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Marfan syndrome

The complex road to an optimal treatment strategy

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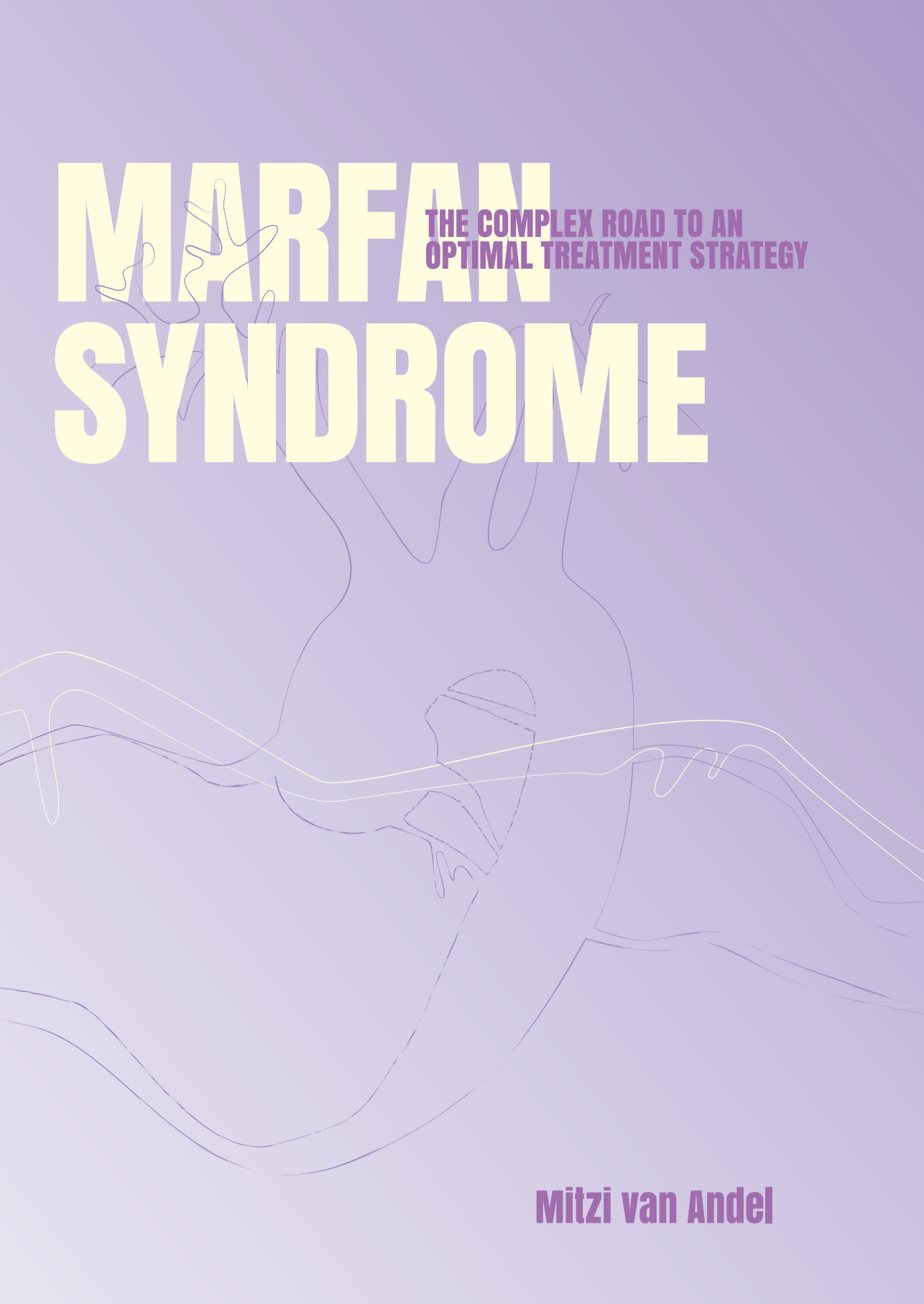
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MARFAN SYNDROME

A stylized, light-colored line drawing of a person in motion, possibly running or jumping, is overlaid on the purple background. The drawing is composed of simple, flowing lines that suggest movement and form.

THE COMPLEX ROAD TO AN
OPTIMAL TREATMENT STRATEGY

Mitzi van Andel

MARFAN SYNDROME

The complex road to an optimal treatment strategy

Mitzi Marlotte van Andel

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MARFAN SYNDROME

The complex road to an optimal treatment strategy

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 24 maart 2023, te 10.00 uur

Door

Mitzi Marlotte van Andel
geboren te Amsterdam

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Faculteit der Geneeskunde

When you talk, you are only repeating what you already know.

But if you listen, you may learn something new.

Dalai Lama

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INTRODUCTION

Marfan syndrome (MFS) is a heritable connective tissue disorder affecting the ocular, skeletal and cardiovascular system. Prevalence has been estimated at 2 to 3/10,000, and 25-30% of cases represent new mutations (1, 2). MFS is caused by mutations in the Fibrillin-1 (FBN1) gene, located on chromosome 15q21, and encoding a large glycoprotein called fibrillin-1 forming fibers in the extracellular matrix (ECM). MFS is a complicated disorder to study due to the large number of unique mutations reported (>3000), causing heterogeneity in phenotype. Moreover, clinical heterogeneity also exists among individuals with the same mutation, even within one family. To effectively guide all MFS patients it is of importance to find common ground on diagnosis, treatment options and risk stratification.

Diagnosis

Early identification and establishment of the diagnosis is of considerable importance to timely intervene when necessary. Nowadays, the diagnosis of MFS has to be made on clinical grounds, following the revised Ghent criteria (3). A definite diagnosis is based on the coexistence of aortic root aneurysm or aortic dissection together with either a lens dislocation, a pathogenic FBN1 mutation or a positive family history. Prognosis is mainly determined by progressive aortic (root) dilatation, which at the same time is the most common cardiovascular manifestation of MFS. Ultimately, aortic dilatation can lead to aortic rupture and death, which needs to be prevented.

Treatment options

Fortunately, both pharmacological and surgical therapies have improved life expectancy substantially up to a median survival of 60-70 years (4). Pharmacological treatment is based on blood pressure lowering (β -blocker/angiotensin-II receptor blockers) and blockade of TGF- β signaling pathways (angiotensin-II receptor blockers). Although these drugs offer some benefit in reduction of aortic dilatation and in the occurrence of aortic dissection (5), they do probably not sufficiently target the underlying cause of the progressive aortic degradation. Therefore, clinical management is directed at prophylactic aortic root replacement, based on threshold values for aortic diameters (50 mm; 45 to 50 mm in patients with family history of dissection).

The three available surgical techniques include; total root replacement surgery (TRR), valve-sparing root replacement surgery (VSRR), and a relatively novel surgical approach with the aim of stabilizing the aortic root size with a personalized external aortic root support (PEARS). Replacement of parts of the aorta beyond the aortic root is usually recommended before reaching 50 mm, which is the threshold for intervention in distal aortic diseases of any etiology. However, this threshold is insufficient for dilatations of the thoracic descending aorta, since patients with only modest dilatation (>27 mm) are shown to be already at increased risk of type B aortic dissections (6).

Risk stratification

Although it is encouraging that surgical techniques are still improving, and thereby increasing life expectancy in patients with MFS, it remains that such surgery itself is associated with morbidity,

occasional mortality, and is not available at all healthcare centers. Moreover, after aortic root replacement, the distal aorta is even more at risk for type B dissection (6), highlighting the need for more sensitive risk stratification to predict the occurrence of aortic complications.

According to current guidelines, accepted additional risk factors for aortic complications are rapid aortic aneurysm growth and a family history of aortic dissection. Nevertheless, there is a need for novel biomarkers, or known biomarkers with more convincing evidence, that can provide insight into disease severity.

Biomarkers concerning imaging techniques (e.g. tortuosity (7), distensibility (8), pulse wave velocity and wall shear stress (9)), biomarkers obtained from blood samples (e.g. Fibrillin-1 fragments (10), elastin fragments (desmosin), TGF- β (11), MFAP4 (12) and potentially Asprosin) and genotype-phenotype correlations (13) could play an important role. In cardiovascular disease, the use of genetic background in risk assessment, and in some cases even in clinical management has already been applied (14). The FBN1 mutations in MFS patients can also be classified according to their effect on protein level as dominant negative (DN) or haploinsufficient (HI) variants (15). DN variants lead to proteins with altered structure/function but with normal expression level, where HI mutations result in reduced expression of the mutant allele and thus to reduced total amount of fibrillin-1.

Several investigated risk factors, including these HI type of FBN1 mutation, male sex and history of aortic root replacement have been shown to negatively affect prognosis in MFS patients. However, except for rapid aortic aneurysm growth and a family history of aortic dissection, none of these additional factors have reached the level of clinical importance to justify surgical intervention at aortic diameters below 50 mm.

Optimal treatment approach

The management of patients with MFS requires a multidisciplinary approach, and includes physical symptoms, as well as psychological factors. Optimal long-term outcome in patients with MFS is mainly focused on slowing down the aortic root dilatation rate, and to prevent aortic complications. It demands lifelong follow-up, with imaging of the aortic root at regular intervals, and in many patients lifelong pharmacological treatment, and surgery at young age.

It is however intriguing that in this era of drug development, no pharmacological treatment strategy has been identified that can inhibit aortic disease in patients with MFS. Therefore, the main objective of this thesis is to obtain more insight into a novel pharmacological strategy. Furthermore, it is of great importance to establish parameters that could help to determine aortic disease severity in patients with MFS, in order to provide an optimal treatment strategy for individual patients. In that light we also aim to obtain more insight into biomarkers that potentially, identify patients at high risk for aortic complications.

OUTLINE OF THE THESIS

Work presented in this thesis explores pharmacological treatment options, potential predictors of aortic events and psychological features in patients with MFS. Data from the randomized COMPARE trial and from the RESVcue Marfan study are used.

Patients with MFS are prone to develop aortic aneurysms, frequently resulting in a necessity of aortic surgery at early age. Although prophylactic surgery improved life expectancy, complications such as dissections and ruptures have remained a significant source of morbidity and mortality in patients with MFS. Improved pharmaceutical treatments and predictors of aortic events are therefore highly needed. In addition to exploring a new treatment strategy in chapters 2-4, we first investigate the long-term clinical outcomes of treatment with the angiotensin-II receptor blocker Losartan in patients with MFS in **Chapter 1**.

In chapters 2-4, we focus on a novel pharmacological strategy to prevent aortic dilatation and aortic complications in MFS. **Chapter 2** provides an overview of the potential beneficial effects of treatment with the food supplement Resveratrol on the various cardiovascular symptoms in patients with MFS. **Chapter 3** shows the rationale and design of the RESVcue Marfan study, which investigates the effect of treatment with Resveratrol in patients with MFS. The primary endpoint in this study is aortic dilatation rate measured by Magnetic Resonance Imaging (MRI). Furthermore, it investigates aortic elastic properties and wall shear stress (WSS), measured by 4D-flow MRI. **Chapter 4** displays the first results of the RESVcue Marfan pilot study and shows whether Resveratrol affects aortic degenerative disease in patients with MFS beneficially, and can potentially be a suitable treatment option for patients with MFS.

Unfortunately, aortic diameters alone are often insufficient to predict the risk for aortic events beyond the aortic root in MFS patients. To aid risk assessment in these patients, we investigate aortic flow and WSS by 4D flow MRI and compare the results with healthy volunteers in **Chapter 5**.

FBN1 mutations cause changes in the fibrillin-1 protein, which forms long and strong fibers in the extracellular matrix (ECM) of many tissues, including the aorta. These fibrillin-1 fibers are also the core of elastin fibers. Improper fibrillin-1 ECM network formation can cause fragmentation of elastic fibers, which is thought to play a major role in aortic aneurysm development, which can ultimately lead to aortic dissection. These fragmented elastic fibers cause reduced aortic distensibility, a variable that was previously shown to predict progressive dilatation of the descending aorta. To further investigate new predictors of aortic events, we investigate longitudinal changes in distensibility in **Chapter 6**.

Differential methylation patterns of the FBN1 locus affect FBN-1 expression, and may be associated with MFS phenotypic diversity. In **Chapter 7**, we undertake the first epigenome-wide association study (EWAS) in blood cells from patients with MFS, aiming at identification of DNA methylation loci associated with MFS phenotypes that may shed light on the disease process.

Chapter 8 gives insight in the prevalence of severe fatigue, anxiety, and symptoms of depression in patients with MFS, in comparison to the general population. Thereby, it assesses the degree to which sociodemographic variables and especially clinical severity of the disease are associated with fatigue, anxiety and symptoms of depression.

The thesis is completed with concluding remarks and future perspectives, which intends to provide a risk profile for patients with MFS, and the best additional treatment accordingly.

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