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## Marfan syndrome and related connective tissue disorders

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*  
2014

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Aalberts, J. (2014). *Marfan syndrome and related connective tissue disorders: Cardiological and genetic aspects*. [Thesis fully internal (DIV), University of Groningen]. s.n.

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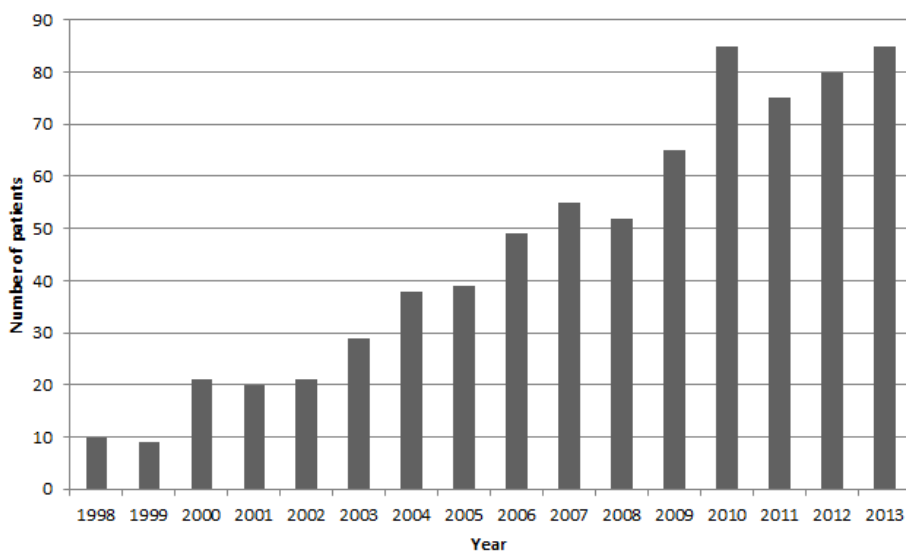
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## **Discussion and future perspectives**

## DIAGNOSTIC PROCESS

Diagnosing a particular connective tissue disorder with cardiovascular involvement is a challenging adventure. Most patients are being referred for evaluation because of suspicion of a specific connective tissue disorder, MFS for example. Multidisciplinary evaluation of these patients is important, because when MFS is excluded, other hereditary connective tissue disorders can be present. Therefore the Marfan outpatient clinics in Groningen, Leiden, Amsterdam and Nijmegen do not just provide a diagnostic process to confirm or to exclude MFS, but also an evaluation for connective tissue disorders in general (see figure I for the number of patients screened throughout



**Figure I.** Number of patients screened at the Groningen Marfan outpatient clinic from 1998-2013

the years at the Groningen Marfan outpatient clinic). The key player in this process is the clinical geneticist with a knowledge of connective tissue disorders. He/she can direct other specialists in the diagnostic work-up, for example, the ophthalmologist and the orthopaedic surgeon. There is also an important task for the cardiologist or paediatric cardiologist, since he/she is the expert on cardiovascular pathology and, in many connective tissue disorders with cardiovascular involvement, complications in this area significantly impact life expectancy. Even if initial cardiovascular screening does not reveal abnormalities, repeated examinations can be necessary as features may develop over time.

However, before the diagnostic work-up can be initiated, there needs to be the suspicion of a connective tissue disorder. Every physician can recognize features that potentially point to a connective tissue disorder, for example, a long and slender body habitus, aortic pathology at a young age (<50 years), easy bruising, translucent skin, abnormal uvula, joint laxity and lens (sub)luxation. Unfortunately, most of these characteristics are neither sensitive nor specific for a particular

connective tissue disorder, making it difficult to say which patients should be referred for evaluation for a connective tissue disorder. In the case of a family history of a connective tissue disorder, sudden death or aortic pathology at a young age (aneurysm, dissection, rupture), there is no doubt that an evaluation should take place. In other cases, the decision to refer a patient for evaluation is more arbitrary. Recently, Sheikhzadeh et al. have tried to make this more objective for patients with possible MFS.<sup>1</sup> They made a prediction model using seven clinical variables to estimate the probability of MFS. The following variables were given points: ectopia lentis (4 points), family history of MFS (2 points), previous aortic surgery (1 point), pectus excavatum (1 point), wrist and thumb sign (1 point), previous pneumothorax (1 point) and skin striae (1 point). If a patient had a score  $\leq 1$  point the probability of MFS was 12%, with a score of 1-3.5 the probability of MFS was 42%, and with a score  $>3.5$  the probability of MFS was 92%. Although this was an interesting attempt to better identify patients specifically at risk for MFS, the negative predictive value is too low to exclude MFS in the low-risk group. In addition, there was no attention paid to other connective tissue disorders with cardiovascular involvement, making this prediction model ineffectual in clinical practice. It seems unlikely that it will be possible in the future to precisely determine which patients should and which should not be evaluated for a connective tissue disorder. Just as in the diagnostic process of many other diseases, we must trust the general awareness, skills and experience of doctors to recognize this patient category. Of course, there is also a role for patient organisations, which can help create awareness of connective tissue disorders. The "Contactgroep Marfan Nederland" is very useful in providing information and creating awareness, not only for established MFS patients but also for general practitioners and other health professionals. In addition, the next generation sequencing techniques in genome diagnostics, which are getting more cost-effective all the time, could be helpful in this respect, because even without clinical pre-selection, they can help establish a diagnosis. Of course, finding a mutation points to, but does not establish, a clinical diagnosis.

### 2010 Ghent nosology

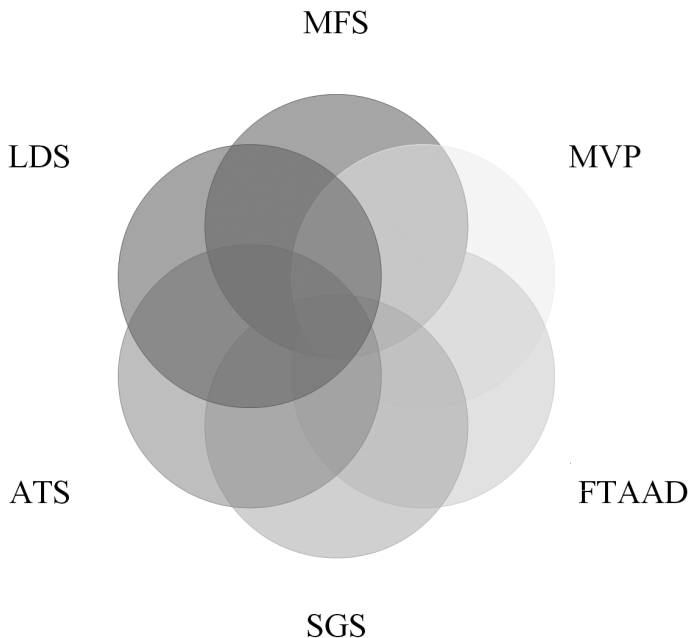
Connective tissue disorders are relatively rare diseases with great clinical variability, making it important to cautiously evaluate individuals suspected of having such a disease. The diagnostic process has to be done meticulously and criteria for a specific disorder should be clear-cut. Ideally, all cases are recognized in the diagnostic workup and no one is incorrectly diagnosed with a specific connective tissue disorder. Clinical practice is, of course, not done in utopia, giving rise to under-diagnosis as well as over-diagnosis. To eliminate these undesirable outcomes as much as possible, regular critical assessment and, if needed, adjustment of diagnostic criteria is essential. In MFS, re-assessment and re-adjustment of the diagnostic criteria has taken place over the years, leading us from the Berlin nosology in 1986 to the Ghent nosology in 1996, and to the revised Ghent nosology in 2010.<sup>2-4</sup> Even though the 2010 Ghent nosology is more direct in diagnosing MFS compared to the 1996 nosology, makes more use of specific criteria of MFS, and is more ambitious in providing a better differential diagnosis, it is still not perfect. For example, it is unclear why the diagnostic

threshold of MVPS has been adjusted. The fact that familial occurrence is no longer required (in contrast to the 1996 nosology) serves no apparent clinical purpose and led to 23 extra patients with MVPS in the study in **Chapter 2**. Perhaps the authors of the 2010 Ghent nosology meant to diagnose patients with merely a MVP and limited systemic features (systemic score less than 5) as MVPS. The consequence of this definition is that patients without any systemic features and a MVP also have MVPS. Isolated mitral valve prolapse is a common valvular disorder and it is inappropriate to label these patients as having a syndrome.

Another shortcoming of the 2010 Ghent nosology is the subjective criteria for mitral valve, aorta, skin, skeletal (MASS) phenotype. To be more specific, the criterion of borderline aortic root dilatation is unsatisfying and clinically difficult to use.

### Pathophysiology of connective tissue disorders

In the introduction to this thesis, the considerable overlap in the pathophysiology and clinical manifestations of the different connective tissue disorders with cardiovascular involvement was discussed. Following this overlapping principle, one could see all connective tissue disorders with cardiovascular features together in a Venn diagram (figure II). That diagram shows the different connective tissue disorders sharing a common space and TGF- $\beta$  is a crucial component of that



**Figure II.** Venn diagram of connective tissue disorders with cardiovascular involvement in which TGF- $\beta$  plays a role in the pathophysiology.

ATS; arterial tortuosity syndrome, FTAAD; familial thoracic aneurysms and/or dissection, LDS; Loeys-Dietz syndrome, MFS; Marfan syndrome, MVP; (myxomatous) mitral valve prolapse, SGS; Sphrintzen-Goldberg syndrome

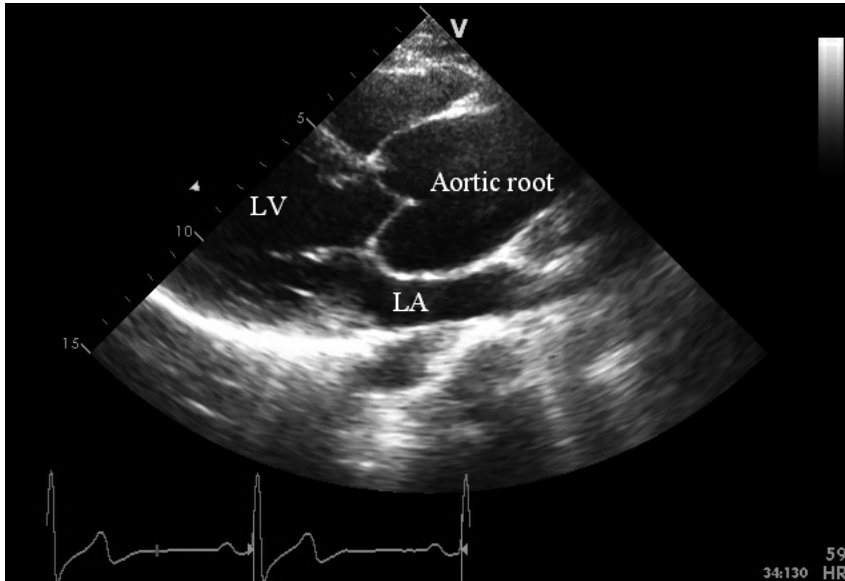
common space. Disturbed TGF- $\beta$  signalling is known to play a role in MFS, LDS, familial myxomatous valve degeneration, FTAAD, arterial tortuosity syndrome, and Sphrintzen-Goldberg syndrome, and its role in other connective tissue disorders with cardiovascular involvement might follow in the future as new genes and pathophysiologic pathways are unravelled using genetic techniques like whole exome sequencing (WES) and even whole genome sequencing.<sup>5-13</sup> At the moment, WES is too expensive to use in daily clinical practice and there are still ethical issues around this technique that need to be discussed.

## **Marfan syndrome**

### ***Aortic root size and shape***

Over the years the diagnostic criteria for Marfan syndrome have been refined and, currently, diagnostic evaluation takes place following the 2010 Ghent nosology. Even with the latest diagnostic criteria, there are still issues that need to be addressed to further increase the sensitivity and specificity of the diagnostic criteria. One of these points concerns the definition of aortic root dilatation. At the moment, aortic root dilatation is defined as a Z-score  $\geq 2$ . The problem with this definition is that it seems to underestimate aortic root dilation in patients with large BSAs ( $>2.0 \text{ m}^2$ ), as linearity between BSA and aortic root diameter above a BSA of  $2.0 \text{ m}^2$  has been assumed but not proven.<sup>14</sup> Studies in healthy subjects have shown that the upper limit diameter of a normal aortic root is 4.0 cm in men and 3.4 cm in women, suggesting that every aortic root with a diameter  $\geq 4.0$  cm is aneurysmatic. Radonic et al. have presented six patients with a mean BSA of  $2.1 \text{ m}^2$ , an aortic root diameter  $\geq 4.0$  cm and an aortic root Z-score  $< 2$  in which the MFS diagnosis might have falsely been rejected (if the Z-score would have been  $\geq 2$  they all would have fulfilled the diagnostic criteria for MFS).<sup>15</sup> This indicates that a better definition of aortic root dilatation is needed. Perhaps the Z-score can be used until an absolute aortic diameter of  $< 4.0$  cm and all diameters  $\geq 4.0$  cm should be regarded as dilated. However, one important point should be kept in mind: accurate measurement of the aortic root diameter is crucial, and just a few millimetres can make the difference between a dilated aortic root and a normal one. It can sometimes be very difficult to measure the aortic root precisely by echocardiography and it is challenging to measure the aortic root in the exact same way in follow-up investigations. Magnetic resonance imaging (MRA) of the aorta can be used if the aortic root diameter cannot accurately be measured by echocardiography, and it may be that all patients should be repeatedly evaluated by MRA.

Another aspect of the aortic pathology in MFS is the shape of the aorta. In MFS, the aortic root is typically pear-shaped (figure III) and Radonic et al. have suggested that new parameters may be needed to make an objective evaluation of this morphologic characteristic of the Marfan aortic root so that it could also be included in the diagnostic criteria. Further research on how best to define and measure aortic root pathology is needed because aortic root dilatation is a crucial diagnostic criterion in the Ghent nosology.



**Figure III.** Echocardiographic image of a pear-shaped aortic root in a patient with Marfan syndrome (parasternal long axis view)

### **Sex differences**

Just as in healthy subjects, there is a sex difference in the aortic root diameter in patients with MFS, even after correction for differences in BSA. As reported in in **Chapter 8**, women have a significantly smaller average aortic root diameter. Meijboom et al. previously observed this in a study on aortic root growth in 221 patients with MFS.<sup>16</sup> The difficulty with this finding is that the clinical implications are uncertain. Do we need to lower the threshold diameter for a dilated aortic root in women? Do we need to lower the threshold for elective aortic root replacement in women? To date, there have not been any studies showing significantly more aortic root complications in women with MFS, but more research is needed to clarify this issue.

### **Ventricular dysfunction**

It has become clear that ventricular dysfunction, independent of valvular disease and aortic elasticity, is present in MFS. This has already been demonstrated by several studies using echocardiography as well as CMR.<sup>17-21</sup> Although ventricular dysfunction can be present in MFS, the clinical implications of this finding are uncertain. Ventricular dysfunction is mild in most cases and clinically significant heart failure in patients with MFS without valvular disease is rare. This might become more of a problem in the future as patient life expectancy increases due to improved treatment, and MFS patients have more time to develop pronounced ventricular dysfunction.

## Treatment

Established therapy for the cardiovascular manifestations of MFS consists of  $\beta$ -blockade and prophylactic aortic root replacement. Recently, the results of the COMPARE study demonstrated that losartan, which antagonizes the effects of TGF- $\beta$ , reduces aortic root dilatation rate in adults with MFS.<sup>22</sup> Results of comparable studies are eagerly awaited and could lead to a better drug-based management of MFS, hopefully reducing aortic complications and the need for prophylactic aortic replacement.<sup>23-26</sup> The COMPARE study also investigated the influence of losartan on ventricular function, however the results of this sub-study are not yet available.

Prophylactic aortic surgery is an important part of the treatment of MFS and should take place in hospitals with a dedicated and experienced Marfan team. In the European Society of Cardiology guideline, the threshold diameter for aortic root replacement is set at >5.0 cm. In the case of a family history of dissection or progressive dilatation (>2 mm/year) or severe aortic regurgitation/MR or desire to become pregnant, replacement should take place at a diameter of 4.6 – 5.0 cm (table I).<sup>27</sup> These guidelines thus focus on an absolute aortic root diameter to establish the indication for prophylactic replacement. However, the study in **Chapter 8** showed that a protocol for prophylactic aortic root replacement based on BSA was effective and safe in terms of preventing

**Table I.** European Society of Cardiology guideline for prophylactic aortic root replacement in MFS

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Aortic root diameter >5.0 cm
Aortic root diameter >4.5 – 5.0 cm AND
Family history of dissection OR
Progressive >0.2 cm/year confirmed by repeated measurement OR
Severe aortic or mitral regurgitation OR
Desire of pregnancy
Aortic root replacement should be considered when other parts of the aorta >5.0 cm

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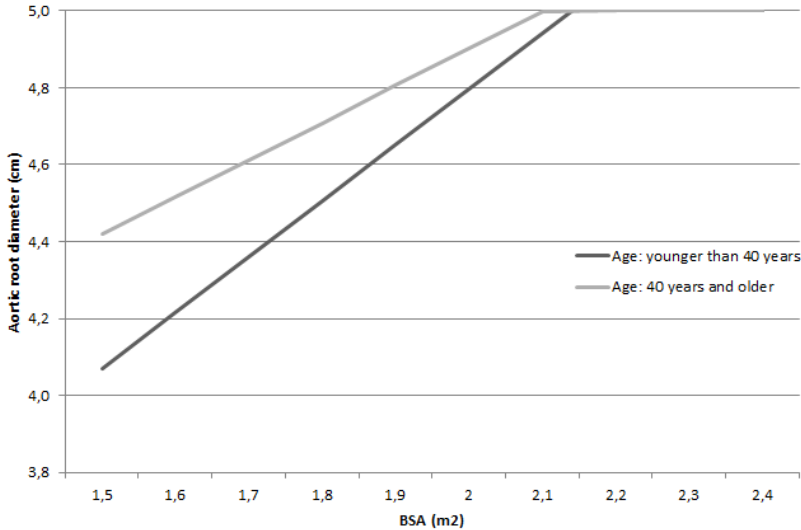
aortic dissections. The findings of this study need to be confirmed in future research, but there are reasons to support a protocol based on a relative aortic size: it is in line with the definition of a dilated aorta in the 2010 Ghent nosology as it also uses a relative aortic size, and, in addition, in non-Marfan patients with an aortic aneurysm a relative aortic size has been shown to better predict aortic complications. Nonetheless, the aortic root should not exceed 5.0 cm\* irrespective of (a large) BSA due to under-representation of patients with larger BSAs in studies, thereby underestimating the risk of aortic complications.<sup>28</sup> There is also evidence from studies of non-Marfan patients for an absolute maximum aortic diameter which is safe, irrespective of (a large) BSA.<sup>29</sup> In the same way, a cut-off diameter of 5.0 cm for smaller people is probably too lenient and underestimates the risk for

\* In the study in Chapter 8 it is stated that the aortic root should not be allowed to exceed 5.5 cm irrespective of BSA.<sup>30</sup> This was however based on the international guideline for prophylactic aortic root replacement at that time, recommending aortic root replacement at an aortic root diameter of 5.0-5.5 cm. Current guidelines recommend replacement at a diameter of >5.0 cm.



complications at diameters a few millimetres below 5.0 cm.

To summarize this somewhat confusing issue concerning relative and absolute aortic diameter: it is safe to use a protocol based on BSA for prophylactic aortic root replacement in MFS as long as the aortic diameter does not exceed 5.0 cm (see figure IV). Further studies are needed to precisely determine how to deal with these issues.



**Figure IV.** Aortic root diameter as function of BSA at which prophylactic surgery should take place. Derived from Roman et al., Legget et al. and Aalberts et al.<sup>14,28,30</sup> See appendix B for details.

### Loeys-Dietz syndrome

This connective tissue disorder was first described in 2005, but has existed for much longer. In Victor McKusick's landmark article on MFS from 1955, a 24-year-old male patient is described with the following features: slender body habitus, pectus excavatum, partial club foot, flexion deformities of the fingers, a bifid uvula, lumbar kyphosis and a type A aortic dissection.<sup>31</sup> With our current knowledge this patient must have suffered from LDS instead of MFS, which underscores the importance of keeping an open mind towards assumed known diseases. Clinically, it is important to determine whether a patient has LDS or MFS. Aortic pathology appears to be more aggressive in LDS, with rupture and dissection occurring at smaller aortic diameters.

LDS is a rare disorder, making it difficult to collect a substantial number of patients for further research. From a management point of view, there are several questions that need to be answered: How should patients with LDS be treated? Should medical therapy consist of  $\beta$ -blockers or losartan? How should they be followed up with regard to generalized vascular pathology? Although there are recommendations for prophylactic aortic surgery, they are based on the experiences of a single centre. At the moment, these recommendations should be used and evaluated to establish if they are effective in preventing aortic complications. Animal models could also be used to gain more

insight into LDS and could lead to the discovery of possible drug treatments.

### **Mitral valve prolapse**

At the moment, mutations in *FLNA* are the only known causes of myxomatous valve degeneration, of which MVP is the most common form. It is likely that in the coming years other genes will be discovered and this will, hopefully, also help in unravelling the pathophysiology of this clinically heterogeneous disorder. In particular, the sudden cardiac death associated with this disorder remains mysterious: why do ventricular arrhythmias occur in patients without apparent ventricular dysfunction or significant MR?

As malignant forms of MVP are rare, i.e. MVP combined with ventricular arrhythmias, it would be useful to set up an international and/or national study or database. This would increase patient numbers significantly and should lead to a better understanding of this disease. Of course, once ventricular arrhythmias are present, there is no doubt treatment should be aggressive. However, at the moment, discriminating tools to identify those patients with 'merely' an MVP at risk for ventricular arrhythmias are lacking. In a recent study by Sriram et al., bileaflet MVP was present in 10 out of 24 patients with idiopathic out-of-hospital cardiac arrest (the remaining 14 patients had normal mitral valves).<sup>32</sup> Significantly more females were present in the group of patients with bileaflet MVP compared to the patients with normal mitral valves (90% vs. 50%;  $p=0.04$ ). In addition, the bileaflet MVP-patients had a higher prevalence of biphasic/inverted T waves inferolateral (77.8% vs. 29%;  $p=0.04$ ). This suggests that bileaflet MVP, being female, and inferolateral repolarization abnormalities are all risk factors for ventricular arrhythmias in patients with an MVP. The greatest limitations of the study by Sriram et al. were the retrospective design and the fact that the patients were highly selected, as they had already experienced a ventricular arrhythmia. A prospective study following patients with an MVP could help to clarify these issues.

### **Final remarks**

In summary, much progress has been made in the diagnostic process, genetics, pathophysiology and treatment of MFS. In particular fundamental research has led to a new rational therapy for MFS, i.e. treatment with losartan. Although the results of further studies need to be awaited, the results of the COMPARE study are promising and treatment with losartan will probably further improve the prognosis of patients with MFS.<sup>22</sup> Still there remains work to be done. The diagnostic criteria should be further improved and the pathophysiology needs to be understood more fundamentally. Hopefully, attaining the latter will lead to new treatment options.

For LDS the greatest achievement is that it has been identified as a distinct connective tissue disorder. Due to the rarity of the syndrome, clinical research will be challenging, but should still be performed.

Finally, in the near future hopefully other genes besides *FLNA* as a cause of familial myxomatous MVP will be discovered.

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