Marfan syndrome: Getting to the root of the problem
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Citation for published version (APA):

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Introduction and outline of the thesis
Introduction

In 1896 Antoine-Bernard Marfan was the first to describe a 5-year-old patient with the typical MFS appearance, i.e. long slender fingers and extremities. After this first delineation, other pleiotropic and phenotypic features were attributed to this disorder, which finally was named ‘the Marfan syndrome’ (MFS). Currently, MFS is known to be a heritable connective tissue disorder with a prevalence of 1 per 5000 individuals. MFS affects multiple organ-systems, including the lungs, eyes, the skeleton and the aorta. Aortic dilation is present in the vast majority of MFS patients, and may lead to the feared aortic dissection, an important cause of morbidity and mortality. Since the introduction of prophylactic aortic root surgery, life expectancy has significantly increased. However, aortic root surgery is an invasive procedure during which the sternum is divided, the heart-lung machine is used, and finally the dilated first part of the aorta is replaced. Complications later in life may be accelerated by aortic root surgery due to altered hemodynamic factors and wall dynamics, which affects the distal part of the aorta. Normally, patients with MFS are pharmacologically treated with β-blockers, which reduce the stress on the aortic wall by decreasing inotropy, reducing chronotropy and lowering the average blood pressure. However, aortic dilation is terminated in all patients, and aortic dissection may still occur. Therefore, novel treatment strategies are necessary.

A major breakthrough in understanding the pathophysiology of MFS was the discovery of the \textit{FBN1} gene in 1991. Currently, \textit{FBN1} mutations are found in approximately 90% of MFS patients. Remarkably, MFS patients have a highly variable phenotype. Differences are found in features, in the severity of the features, and in responsiveness to medical treatment both between families as well as among family members. In general, MFS is a progressive disorder. However, owing to the large variability also at the age of onset of clinical features, outcome is hard to predict for the individual patient.

In order to get to the root of the problem of MFS, the main objectives of this thesis are to obtain more insight in the diagnosis, prognosis and markers of aortic disease, to obtain more knowledge about the importance of genetics in MFS, which is interlaced with all aspects of the syndrome, and to obtain more insight in novel pharmacological strategies to prevent aortic complications.

Outline of the thesis

In the first chapters of this thesis, we focus on the diagnosis, prognosis and markers of aortic disease in MFS. In 2010, the Ghent criteria for assessing the MFS diagnosis were revised, placing more emphasis on aortic root dilation, ectopia lentis and \textit{FBN1} mutation testing. Although the revised criteria are easier to apply, some remarks have to be made.
In addition to diagnostic adjustments, more understanding of the pathophysiology has led to novel treatment strategies. Chapter 1 provides a critical appraisal of the revised criteria, and highlights the future perspectives regarding the prevention of aortic complications in MFS patients.

The Ghent criteria are primarily based on clinical features of Caucasian MFS populations. However, the Asian population currently accounts for more than one-fifth of the total world population. Previous research has also shown that specific MFS features, such as myopia and scoliosis, have a higher frequency in the general Asian population. Chapter 2 therefore determines whether the revised Ghent criteria apply also to Asian MFS populations.

Advances in aortic surgery and MFS screening have significantly reduced mortality due to aortic dissection. With the increased longevity of MFS patients, an increased incidence of complications beyond the ascending aorta has been identified. Chapter 3 delineates patients at risk for aortic dissection by introducing the aortic tortuosity index measured by means of magnetic resonance imaging.

Fibrillin-1 is a structural protein, which binds to the inactive form of transforming growth factor-β (TGF-β). Mutations in the gene encoding for the fibrillin-1 protein (the \( FBN1 \) gene) cause defective or deficient fibrillin-1 protein, which lead to altered matrix sequestration, a less comprehensive aortic wall structure, and moreover activation and enhanced release of TGF-β into the extracellular environment. Chapter 4 investigates the role of plasma TGF-β as a biomarker for progressive aortic dilation and dissection.

In chapters 5, 6 and 7 we focus more deeply on the importance of genetics in MFS. Chapter 5 provides an overview of all \( FBN1 \) mutations described in the universal \( FBN1 \) database. \( FBN1 \) mutations are classified based on their action on DNA level, and we identified some interesting genotype-phenotype correlations. The findings of chapter 5 resulted in the classification of \( FBN1 \) mutations into two groups based on their effect on the fibrillin-1 protein: haploinsufficiency (HI) or dominant negative effects (DN). In HI-\( FBN1 \) mutations only non-mutated fibrillin-1 is produced due to degradation of mutated fibrillin-1 mRNA or of protein, leading to a decreased amount of normal functioning fibrillin-1 protein incorporated in the aortic wall. In DN-\( FBN1 \) mutations, non-mutated as well as mutated fibrillin-1 proteins are incorporated in the extracellular matrix. Chapter 6 prospectively assesses the impact of \( FBN1 \) mutation type (HI versus DN) upon survival and dissection-free survival in MFS patients. On top of that, chapter 7 aims to validate the results of chapter 6 in a Spanish cohort of MFS patients and determines the relationship between HI and DN mutations upon aortic dilation rate and aortic complications (dissection and cardiovascular mortality).

Finally, we focus on novel pharmacological strategies to prevent aortic dilation and aortic complications in MFS. Chapter 8 determines whether losartan reduces the aortic dilation rate in adults with MFS and - although underpowered - assesses if losartan
influences the incidence of aortic dissection, elective aortic surgery, or cardiovascular death in a multicentre, open-label, randomized controlled trial with blinded endpoints. **Chapter 9** determines if TGF-β might function as therapeutic biomarker for effectiveness of losartan on aortic dilation rate. **Chapter 10** investigates the effect of losartan on aortic root dilation rate between MFS patients with a HI-FFN1 mutation and those with a DN-FFN1 mutation. To finalize, **chapter 11** examines the efficacy of anti-inflammatory therapies in attenuating aortic root dilation in the MFS mouse model which was first used to test the effectiveness of losartan therapy.

The thesis is completed with a summary and future perspectives in **chapter 12**, which includes an overview of all finished randomized losartan trials in MFS patients so far, and intends to give a treatment advice. **Chapter 13** gives the Dutch summary, including the Dutch publication of chapter 8.

### Reference list