient has specific clinical or molecular observations, which could reveal alternative and often more serious diagnoses. In these cases a delayed or ambiguous diagnosis of MFS is prevented by requiring additional diagnostic tests to prove or exclude newly introduced syndromes, such as ectopia lentis syndrome, Loeys-Dietz syndrome and mitral valve
prolapse syndrome. However, in patients under 20 years of age these new syndromes are not eligible, because phenotype may evolve with time. For these patients ‘potential MFS’ was proposed. Above revisions of the Ghent criteria have ultimately resulted in the revised Ghent nosology of 2010.

**Table 2. Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions**

<table>
<thead>
<tr>
<th>In the absence of family history of Marfan syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ao (Z ≥ 2) AND EL = MFS*</td>
</tr>
<tr>
<td>2. Ao (Z ≥ 2) AND FBN1 = MFS</td>
</tr>
<tr>
<td>3. Ao (Z ≥ 2) AND Syst (≥ 7 points) = MFS*</td>
</tr>
<tr>
<td>4. EL AND FBN1 associated with Ao = MFS</td>
</tr>
<tr>
<td>EL with or without Syst AND with an FBN1 not previously been associated with Ao or no FBN1 = ELS</td>
</tr>
<tr>
<td>Ao (Z &lt; 2) AND Syst (≥ 5 points) with at least one skeletal feature, without EL = MASS</td>
</tr>
<tr>
<td>MVP AND Ao (Z &lt; 2) AND Syst (&lt; 5) without EL = MVPS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In the presence of family history of Marfan syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. EL AND FH = MFS</td>
</tr>
<tr>
<td>6. Syst (≥ 7 points) AND FH = MFS*</td>
</tr>
<tr>
<td>7. Ao (Z ≥ 2 above age of 20 years, ≥ 3 below age of 20 years) AND FH = MFS*</td>
</tr>
</tbody>
</table>

Scoring of systemic features

- Wrist AND thumb sign – 3 (wrist OR thumb sign – 1)
- Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
- Hindfoot deformity – 2 (plain pes planus – 1)
- Pneumothorax – 2
- Dural ectasia – 2
- Protrusio acetabuli – 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis – 1
- Scoliosis or thoracolumbar kyphosis – 1
- Reduced elbow extension – 1
- Facial features (3/5) – 1 (doliachocephaly, enophthalmos, downsloping palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae – 1
- Myopia > 3 diopters – 1
- Mitral valve prolapse (all types) – 1

Maximum total: 20 points; score ≥ 7 indicates systemic involvement

Caveat: without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome or vascular EDS syndrome. If present then TGFBR1/2 testing, collagen biochemistry, COL3A1 testing. Other conditions/genes will follow with time.

Abbreviations: Ao, aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; Z, Z-score; EL, ectopia lenti; MFS, Marfan syndrome; FBN1, fibrillin-1 mutation; Syst, systemic score; ELS, ectopia lentis syndrome; MASS, myopia, mitral valve prolapse, borderline (Z<2) aortic root dilatation, striae, skeletal findings phenotype; MVP, mitral valve prolapse; MVPS, mitral valve prolapse syndrome; FH, family history; US/LS, upper segment/lower segment ratio
Clinical implications of the Revised Ghent Nosology

Radonic et al. recently reported the practical applicability of the revised Ghent criteria by applying them in an established adult Marfan population of 180 patients. In 164 patients (91%) diagnosis of MFS was confirmed with the revised Ghent nosology. In three patients (2%) the syndrome was rejected, due to altered weight given to dural ectasia in the revised criteria. These patients showed little or no other features of MFS, besides aortic root dilation and dural ectasia. In 13 patients (7%) MFS was rejected due to absence of aortic root dilation defined as Z-score ≥ 2. In this group, an aortic root diameter of more than 40 mm was present in six patients, four of whom received an alternative diagnosis, such as ectopia lentis syndrome and MASS phenotype. The other seven patients with an aortic root diameter of less than 40 mm had an aortic root shape typically for MFS of whom three patients were diagnosed differently.

Faivre et al. performed a similar kind of study, including 1009 probands with a pathogenic FBN1 mutation and a phenotype compatible with a connective tissue disorder. Each patient with a pathogenic FBN1 mutation had been classified according to the Ghent criteria as well to the revised Ghent criteria, resulting in respectively 89% and 83% patients with MFS. Almost 90% of patients in the adult cohort who received the diagnosis of MFS according to the Ghent criteria of 1996 kept the diagnosis MFS by using the revised criteria; 8% were reassigned to ectopia lentis syndrome and 2% were reassigned to MASS. Both studies have a confirmation of 90% for the diagnosis of MFS when using the Ghent criteria of 1996 or the revised Ghent criteria of 2010.

Critical appraisal

The revised Ghent nosology offers some advantages as compared to the old nosology. The guidelines seem to be easier to apply by physicians, because more weight is given to ectopia lentis and aortic root aneurysm. Furthermore, several minor criteria which were often subjective and difficult to assess have been eliminated. In addition, the use of the revised criteria narrows the diagnosis of MFS to patients with fully expressed disease and various new diagnoses are suggested to decrease the risk of premature diagnosis. By introducing the revised Ghent criteria more specificity has been achieved while maintaining clinical relevance. However, the revised Ghent criteria of 2010 also raise some remarks as compared to the guidelines of 1996 which will be described in the following section.

Z-scores and body surface area

Comments can be made regarding one of the major changes in the new nosology, including the use of Z-score measurement for aortic root dilation in adults. Normal values for aortic root dilation depend on age, height and weight (body surface area (BSA)).
The Z-score is a common statistical way of standardizing data on one scale in which each Z-score corresponds to a point in a normal distribution (appendix).

**Appendix - Z-score and mean dependent on age and body surface area**

The Haycock formula:

\[ \text{BSA (m}^2) = 0.024265 \times \text{Height (cm)}^{0.3964} \times \text{Weight (kg)}^{0.5378} \]

Z-score for aortic root diameter:

\[ \text{Z-score} = \frac{\text{AoD (mm)} - \text{mean (mm)}}{\text{SD (mm)}} \]

Mean aortic root diameter:

- Age < 18 years: mean = 1.02 x (0.98 x BSA (m²))
- Age < 40 years: mean = 0.97 x (1.12 x BSA (m²))
- Age > 40 years: mean = 1.92 x (0.74 x BSA (m²))

BSA = body surface area (m²), Z = Z-score, AoD = aortic root diameter (mm), mean = mean aortic root diameter in general population dependent on age and body surface area (mm), SD = standard deviation (mm)

An aortic root diameter with Z-score ≥ 2 assumes an aortic root diameter with a value, two standard deviations beyond its expectation value corrected for age and BSA. However, instead of a linear distribution between BSA and aortic root diameter, the curve appears to flatten with increasing BSA in subjects above the 95th percentile for height in a nonlinear correlation with maximum aortic root diameters of 40 mm.28,31,32 A large study of 2317 highly trained athletes with high hemodynamic stress on aortic wall demonstrated an upper normal limit (> 99 percentile value) of the aortic root diameter of 40 mm in men (n=17) and 34 mm in women (n=10).33 These data suggest that aortic root diameters of more than 40 mm are dilated.

A Marfan population differs significantly from the healthy population regarding BSA and aortic root size variability.34 In addition, in MFS patients aortic root dilation is generally located at the level of the three sinuses of Valsalva and may terminates abruptly at the sinotubular junction, resulting in a pear-shaped aortic root (Figure 2).35 Oosterhof et al. have demonstrated that in 17 patients with a juvenile form of ascending aortic dilation without MFS the aneurysm was mostly fusiform, whereas in 78 patients with aortic root dilation in MFS all patients had pear-shaped dilations.36

Currently used Z-scores may underestimate aortic enlargement in patients with a large BSA and may not reflect the potential progressive nature of it. Therefore, we propose to define aortic root dilation (corrected for BSA and age) as a Z-score > 2 and/or an absolute aortic root diameter of more than 40 mm. However, an appropriate definition of aortic root involvement in adult Marfan patients should also take into account the typical pear-shaped aortic root.35,37-39
To determine whether a \textit{FBN1} mutation is associated with aortic root dilation, the clinician needs to have access to a public up-to-date database of known pathogenic mutations. Unfortunately, such an updated database is not available at this moment.

In the revised Ghent criteria more emphasis is placed on pathogenic \textit{FBN1} mutations. However, the criteria for pathogenicity of these mutations as formulated by Loeys et al.\textsuperscript{14} are incomplete and inaccurate. For example, the epidermal growth factor-like (EGF) consensus sequence as shown in the revised Ghent criteria paper is represented as (D/N) X(D/N)(E/Q)Xm(D/N)Xn(Y/F), implying that aspartic acid (D) as the first residue of an EGF-like domain can be replaced by asparagin (N) without effect. However, the negative charge of aspartic acid at this position is essential for calcium binding and this type of mutation will undoubtedly lead to protein instability. Consequently, any missense mutation involving the first aspartic acid of any calcium binding EGF-like domain in \textit{FBN1} should be considered pathogenic. A more complete and comprehensive discussion will be presented in chapter 5..

\textbf{Differential diagnosis of MFS}

The differential diagnosis of MFS includes mitral valve prolapse syndrome, ectopia lentis syndrome and MASS phenotype. MASS phenotype is a syndrome including at least two, but preferably three of the following manifestations: myopia, mitral valve prolapse, borderline aortic root enlargement (Z-score < 2), skin and minor skeletal features.\textsuperscript{13} The term ‘borderline aortic root enlargement’ assumes a non-progressive nature of the aortic root dilation, but it is currently unknown to what proportion of patients have
this applies. In patients with mitral valve prolapse syndrome, clinical features include mitral valve prolapse, pectus excavatum, scoliosis and mild arachnodactyly. However, aortic enlargement and ectopia lentis preclude the diagnosis of mitral valve prolapse syndrome. In patients with ectopia lentis syndrome, ectopia lentis is often accompanied by some skeletal features of MFS and a $FBN1$ mutation; a key characteristic of ectopia lentis syndrome is the absence of aortic disease.

In the revised Ghent criteria, annual cardiovascular monitoring is advised in individuals who meet the criteria for MFS, MFS related connective tissue disorders and individuals with features of connective tissue disorders under age 20. The reason for this strict monitoring is the gradual dilation of the aortic root in MFS which can appear at all ages, therefore the named syndromes may still evolve to MFS.$^{38,40,41}$

However, diagnostic criteria should not be flexible, but reliable and clear, in order for physicians and patients to know what to expect and know how to manage the disease properly. Dynamic diagnosis implies follow-up in patients with a diagnosis other than MFS even without cardiovascular disease, which creates a great burden on the hospital capacities. In addition, patients with either ectopia lentis syndrome or MASS phenotype should be counselled about the risk of a more severe presentation in their offspring since aortic enlargement may evolve over time. This might be a psychological and unnecessary burden for patients. Finally, genetic counselling should be uniform in members of the same family to ensure that patients with the same mutation obtain the same diagnosis.

In order to determine the proportion of patients who will meet the criteria for MFS later in life, a follow-up study of patients with such MFS-related diagnoses is required.

Optional additions to the revised criteria

Faivre et al. demonstrated that several patients have not been diagnosed with MFS by applying the new criteria, but should be carefully monitored on aortic root dilation.$^{29}$ For example, for patients with a systemic score of $<7$ without aortic dilation or ectopia lentis, but with a positive family history of MFS and a known pathogenic $FBN1$ mutation associated with aortic dilation. These patients were classified as MFS in the study by Faivre et al., so that members from one family, who are carrying the same $FBN1$ mutation, will achieve similar diagnoses.

For patients with a systemic score $\geq7$ and a known pathogenic $FBN1$ mutation without family history no specific group is defined. Faivre et al. have proposed an adaptation in the revised Ghent criteria so these patients can be diagnosed with MFS.
Progress in treatment of Marfan syndrome

Currently, several pharmacological drugs are prescribed in order to slow down aortic dilation in patients with MFS and their aim is to prevent surgical interventions. The most frequent prescribed medicines in MFS are β-blockers. The pharmacological rationale of the use of β-blockers is based on reduction of stress on the proximal aorta by decreasing inotropy and chronotropy as well as lowering of the average blood pressure. Although the only randomized clinical trial assessing the effect of β-blockers has demonstrated a reduction in the rate of aortic root dilation, β-blockers did not show any beneficial effect on clinical cardiovascular endpoints such as aortic dissection or aortic rupture. The beneficial effect of β-blockers is thought to derive from reducing the hemodynamic stress on the aorta; however, they do not prevent the development of cystic medial degeneration, the pathological substrate for aortic disease in MFS. Cystic medial degeneration in MFS is mostly characterized by vascular smooth muscle cell apoptosis, elastolysis as well as accumulation of collagen and proteoglycans.

Several cascades have shown to contribute to the development of MFS, of which pathways leading to TGF-β signal transduction appear to be most important. A deficiency of fibrillin-1, due to \( FBN1 \) mutations, may lead to increased TGF-β signal transduction, which in turn leads to cystic medial degeneration. Another major pathway leading to an increased TGF-β signal transduction is the angiotensin II cascade. Angiotensin II has a primarily role in the renin-angiotensin system as well as a contributive role to the development of cystic medial degeneration in the aortic wall. The effect of angiotensin II is mediated by two receptors. Angiotensin II receptor type 1 (AT1R) increases TGF-β signal transduction, while in most cell types and tissues angiotensin II receptor type 2 (AT2R) signalling has shown to oppose AT1R mediated enhancement of TGF-β signal transduction. However, AT2R signalling has also shown to induce vascular smooth muscle cell apoptosis and thereby contributes to cystic medial degeneration.

Improved understanding of the histological abnormalities causing MFS has identified several potential pharmacotherapies directly targeting cystic medial degeneration. Most promising of all pharmacological treatment strategies is losartan, an AT1R blocker which has already been prescribed in other cardiovascular diseases. Losartan, has drawn interest for MFS treatment, after Habashi et al. demonstrated no difference in absolute aortic root diameter between losartan treated MFS mice compared to wild-type mice. In addition, in the losartan treated MFS mice TGF-β signal transduction was diminished and cystic medial necrosis development as well as elastic fibre fragmentation was prevented. However, a major limitation of the study by Habashi et al. was the use of a mouse model with one specific \( FBN1 \) mutation, while in humans more than 1700 different \( FBN1 \) mutations have been reported. Following this study, Brooke et al. noticed in retrospect a significant decrease in aortic root growth rate and absolute sinotubular junction.
These compelling findings have resulted in the initiation of multiple multicentre randomized controlled trials assessing the effects of losartan on aortic root growth in humans with MFS (Table 3). If losartan demonstrates beneficial effect on the aortic root in these trials, it may be the first potential pharmacotherapy directly preventing aortic disease associated with MFS.

**Table 3. Ongoing losartan trials**

<table>
<thead>
<tr>
<th>Institution (Study)</th>
<th>Start date</th>
<th>Follow up (months)</th>
<th>Design</th>
<th>Age range (Years)</th>
<th>Target no. cases</th>
<th>Clinical Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Children's Hospital, Pediatric Heart Network - Lacro et al.</td>
<td>January 2007</td>
<td>36</td>
<td>DB, RCT; losartan vs atenolol</td>
<td>0.5-25</td>
<td>604</td>
<td>Change in AoR</td>
</tr>
<tr>
<td>Brigham and Women's Hospital - Creager et al.</td>
<td>October 2007</td>
<td>6</td>
<td>DB, RCT; losartan vs atenolol</td>
<td>≥ 50</td>
<td>50</td>
<td>Aortic biophysical properties</td>
</tr>
<tr>
<td>Heart and Stroke Foundation of Canada - Sandor et al.</td>
<td>January 2008</td>
<td>12</td>
<td>DB, RCT; losartan vs atenolol</td>
<td>12-25</td>
<td>30</td>
<td>Aortic biophysical properties</td>
</tr>
<tr>
<td>Academic Medical Center (COMPARE) - Mulder et al.</td>
<td>February 2008</td>
<td>36</td>
<td>OB, RCT; losartan vs no losartan</td>
<td>≥ 18</td>
<td>330</td>
<td>Change in AoR</td>
</tr>
<tr>
<td>Policlinico St. Matteo Hospital - Gambarin et al.</td>
<td>July 2008</td>
<td>48</td>
<td>OB, RCT losartan vs nebivolol or combined</td>
<td>1-55</td>
<td>291</td>
<td>Change in AoR</td>
</tr>
<tr>
<td>Hospital Bichat Paris (Marfan Sartan) - Detaint et al.</td>
<td>September 2008</td>
<td>36</td>
<td>DB, RCT losartan vs placebo</td>
<td>≥ 10</td>
<td>300</td>
<td>Change in AoR</td>
</tr>
<tr>
<td>Ghent Hospital (Ghent Marfan Trial) - Moberg et al.</td>
<td>June 2009</td>
<td>36</td>
<td>DB, RCT losartan vs placebo</td>
<td>≥ 10</td>
<td>174</td>
<td>Change in AoR, CA diameter</td>
</tr>
<tr>
<td>Royal Brompton Harefield Foundation (The AIMS Trial) - Mullen et al.</td>
<td>September 2010</td>
<td>45</td>
<td>DB, RCT irbesartan vs placebo</td>
<td>6-40</td>
<td>490</td>
<td>Change in AoR</td>
</tr>
<tr>
<td>Hospital Universitario Vall d’Hebron - Forteza et al.</td>
<td>October 2010</td>
<td>36</td>
<td>DB, RCT losartan vs atenolol</td>
<td>5-60</td>
<td>150</td>
<td>Change in AoR, CA diameter</td>
</tr>
</tbody>
</table>

AoR Aortic root; CA carotid artery; DB double-blind; echo: echocardiography; MRI magnetic resonance imaging; OB open label, blinded endpoints; RCT randomized controlled trial;
Conclusion

The revised Ghent nosology of 2010 is an improvement in the diagnostic assessment of MFS as compared to the Ghent criteria of 1996. However, the revised Ghent criteria provoke some critical remarks. First, the use of Z-score for aortic root dilation is not validated for patients with a large BSA, which is often the case in patients with MFS. Besides Z-scores, an appropriate definition of aortic root involvement in adult Marfan patients should take into account an upper normal limit of the aortic root of 40 mm as well as the typical pear-shaped aortic root. Second, proper use of the criteria requires a public up-to-date database with known mutations correlated to aortic root dilation and a better understanding of pathogenicity of mutations in \( FBN1 \). As mentioned above, this will be discussed in a separate paper. Third, in the revised Ghent criteria a gap for two subgroups of patients with \( FBN1 \) mutations is described, who should be diagnosed with MFS. For example, patients with a systemic score of < 7, without aortic dilation or ectopia lentis but with a positive family history of MFS and a pathogenic \( FBN1 \) mutation. In addition, patients with a systemic score \( \geq 7 \) and a known pathogenic \( FBN1 \) mutation without family history should also be diagnosed with MFS. Fourth, genetic counselling should be uniform in members of the same family to ensure that patients with the same mutation obtain the same diagnosis.

In all MFS related disorders (MASS phenotype, mitral valve prolapse syndrome and ectopia lentis syndrome) annual cardiovascular monitoring is advised, because they can evolve in MFS. However, according to their definition, these MFS related disorders do not include patients with (severe) aortic root dilation. This annual monitoring is a great burden on hospital capacities, patients and their offspring. In order to avoid unnecessary cardiovascular monitoring in diseases without development of severe aortic dilation, criteria should not be flexible.

Currently, \( \beta \)-blockers are the most frequent prescribed medicines to slow down aortic dilation in patients with MFS. The use of \( \beta \)-blockers is based on reduction of repetitive stress on the proximal aorta, by decreasing heart rate as well as lowering of the average blood pressure. However, the knowledge of pathophysiology of Marfan syndrome has been increased, leading to new pharmacological treatment strategies. Losartan, an AT1R blocker, has been shown to inhibit TGF-\( \beta \) signal transduction thereby, preventing aortic root dilation in a mouse model of MFS. These findings have led to initiation of multiple multicentre randomized clinical trials assessing the effects of losartan on aortic root growth in MFS patients.

In conclusion, the revised Ghent criteria offer some advantages as compared to the old nosology, since guidelines are easier to apply and patients with only fully expressed disease are diagnosed with MFS. However, the remarks made above may require a re-evaluation of criteria for diagnosing MFS at short notice.
References