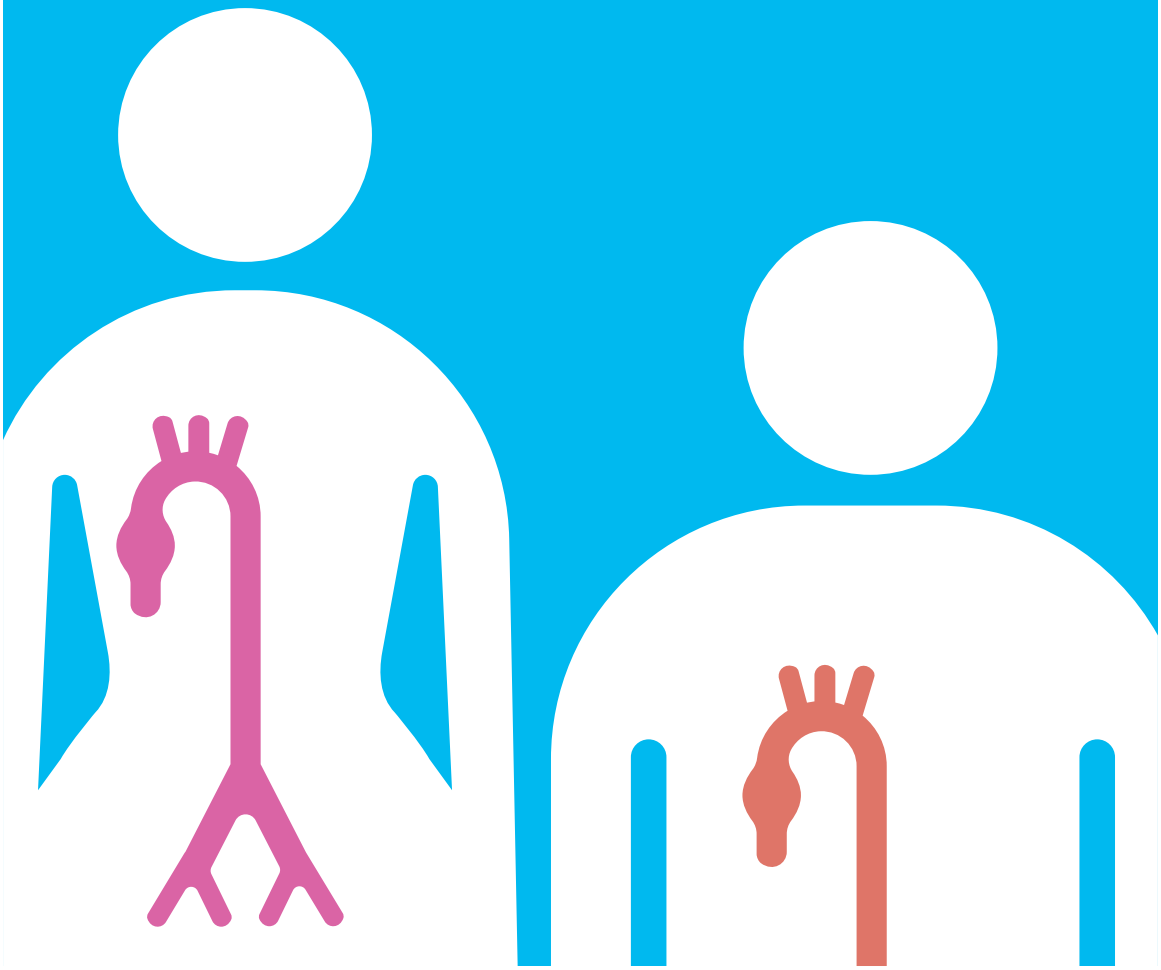
Carlijn Thijssen

PATIENT SPECIFIC INSIGHTS INTO THORACIC AORTIC DISEASE

EXPLORING MALE-FEMALE DIFFERENCES



Patient Specific Insights into Thoracic Aortic Disease

Exploring male-female differences

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Printing: ProefschriftMaken || www.proefschriftmaken.nl

ISBN 978-94-6469-544-1

Patient Specific Insights into Thoracic Aortic Disease

Exploring male-female differences

Patiënt-specifieke inzichten in thoracale aorta ziekten

Een onderzoek naar man-vrouw verschillen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
donderdag 12 oktober 2023 om 15.30 uur

door Carlijn Gerlinde Elise Thijssen
geboren te Rotterdam.

ERASMUS UNIVERSITEIT ROTTERDAM

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Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

CONTENTS

General introduction

The thoracic aorta

The aorta is the largest artery of the human body, and its function is to transport oxygenated blood from the heart to all parts of the body. The diaphragm separates the aorta in the thoracic and abdominal aorta. The thoracic aorta can be divided into four segments (Figure 1): the aortic root, the ascending aorta, the aortic arch and the descending aorta.

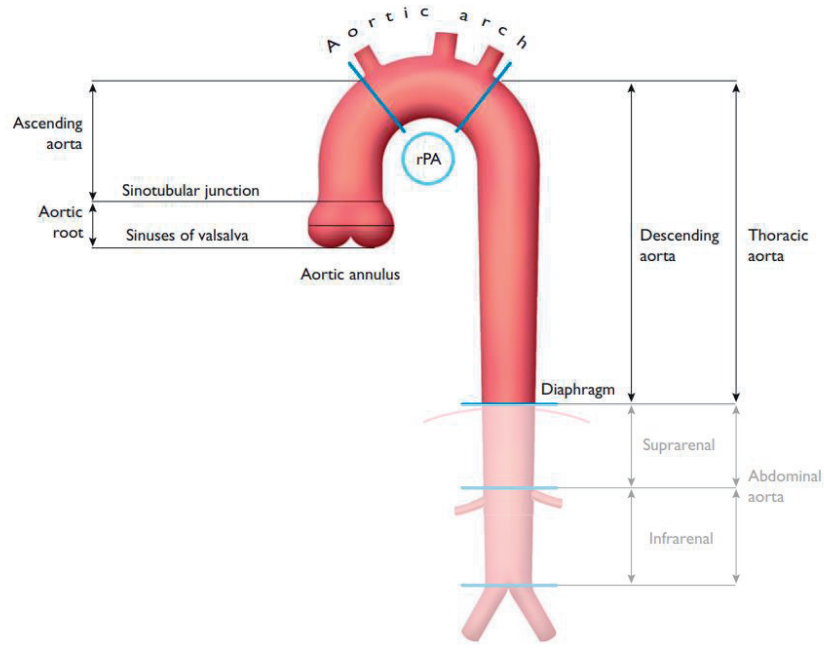

Figure 1. Segments of the aorta
Originally form Erbel et al. Eur Heart J 2014[1].By permission of Oxford University Press on behalf of the European Society of Cardiology.

The aortic wall consist of three layers: the inner layer is the tunica intima, the middle layer is the tunica media and the outermost layer is the tunica adventitia[1]. The tunica adventitia is a collagenous layer that contains the vasa vasorum, nerve and lymphatics. Although it is thin, its rich collagen content gives the adventitia the greatest tensile strength of the three aortic wall layers. The tunica media normally accounts for up 80% of the aortic wall thickness and consists of smooth muscle cells and elastic tissue with proteins such as collagen and elastin. The intima is the thin inner layer, characterized histologically by a basement membrane lined with endothelium that is in direct contact with the blood. Because of its delicate structure, the intima is most susceptible to injury[2].

Thoracic aortic disease

Physiology

The diameter of the aorta tapers gradually downstream. The aortic diameter at all levels is known to increase slowly with age[3]. Thoracic aortic aneurysm (TAA) is a localized abnormal dilatation of the thoracic aorta. A diameter of 40 mm has been proposed as threshold for thoracic aortic aneurysm[4,5]. However, age, sex and body size have been shown to be correlated with thoracic aortic diameter[6,7]. Ideally, patient tailored care should be provided and therefore these factors are increasingly considered when determining the upper limits of aortic diameters[6]. About two-third of patients with thoracic aortic diseases are male. Hence, the predominant part of study populations has traditionally been comprised of male patients. Males are known to have a larger absolute thoracic aortic diameter than females, since females usually have a smaller body size[6]. Consequently, aortic diameters might be relatively larger in females. This is why it may be important to use male-female specific reference values when assessing aortic diameter.

Epidemiology

TAA is usually asymptomatic. The prevalence of TAA is therefore often underestimated. The incidence of thoracic aortic disease including both thoracic aortic aneurysm and dissection is reported to be 16/100,000 per year in males and 9/100,000 per year in females and increasing over the past decades[8]. Due to its asymptomatic nature, TAA is often diagnosed as a coincidental finding, or discovered during family screening for aortic disease. Currently, TAA can be detected using echocardiography for the proximal portion of the aorta. Computed tomography (CT) and magnetic resonance imaging (MRI) are the imaging methods of choice for the total aorta.

Etiology

TAA can be sporadic or hereditary. Patients without family history of thoracic aortic disease or syndromic features are referred to as sporadic TAA. Degradation of the components of the thoracic aortic wall can occur as an acquired process, influenced by factors that potentially influence thoracic aortic wall weakness, such as age and hypertension. In approximately 20% of cases an inherited pattern of TAA is found[9], which is referred to as hereditary thoracic aortic disease (HTAD). HTAD denotes conditions in which abnormalities lead to thoracic aortic wall weakness or abnormal hemodynamic profiles in the thoracic aorta, predisposing patients to aneurysm formation and dissection. Various connective tissue disorders are known to cause HTAD, the majority of which have an autosomal dominant inheritance pattern. Below we will describe some of the most prevalent connective tissue disorders that are known to be associated with HTAD.

Marfan syndrome is the most well-known and well-studied syndromic form of TAA. This disorder is caused by mutations in one of the genes for fibrillin-1, which is a structural protein that is the major component of microfibrils of elastin. The mutation results in both a decrease in the amount of elastin in the aortic wall and a loss of elastin's structure, resulting in cystic medial degeneration. Aneurysms in these patients are mostly located at the aortic root, but can be found at any level of the aorta[10]. Cardiovascular complications are the main cause of death in patients with Marfan Syndrome[11,12].

Loeys-Dietz syndrome (LDS) has various subtypes which are caused by a mutation in one of the following genes: S*MAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1* or *TGFBR2*. Mutations in one of these genes cause irregularities in the TGF-β pathway which regulates collagen syntheses and degradation. Consequently, individuals with Loeys-Dietz syndrome are predisposed to widespread and aggressive arterial aneurysms throughout the arterial tree[13,14]. Furthermore, they often show a strong predisposition for inflammatory diseases including gastrointestinal inflammatory diseases and osteoarthritis, although a wide variation in the distribution and severity of clinical features has been reported.

Vascular Ehlers-Danlos syndrome (vEDS) is caused by a mutation in the *COL3A1* gene, which provides instructions for syntheses of type III collagen. This syndrome is characterized by arterial, intestinal, and/or uterine fragility. Vascular dissection or rupture, gastrointestinal perforation, or organ rupture are the presenting signs in most adults with vEDS[15]. Arterial rupture may be preceded by aneurysm formation, arteriovenous fistulae, or dissection, but also occur at normal diameters.

ACTA2 mutations are the most frequent genetic cause of HTAD. *ACTA2* encodes for a critical component of the contractile apparatus of the vascular smooth muscle cell. Patients with *ACTA2* mutations are at high risk of thoracic aortic dissection, even at normal aortic diameters. *ACTA2* mutations are also associated with occlusive vascular disease and ocular manifestations [16,17].

Turner syndrome is caused by a partial or complete absence of the second sex chromosome (XO). Typical clinical features are short stature, ovarian insufficiency and aortic aneurysm or dissection. Because of their short stature, aortic diameter is indexed for body size in these patients. Ascending aortic aneurysm is found in 24% of patients with Turner Syndrome and dissection occurs six times more often than in the general population[18].

Bicuspid aortic valve (BAV) is a non-syndromic disease with a predisposition for thoracic aortic aneurysm, prevalent in 1-2% of the population[19]. In patients with BAV, thoracic aortic dilatation occurs in over 50%[20] and is most often located in the ascending aorta, although the location of aortic dilatation can also occur in the aortic root and/or extend

to the aortic arch. The localization of aortic dilatation was found to be associated with the type of BAV as classified by morphologic valve-fusion patterns[20].

Table 1. Hereditary thoracic aortic diseases

Connective tissue disorder	Genetic mutation	Molecular pathway	Thoracic aortic disease	Indication preventive thoracic aortic surgery	References
Marfan syndrome	*FBN 1*	Extracellular matrix	Aneurysm mostly located at the aortic root	50 mm (45 mm if additional risk factors are present)*	[1]
Loeys-Dietz syndrome	Type 1: *TGFBR1* Type 2: *TGFBR2* Type 3: *SMAD3* Type 4: *TGFB2* Type 5: *TGFB3*	TGF-β signaling	Aneurysms and / or dissections throughout arterial tree	Should be considered when TAA diameter is 40-45 mm	[1,21]
Vascular Ehlers-Danlos syndrome (type IV)	*COL3A1*	Extracellular matrix	Aortic dissection often occurs at normal aortic diameters	No specific diameter (avoid surgery if possible because of highly friable vascular tissue)	[1]
ACTA2 mutation	*ACTA2*	SMC contraction	Aortic dissection often occurs at normal aortic diameters	50 mm (45 mm if additional risk factors are present)*	[16,17]
MYLK mutation	*MYLK*	SMC contraction	Aortic root or ascending aortic aneurysm Aortic dissection often occurs at normal aortic diameters	45-50 mm Age > 40 years has been proposed for aortic root and ascending aortic surgery	[22,23]
MYH-11 mutation	*MYH11*	SMC contraction	Aortic dissection and patent ductus arteriosus	45-50 mm	[22,23]
Bicuspid aortic valve (BAV)	*NOTCH1 / TGFBR2*		Aneurysm mostly located at the ascending aorta	55 mm (50 mm if additional risk factors are present)*	[1]
Turner syndrome	*45X*		Aneurysm most prominent at ascending aorta	ASI ≥27.5 mm/m^2	[1]

* Risk factors: family history of dissection, size increase of >3 mm/year (in repeated examinations using the same technique and confirmed by another technique), severe aortic regurgitation, or desire for pregnancy.
ASI= Aortic Size Index, calculated by dividing thoracic aortic diameter by Body Surface Area; SMC= smooth muscle cell; TGF= transforming growth factor.

Natural history of TAA

Generally, TAA's expand gradually over time. Before the introduction of diameter guided preventive surgery, when patients probably had larger aneurysm diameters, the average ascending aneurysmal aorta was found to expand about 1.0 mm/ year whereas the descending aneurysmal aorta expanded 2.9 mm/ year[24]. In the current days, mean ascending aortic aneurysm growth rate has been reported to be 0.2-2.8 mm/year[25]. For descending aortic aneurysms and thoraco-abdominal aneurysms this is 1.9-3.4 mm/year[25].

Several factors are known to be associated with faster TAA expansion. The most well-known are: etiology, aortic diameter and aneurysm location. Lower growth rates have been reported in the proximal segments of the aorta (aortic root and ascending aorta) compared to the more distal segments (descending and thoraco-abdominal aorta)[25]. In patients with BAV ascending aortic aneurysm growth rate has been reported to be 0.8 mm/year versus 0.3 mm/year in patients with tricuspid aortic valve[26]. In patients with Marfan Syndrome the aortic root aneurysm expansion rate seems much higher up to 2.6 mm/year[27]. In patients with Loeys-Dietz syndrome aortic root expansion rates of 1.1-6.7 mm/year have been reported[28].

Patients with TAA are at risk for thoracic aortic dissection or rupture. Expansion to larger aortic diameters increases the risk of thoracic aortic dissection or rupture. TAA usually remains asymptomatic. TAA's that produce symptoms are often very large and at high risk for dissection or rupture.

Dissection

Thoracic aortic dissection or rupture is a diagnosis with high mortality (33-47%) and morbidity[29,30]. Recently an estimated incidence of 12/100,000 per year was reported for ascending aortic dissections or rupture[31]. Aortic dissection consists of a tear in the tunica intima of the aorta, which leads to separation of the tunica media of the aortic wall. When blood enters the separated tunica media, this creates two lumina within the aorta: one lumen delineated by the original intimal layer (true lumen), and a second lumen within the media of the aorta between the intimal layer and tunica adventitia (false lumen). Aortic dissections can occur in all parts of the aorta, and are classified according to the Stanford or DeBakey classifications according to the location of the dissection (figure 2). In both classifications the location of the intimal tear does not play a role. The Stanford classification is mostly used in clinical practice, as it separates the life-threatening type A dissection, with an indication for emergency aortic surgery from the more benign type B dissection, which is preferably treated medically.

Patients with Stanford type A dissection generally receive immediate emergency surgery after diagnosis. These patients have a 30-day mortality rate of about 20-25% [32,33].

Furthermore, morbidity including neurological complications is high. For Stanford type B dissection in-hospital mortality has been estimated at 13%[34]. Uncomplicated type B dissection is initially treated medically to control pain, heart rate and blood pressure under close surveillance[1]. Complicated type B dissection with signs of malperfusrion of ongoing rupture or expansion is treated with thoracic endovascular aortic repair or open surgery[1].

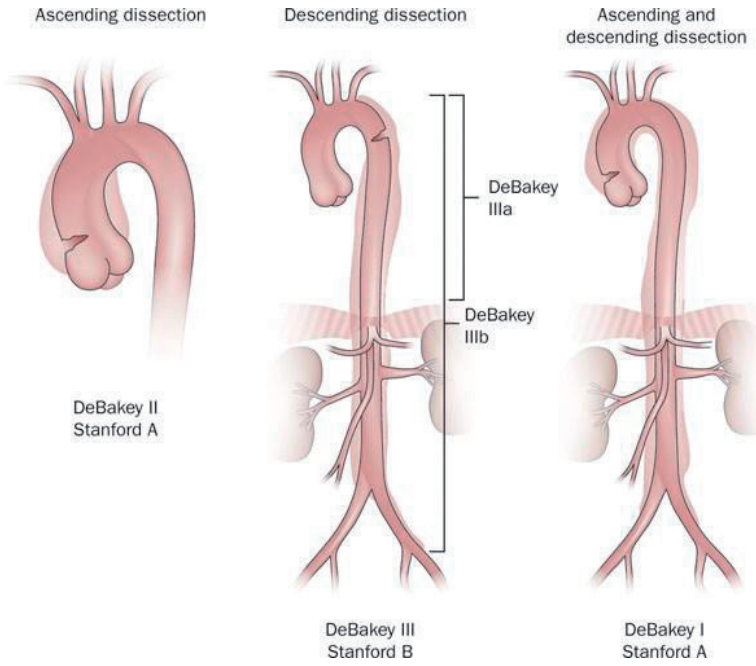

Figure 2. Classifications of aortic dissection
Reprinted by permission from Springer Nature, Nature Reviews Cardiology. Epidemiology of thoracic aortic dissection, LeMaire et al., 2011.

Elective aortic surgery

In order to prevent complications such as aortic rupture and dissection, patients with known TAA are offered preventive surgical replacement of the affected part of the aorta when the diameter reaches a specific value or increases rapidly. Studies have shown an exponential increase of the risk of aortic dissection at an aortic diameter over 60 mm[24]. Therefore 55 mm has been established as an indication for preventive surgery. For some forms of HTAD lower cut-off values have proven necessary, as is shown in table 1. However, it is unknown whether other patient specific factors such as sex, age and body size need to be taken into consideration in order to choose the appropriate timing for preventive thoracic aortic surgery.

Due to preventive aortic surgery, life-expectancy of HTAD patients such as patients with Marfan syndrome has increased significantly[12]. Moreover, outcomes after thoracic aortic surgery have improved over the past decades[35]. Contemporary elective thoracic aortic surgery has a mortality and stroke rate in the range of 2.4-3.0%[36]. Although this might not seem high, ascending aortic surgery is a major procedure which involves (deep hypothermic) circulatory arrest, the use of extracorporeal circulation and sometimes cerebral perfusion. Therefore, it is important to weigh the risk of aortic complications with associated mortality and morbidity against the risk of aortic surgery for every individual patient.

Male-female differences

Nomenclature

Sex and gender are often used interchangeably by researchers. However, there is an important difference in the definition of these terms. The World Health Organization defines sex as: "The biological characteristics that define humans as female or male."[37] Gender is defined as "The socially constructed characteristics of women and men- such as norms, roles and relationships of and between groups of women and men."[38] In research, sex is considered a binary variable. Gender, in contrast, is a continuous variable defined by the patient, including a range of characteristics varying with age, ethnicity, geographic location, education, and culture. In scientific research, it is very important to use uniform and correct definitions of key variables such as sex and gender to ensure that research on the topic is reproducible ad can be extrapolated. Furthermore, we must be mindful that often it remains unclear whether the observed effects or associations are attributable to sex, to gender, or to a combination of both. Often the latter is the case, therefore in this thesis we chose to consistently use the term: male-female differences, in order to encompass the broader spectra of both sex and gender.

Outcomes

Less favourable outcomes regarding mortality and morbidity have been reported in female patients, independent of age and comorbidities. This applies to both preventive thoracic aortic surgery as well as surgery for acute dissection[39-41]. The underlying cause of these less-favourable outcomes in females with TAA remains unknown and larger studies were advised to verify these findings.

The lack of male-female specific timing of preventive surgery might play an important role in explaining differences in outcomes between males and females. Females with TAA are often older and have more comorbidities than males. However, one study has shown that the poor outcomes in females are independent of age and comorbidities[39]. It has been suggested that use of absolute aortic size for indication of preventive surgery

is disadvantaging females, who are usually smaller than males with respect to height and baseline aortic diameter. Therefore, use of relative aortic size corrected for body surface area (BSA) has been proposed[42,43]. Although this presumably is a step in the right direction, female sex still seems to be an independent risk factor for aortic dissection, despite indexing for body size[43]. In addition, height and weight might contribute in a different manner. This indicates male-female differences in TAA are complex and cannot be attributed to differences in body size alone.

Biomarkers in thoracic aortic disease

Thoracic aortic diameter might not be the only factor associated with the risk of acute aortic dissection or rupture. In addition to imaging parameters, blood biomarkers have the potential to be easily quantifiable and readily available risk predictors. The term biomarker originates from 'biological marker'. Blood biomarkers are indicators of a biological substance, structure or process quantifiable in human serum or plasma. Blood biomarkers have become a favored modality in clinical practice due to the fact that they are easy to obtain, and provide an objective measurement. However, to this date, the use of biomarkers in TAA has been very limited. Nevertheless, there might be an important role for these blood biomarkers in TAA[44], as they could have potential diagnostic and prognostic value relevant for minimally invasive screening, follow-up and clinical decision making in TAA patients. Ideally, biomarkers could be used to better predict complications, such as acute thoracic aortic dissection. Besides the use of biomarkers for risk prediction, blood biomarkers can help gain insights into the pathophysiological processes of TAA formation as they are mostly linked to certain molecular and cellular pathways. More research is needed to identify blood biomarkers associated with TAA, and assess which blood biomarkers have potential for use in clinical practice.

Living with thoracic aortic disease

Surveillance

Patients with TAA remain under life-long surveillance in order to monitor TAA diameter and dilatation rate, optimize timing of elective TAA surgery and monitor aortic diameters or complications after elective or emergency surgery. The main aim of medical therapy is to prevent rapid aortic dilatation and especially dissection. Evidence on factors influencing thoracic aortic dilatation rate is scarce. Nevertheless, blood pressure control is the cornerstone of medical therapy of TAA, as it makes pathophysiologic sense to reduce aortic wall shear stress on the diseased part of the aorta. Optimal blood pressure targets and preferred anti-hypertensive medication remains controversial[1,45]. The thoracic aorta seems less susceptible for atherosclerotic risk factors compared to the abdominal aorta and peripheral arteries[46]. Nevertheless, smoking cessation and lifestyle modification are encouraged[1,45].

Exercise and physical activity

In the context of TAA, the hemodynamic changes associated with exercise, and specifically the increase in blood pressure, could theoretically be associated with an enhanced risk of aortic growth and acute aortic dissection. However, data on the association between exercise or blood pressure changes and thoracic aortic disease in patients is lacking. Because of the theoretical risk of aortic dissection, many patients with TAA are advised to refrain from contact sports, to limit their static physical exertion and are submitted to strict blood pressure control. Current guidelines state that patients with TAA and hereditary thoracic aortic diseases should avoid strenuous exercise and competitive sports[1,45]. The most recent guidelines state that some form of physical activity is advised in all patients, also when aortic pathology is present[47]. This is important, since it is well known that sedentary lifestyle should be avoided, as this is an important modifiable risk factor for cardiovascular disease and mortality, and physical activity benefits overall fitness and also psychological well-being[48,49].

Quality of life

Attention for psychological well-being is particularly important, because patients with thoracic aortic disease and their family members often face lifelong uncertainties about the risk of sudden rupture of their aorta and possible need for major surgery. Being diagnosed with (hereditary) TAA, especially knowing the risk of acute dissection and the consequences for themselves and their children, is a shock for many patients. This diagnosis imposes increased challenges in daily life and psychosocial distress. Consequently, quality of life in patients with thoracic aortic diseases may be hampered[50,51]. Despite this, evidence on quality of life in patients with TAA is scarce. Quality of life has been reported in HTAD patients, mostly in patients with Marfan Syndrome, and was reduced compared to the general population, but similar to patients with other chronic diseases[50,52,53]. Quality of life after preventive thoracic aortic surgery has been reported as acceptable and often similar to a healthy age- and sex-matched population. No studies have reported on differences in quality of life between male and female patients with TAA, in spite of the fact that quality of life is known to be lower in females than in males in the general population and anxiety and depression are more prevalent in females[54,55]. Which indicates that attention for male-female differences in quality of life is important. The effects of TAA on the quality of life of partners has not yet been investigated either. Quality of life has been increasingly recognized as an important element of clinical decision-making and identifying ways to improve quality of life is crucial to patient-centered care[56].

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide patient specific insights into thoracic aortic disease, and in particular to investigate male-female differences. This is done by researching several aspects of thoracic aortic disease.

First, we will study the normal thoracic aorta and define pathological findings in both persons with and without thoracic aortic disease, in order to gain insights into the characteristics of the normal and abnormal thoracic aorta and other vascular abnormalities associated with thoracic aortic disease. The following research questions will be investigated:

- How much does the normal aortic diameter increase during the adult life-course? (Chapter 1)
- Are there any cardiovascular blood biomarkers available which can be associated with thoracic aortic diameter in patients with thoracic aortic disease? (Chapter 2)
- In addition to aorta abnormalities, are there also neurovascular abnormalities and events in patients with Loeys-Dietz syndrome type III? (Chapter 3)

Second, male-female differences and age-related differences in thoracic aortic surgery and dissection are addressed:

- Are there male-female differences in presentation, timing, procedural characteristics and outcomes of elective thoracic aortic surgery and type A dissection? (Chapter 4 + 5)
- Are there differences between elderly and non-elderly in procedural characteristics and outcomes of elective thoracic aortic surgery? (Chapter 6)

Lastly, we attempt to identify male-female differences in the impact of thoracic aortic disease on quality of life by addressing the questions below:

- Is there evidence to suggest that exercise or sports participation should be discouraged in patients with thoracic aortic disease or a hereditary predisposition? (Chapter 7)
- Is quality of life reduced in patients with hereditary thoracic aortic disease, and are there any male-female differences in quality of life in this population? (Chapter 8-9)
- Is quality of life reduced in males and females who were treated for thoracic aortic dissection? (Chapter 10)

This thesis is part of the 'Size Matters' project, funded by ZonMW, that aims to identify male-female differences and other patient specific insights into thoracic aortic disease diagnosis, treatment and outcomes.

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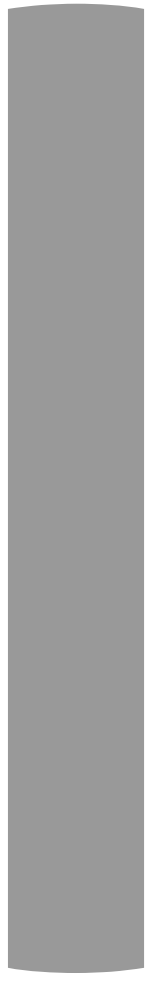

Characteristics of thoracic aortic disease

CHAPTER 1

Longitudinal changes of thoracic aortic diameters in the aged general population

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Heart, 2022

ABSTRACT

Objectives

Longitudinal data on age-related changes in the diameters of the thoracic aorta are scarce. To better understand normal variation and to identify factors influencing this process, we aimed to report male-female and age-specific aortic growth rate in the aging general population and identify factors associated with growth rate.

Methods

From the prospective population-based Rotterdam Study, 943 participants (52.0% female, median age at baseline 65 years [62-68]) underwent serial non-enhanced cardiac computed tomography (CT). We measured the diameters of the ascending (AA) and descending aorta (DA) at two time points and expressed absolute and relative differences. Linear mixed effects analysis was performed to identify determinants associated with change in aortic diameters.

Results

Mean AA diameter at baseline was 37.3±3.6 mm in males and 34.7±3.2 mm in females, mean DA diameter was 29.6±2.3 in males and 26.9±2.2 mm in females. The median absolute change in diameters during follow-up (mean scan interval 14.1±0.3 years) was 1 mm [0-2] for both the ascending and descending aorta. Absolute change per decade in AA diameter was significantly larger in males than in females (0.72 mm/decade [0.00-1.43] vs 0.70 mm/decade [0.00-1.41], p=0.006), as well as absolute change in AD diameter (0.71 mm/decade [0.00-1.42] vs 0.69 mm/decade [0.00-1.36], p=0.008). There was no significant difference between males and females in relative change of their aortic diameters during follow-up. Age, male sex, higher body mass index (BMI), and higher diastolic blood pressure (DBP) showed a statistically significant independent association with increase in AA and DA diameters over time.

Conclusions

Some degree of increase in thoracic aortic diameters is typical in both males and females of an aging population. Factors associated with this change in thoracic aortic diameters were sex, age, BMI and DBP

INTRODUCTION

A thoracic aortic aneurysm (TAA), often defined as a thoracic aortic diameter of ≥ 40 mm[1,2], is associated with an increased risk of aortic dissection and even sudden death. Despite the potentially serious complications of TAA, several knowledge gaps on changes in aortic diameters exist.

First, little information is available on longitudinal age-related changes in the diameters of the normal, non-dilated, thoracic aorta. The Framingham Heart Study reported on longitudinal changes of the Sinuses of Valsalva in the general population[3]. However, the majority of TAA's are not located at the Sinuses of Valsalva[4]. Currently, rapid aortic dilatation is defined as an increase in thoracic aortic diameter at any location of >3 mm / year and is an indication for surgical intervention. This is based solely on expert opinion as there is little evidence on normal and abnormal change in thoracic aortic diameters [5,6].

Second, only limited and contradictory data exist on male-female differences in age-related changes of thoracic aortic diameters. The Framingham Heart study showed faster age-related changes in diameter of the aortic Sinuses in males compared to females of the general population[3]. Bons et al. reported comparable changes in ascending and descending diameters in males and females, although in a high-risk, smoking population[7]. Clearly, there is a need for sex-specific insights into age-related changes in thoracic aortic diameters, in order to improve diagnosis and treatment of TAA in both males and females.

Third, no longitudinal studies have evaluated the change in diameter of the ascending and descending aorta in the general population with the use of reproducible, advanced imaging techniques such as computed tomography (CT). European guidelines recommend measurements perpendicular to the vessel axis using three-dimensionally reconstructed CT scan images for assessment of the thoracic aorta[8], since this approach offers the most accurate and reproducible measurements of true aortic dimensions.

Studying age-related changes of thoracic aortic diameters in the general population, is the first step towards defining pathological aortic dilatation. Therefore, we investigated sex- and age-specific changes in ascending and descending aortic diameters in an aged general population, and identified male-female specific determinants of change in aortic diameters.

METHODS

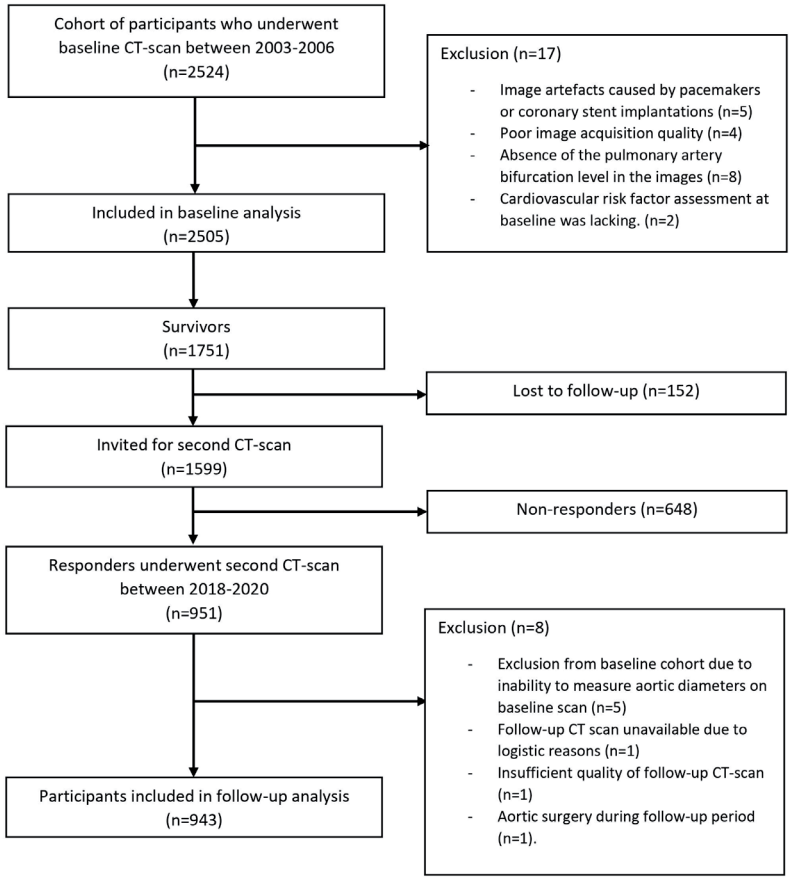


Figure 1. Flowchart of inclusion

Study population

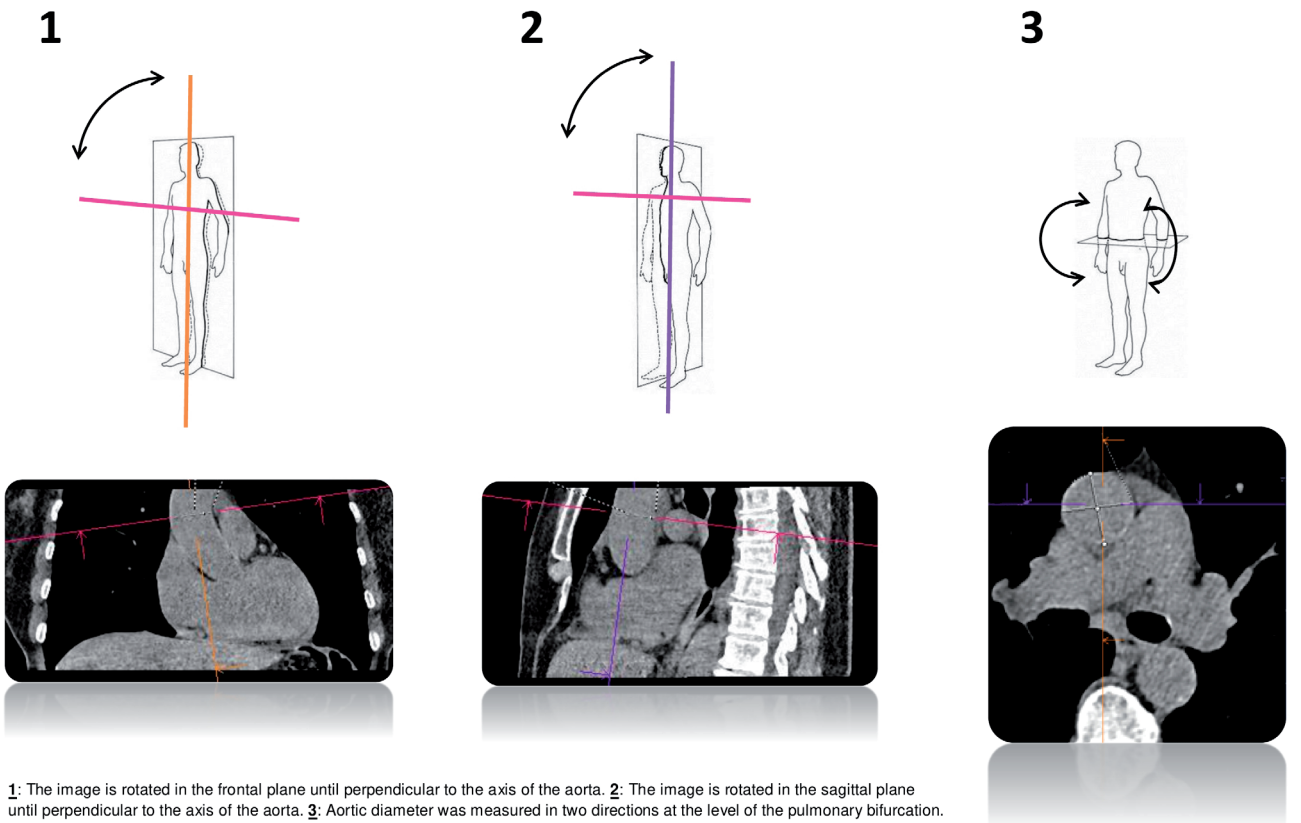
The Rotterdam Study is a prospective population-based cohort study that was initiated in 1990, including participants aged 55 years or older from the Ommoord district in Rotterdam, The Netherlands. Between 2003 and 2006 a random sample of 2524 participants underwent non-enhanced multidetector computed tomography (CT) as part of a large project on arterial calcification. For the current study all participants who were still participating in the Rotterdam Study (n=1599) were invited for a follow-up non-enhanced CT between 2018 and 2020. Figure 1 shows a flowchart of the study population. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport

(license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. This study was designed and performed without patient involvement.

Assessment of aortic diameters

At baseline, non-contrast CT images were obtained using 16-slice (n=775) or 64-slice (n=1730) multidetector CT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany). The protocol included an ECG-triggered cardiac scan covering the apex of the heart to the tracheal bifurcation, which was used to measure the aortic diameters during diastole (R-R interval of 50%). All follow-up non-contrast CT images were obtained using a 128-slice dual source CT scanner (Somatom Drive, Siemens, Forchheim, Germany), with settings that were similar to the baseline scan[9]. Spatial resolution of follow-up CT-scans was 0.4 mm in the z-axis.

The measurements of the thoracic aortic diameters were performed by two investigators (CT and FM) in exactly the same manner as the baseline CT-scans[10]. Both the diameters of the ascending aorta (AA) and descending aorta (DA) were measured in two directions, at the level of the pulmonary bifurcation using the double-oblique method in a reconstruction, perpendicular to the vessel axis (Figure 2). The largest diameter of the two measurements was used for the analysis. Since non-enhanced scans were used, we measured the aortic diameter with the outer edge-to-outer edge method. Assuming that calcified plaques are located in the intimal layer of the aorta, they were included in the measurement. Inter-observer reliability with this method was analysed for the baseline scans and showed to be very high, with an intraclass correlation coefficient (ICC) of 0.985 for the ascending aorta and 0.989 for the descending aorta[10]. Since the follow-up scan measurements were performed by a different team, inter-observer variability was re-assessed for the follow-up scans. Two observers measured the aortic diameters of the first 30 participants. The mean difference of the inter observer variability was 0.29±1.07 for the AA and 0.10±1.08 for DA measurements, as is represented by the Bland-Altman plots in Supplemental file 1. The ICC was 0.969 for the ascending aorta and 0.954 for the descending aorta. To assess intra-observer variability for the follow-up scans one observer re-measured 30 scans after all measurements had been performed. The ICC was 0.982 for the ascending aorta and 0.974 for the descending aorta. Changes in aortic diameters were expressed in absolute change (diameter at follow-up minus diameter at baseline in millimetres) and relative change (the percentage increase in diameter between baseline and follow-up). Absolute and relative change per decade were calculated by dividing the change during follow-up by the number of decades between the baseline and follow-up scan for each individual.



1: The image is rotated in the frontal plane until perpendicular to the axis of the aorta. 2: The image is rotated in the sagittal plane until perpendicular to the axis of the aorta. 3: Aortic diameter was measured in two directions at the level of the pulmonary bifurcation. The largest diameter was used for analysis. These steps were performed separately for measurements of the ascending and descending aorta.

Figure 2. Double-oblique measurement method for thoracic aortic diameters

Determinants of change in aortic diameters

At baseline, information was collected including age, sex, body height and weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), current or past smoking, total and high-density lipoprotein cholesterol levels, diabetes, history of cardiovascular disease (CVD) including stroke, myocardial infarction, percutaneous coronary interventions and coronary artery bypass grafting, and use of cardiovascular medication including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, antithrombotic medication and serum lipid lowering agents. Body Surface Area (BSA) was calculated using the DuBois and DuBois formula: BSA (m2)=0.007184×height $(m)^{0.725}$×weight $(kg)^{0.425}$. Detailed information on the assessment strategy for each determinant has previously been described[6]. Indexed aortic diameters were calculated by dividing absolute ascending and descending aortic diameters by BSA. Body Mass Index (BMI) was calculated as weight (kg) / $height^2$ (m).

Statistical analysis

Baseline characteristics of the study population were compared between the follow-up cohort and non-responders (Supplemental file 2). The data was analysed using the following strategy: First, normal distribution was assessed of all potential determinants of change in aortic diameters and absolute and relative change in AA and DA diameters per decade, using the Shapiro-Wilk test. Subsequently, continuous data were presented as mean and standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when skewed. Categorical data were presented as frequencies with percentages.

Second, male-female specific distributions of absolute and relative changes in AA and DA diameter were calculated as median and interquartile range for the total group and specific age groups (baseline age: 55-64 years, 65-74 years and ≥75 years). Absolute and relative change in AA and DA diameters were compared between males and females, and between different age groups. This was done using the students t-test or non-parametric Mann-Whitney U-test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables.

Third, linear mixed effects models were used to evaluate determinants associated with absolute change in AA and DA diameter over time. Linear mixed effects model analyses were performed using the baseline and follow-up thoracic aortic diameters for the total population (n=943), and stratified for males and females. When applicable, models were adjusted for all abovementioned determinants as well as original Rotterdam Study cohort and baseline scanner type. For adjustment of body size BMI was used. Since both weight and height were important determinants of aortic diameter at baseline, sub-analyses were performed adjusting for height and weight separately instead of BMI. In

12.7% of the participants, ≥1 of the variables were missing and they were handled by multiple imputation with five iterations[10,11]. For imputation the monotone method was used if the data show a monotone pattern of missing values, otherwise, fully conditional specification was used. Data were analysed using IBM SPSS statistics software V.21.0 and *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 3.6.1) using packages '*TableOne'* and '*nlme'*.

TABLE 1. Baseline characteristics of study participants

	Total n=943	Males n=453	Females n=490	P-value
Age - y	65.0 (62.0-68.0)	65.0 (63.0-68.0)	65.0 (62.0-67.0)	0.309
Height - cm	168.4±9.5	175.5±7.2	161.9±6.0	<0.001
Weight - kg	78.7±13.0	85.4±11.7	72.6±11.1	<0.001
BSA - m^2	1.9±0.2	2.0±0.2	1.8±0.1	<0.001
SBP - mmHg	141.0 (130.5-153.0)	141.0 (131.0±153.5)	142.0 (130.0-152.4)	0.801
DBP - mmHg	81.0±10.0	82.6±9.8	79.5±9.9	<0.001
Hypertension[1]	494 (53.5)	256 (57.5)	238 (49.7)	0.020
Hip circumference - cm	102.6 (99.0-107.4)	102.0 (98.7-106.0)	103.4 (99.5-108.8)	<0.001
Smoking				<0.001
Never	300 (31.8)	88 (19.4)	212 (43.3)	
Past	514 (54.5)	292 (64.5)	222 (45.3)	
Current	129 (13.7)	73 (16.1)	56 (11.4)	
Total cholesterol - mmol/L	5.8±1.0	5.5±0.9	6.0±0.9	<0.001
HDL cholesterol - mmol/L	1.4 (1.2-1.7)	1.3 (1.1-1.5)	1.5 (1.3-1.8)	<0.001
Diabetes Mellitus	101 (10.7)	50 (11.0)	51 (10.4)	0.836
Aortic diameter at baseline - mm				
Ascending aorta	36.0±3.7	37.3±3.6	34.7±3.2	<0.001
Descending aorta	28.1±2.6	29.6±2.3	26.9±2.2	<0.001
Indexed baseline aortic diameter[2] - mm/m^2				
Ascending aorta	19.2±2.1	18.6±2.0	19.7±2.1	<0.001
Descending aorta	15.0±1.4	14.8±1.4	15.2±1.4	<0.001
History of cardiovascular disease				
Myocardial infarction	32 (3.4)	24 (5.3)	8 (1.6)	0.003
PCI	25 (2.7)	18 (4.0)	7 (1.4)	0.026
CABG	21 (2.2)	19 (4.2)	2 (0.4)	<0.001
Stroke	18 (1.9)	10 (2.2)	8 (1.6)	0.684
Medication				
Beta-blocking agents	178 (19.1)	90 (20.2)	88 (18.1)	0.461
Calcium blockers	67 (7.2)	35 (7.9)	32 (6.6)	0.530
ACE-inhibitors	136 (14.6)	82 (18.4)	54 (11.1)	0.002
Antithrombotic agents	149 (15.8)	104 (23.0)	45 (9.2)	<0.001
Serum lipid-lowering agents	209 (22.2)	104 (23.0)	105 (21.4)	0.627

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.

BSA= Body Surface Area; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; HDL= High Density Lipoprotein; PCI= Percutaneous Coronary Intervention; CABG= Coronary Artery Bypass Grafting; ACE= Angiotensin Converting Enzyme.

[1] Defined as blood pressure > 140/90 mmHg and/or use of antihypertensive medication

[2] Aortic diameter divided by body surface area

RESULTS

Baseline characteristics

From the 1599 participants that were invited to participate in the follow-up CT study (Figure 1), 951 (59%) participants agreed and received a follow-up CT-scan. Five patients were already excluded from baseline analyses due to inability to measure the aortic diameter for technical reasons[10]. Of the remaining 946 patients we excluded three CT examinations for the following reasons: follow-up CT scan unavailable due to logistic reasons (n=1), insufficient quality of follow-up CT-scan (n=1) and aortic surgery during follow-up period (n=1). Finally, 943 participants were included in the follow-up study (52% female, median age 65 years at baseline, mean follow-up duration 14.1±0.3 years). Participants in the follow-up cohort were significantly younger, had less cardiovascular risk-factors, less cardiovascular diseases and cardiovascular medication use, and smaller AA and DA diameters at baseline compared to participants who passed away and were lost to follow-up (supplemental file 2). Table 1 shows baseline characteristics of the study participants in the follow-up cohort. There was no significant difference in age between males and females at baseline. Cardiovascular risk factors, cardiovascular diseases and cardiovascular medication use were more prevalent in males and males had significantly larger absolute aortic diameters at baseline.

Sex and age-specific changes in aortic diameters

Mean AA diameter at follow up was 38.4±3.9 mm in males and 35.6±3.4 mm in females. Mean DA diameter at follow-up was 30.6±2.7 mm in males and 27.6±2.5 mm in females. The median total change in diameters during follow-up (mean 14.1±0.3 mm years) was 1 mm (0-2) for both the ascending and descending aorta. Sex- and age-specific absolute change in aortic diameters are shown in figure 3. The median change in AA diameter was 0.71 mm/decade (0.00-1.42), and the median change in DA diameter was 0.70 mm/decade (0.00-1.39). Histograms of absolute change in AA and DA diameters in males and females are shown in Figure 4. Absolute change in AA diameter was significantly larger in males than in females (0.72 mm/decade IQR 0.00-1.43 vs 0.70 mm/decade IQR 0.00-1.41, p=0.006). Absolute change in DA diameter was also significantly larger in males compared to females (0.71 mm/decade IQR 0.00-1.42 vs 0.69 mm/decade IQR 0.00-1.36, p=0.008). There was no significant difference between males and females in relative change of aortic diameters (supplemental file 3). Absolute and relative change in AA and DA diameter were not significantly different between the three age categories, except for elderly females (aged ≥ 75) who showed significantly less change in absolute and relative aortic diameters (median AA 0.00 mm [0.00; 1.38] and median DA 0.00 mm [-0.73; 0.69]). The 95th percentiles of change in AA diameters were 2.9 mm/decade for males and females, 95th percentiles of change in DA diameters were 2.9 mm/decade for males and 2.1 mm/decade for females.

A Z-score of 2 was found to represent 2.93 mm per decade change in AA and 2.73 mm per decade change in DA. Rapid change in aortic diameters of ≥3mm/year was not found in any of the participants. There was a significant but modest correlation between absolute change in AA diameters with change in DA diameters (R=0.36, p<0.001). A visualization of changing AA and DA aortic diameters during follow-up is presented in figure 5.

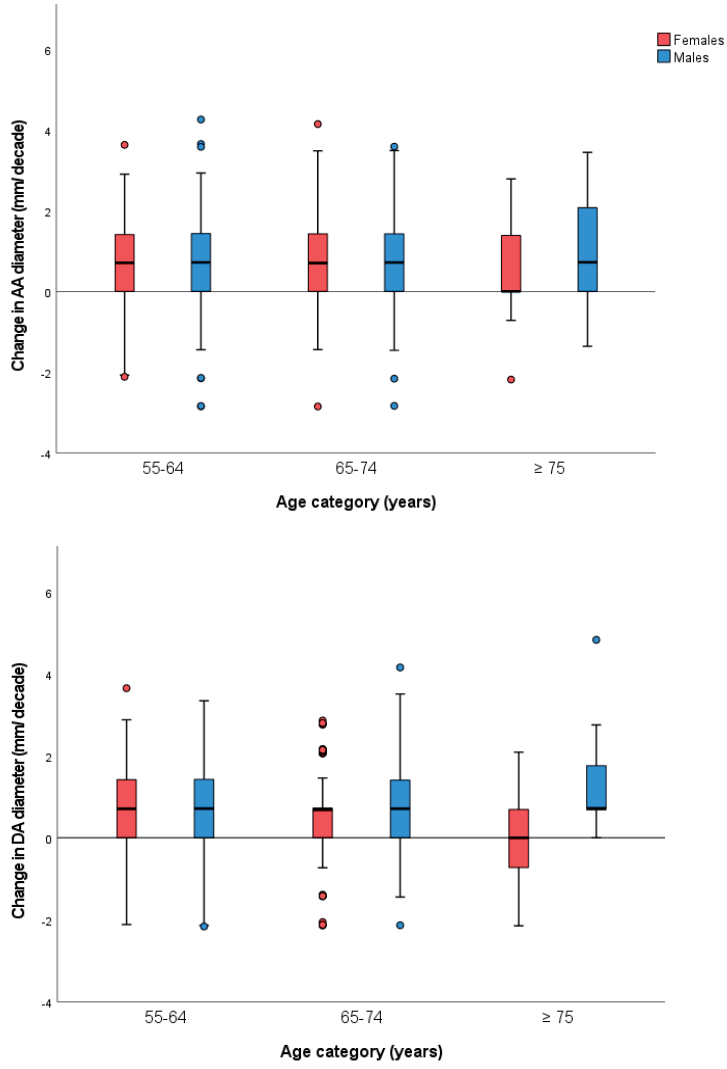


Figure 3. Absolute changes in aortic diameters per decade by sex and age

AA = Ascending aorta; DA = Descending aorta

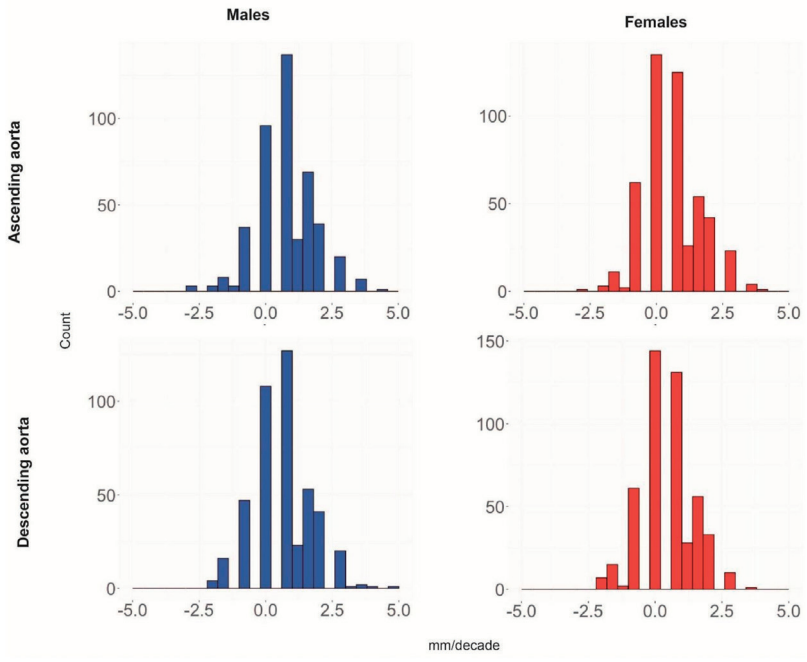


Figure 4. Distribution of sex-specific changes in aortic diameters

Determinants of change in AA diameter

Figure 6 shows the association of baseline determinants with change in AA diameter. Age, male sex, body mass index (BMI) and diastolic blood pressure (DBP) showed a statistically significant association with change in AA diameter. When looking at height and weight separately, neither height nor weight was significantly associated with change in AA diameter. All associations found in the total population remained statistically significant in the stratified analysis for females (age, BMI, DBP). In males, only BMI was significantly associated with change in AA diameter.

Determinants of change in DA diameter

Figure 7 shows the association of baseline determinants with change in DA diameter. Higher age, BMI, DBP and smoking showed a significant association with more change in DA diameter. Use of serum lipid lowering agents was associated with less change in DA diameter. When looking at height and weight separately, only weight was significantly associated with change in DA diameter, whereas height was not. In females, higher age, BMI, DBP and current smoking showed a significant association with more change in DA diameter. Whereas in males higher age, BMI and use of serum lipid reducing agents were significantly associated.

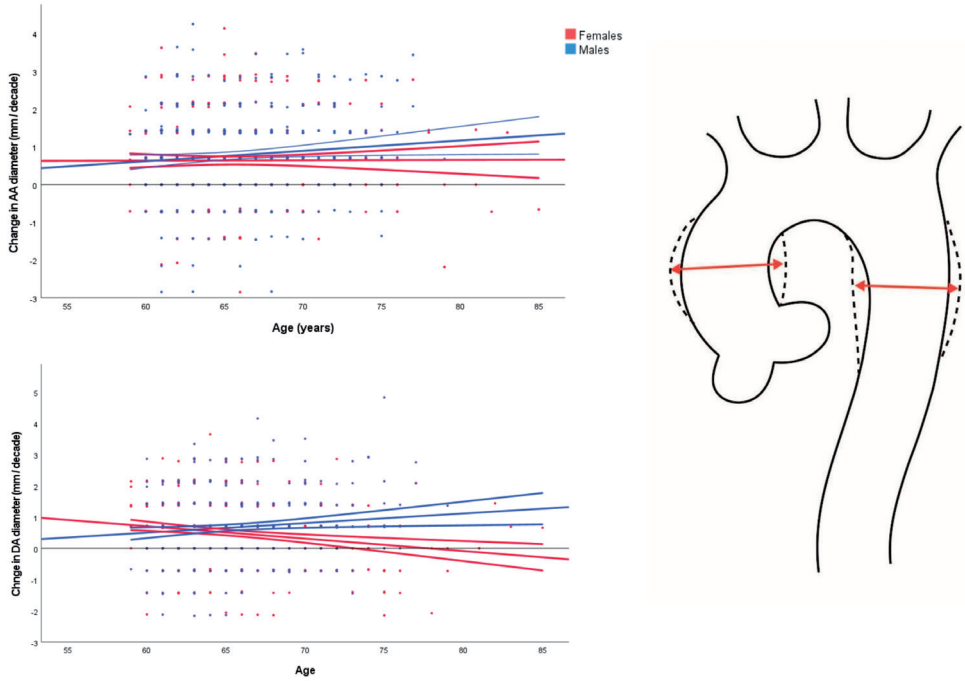


Figure 5. Visualization of changes in AA and DA diameter

AA = Ascending aorta; DA = Descending aorta

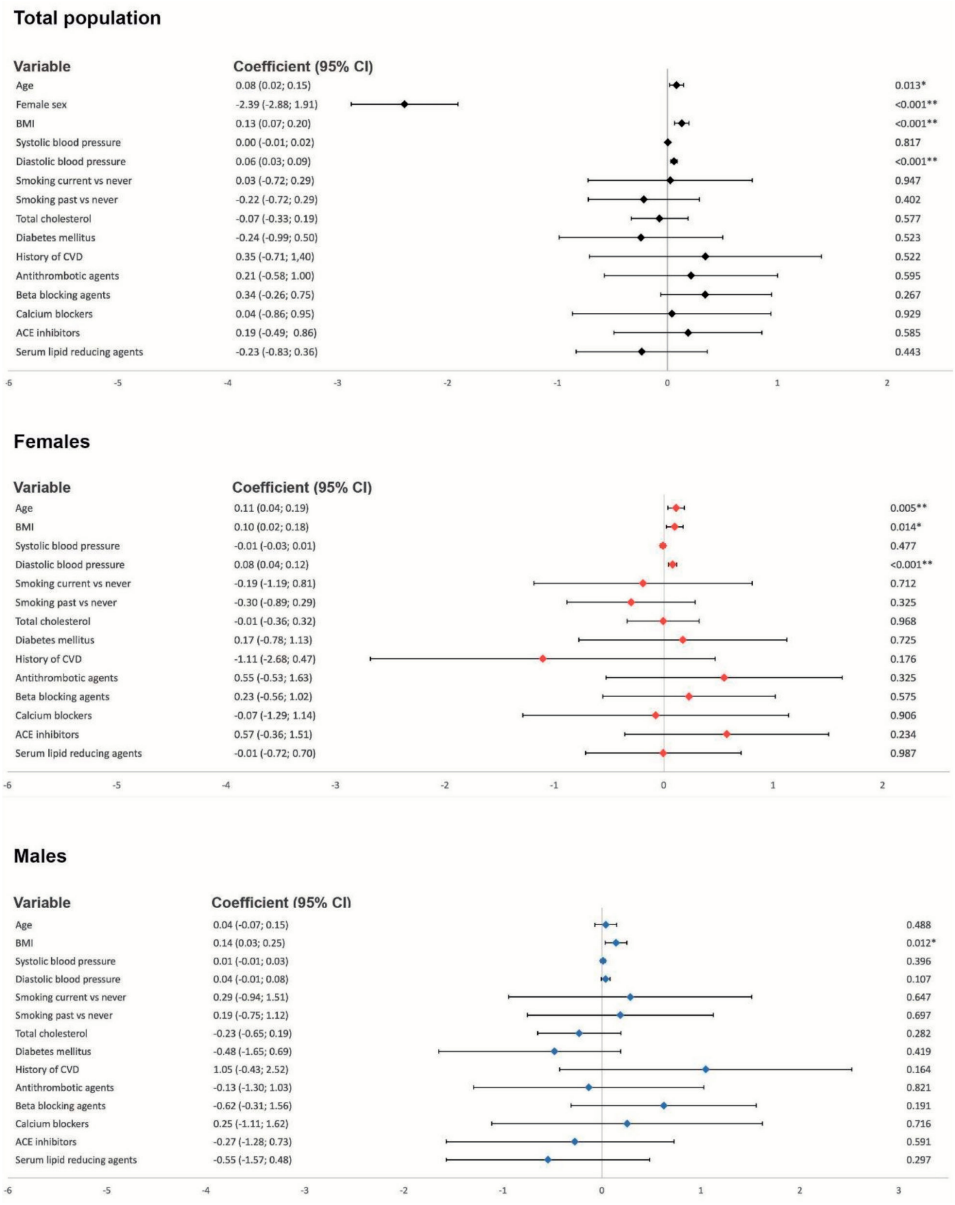


Figure 6. Determinants of change in ascending aortic diameter

Models were further adjusted for cohort and scanner type. The presented coefficients present the beta coefficients of the model. BMI = Body Mass Index; CVD = cardiovascular disease; ACE inhibitor = angiotensin enzyme inhibitor; 95% CI = 95% confidence interval.

*= P-value <0.05; **= P-value <0.01

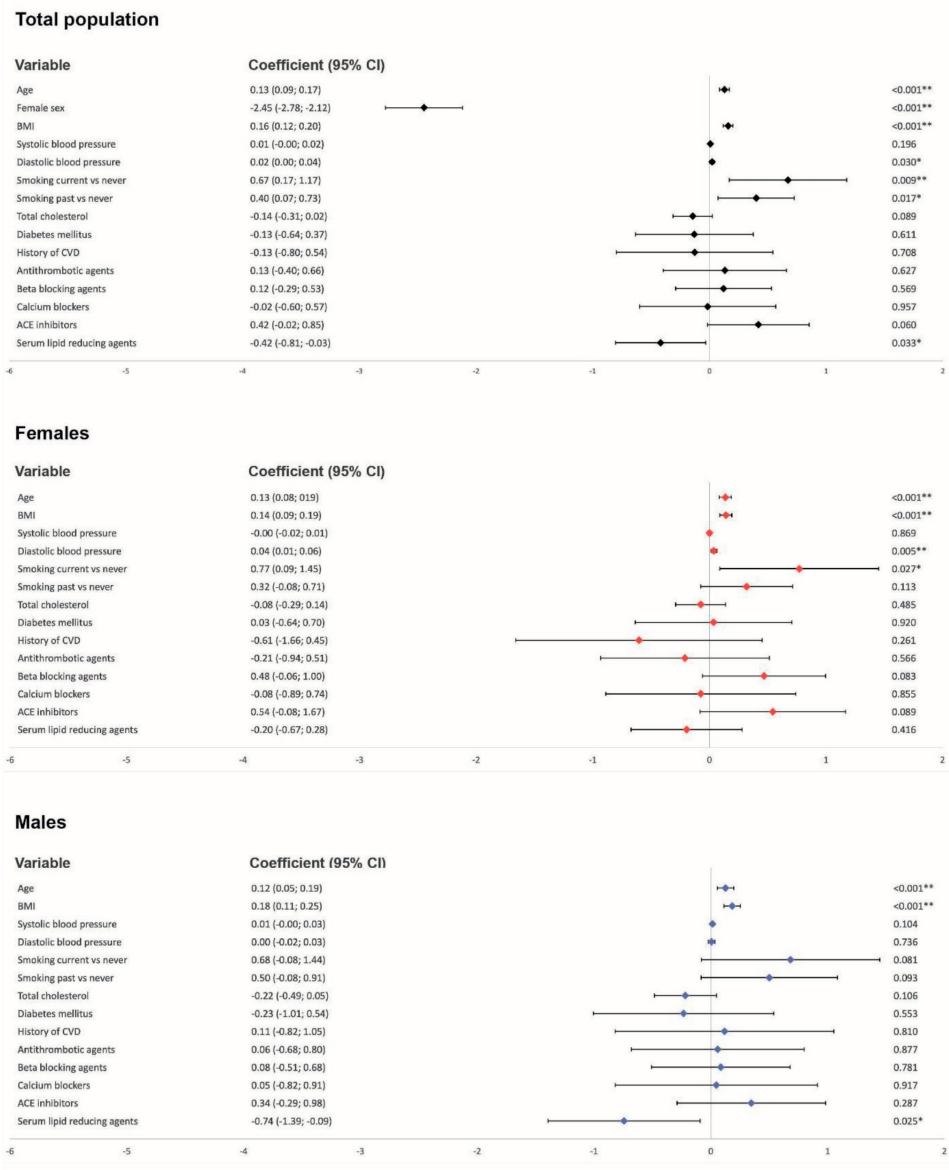


Figure 7. Determinants of change in descending aortic diameter

Models were further adjusted for cohort and scanner type. The presented coefficients present the beta coefficients of the model. BMI = Body Mass Index; CVD = cardiovascular disease; ACE inhibitor = angiotensin enzyme inhibitor; 95% CI = 95% confidence interval.

*= P-value <0.05; **= P-value <0.01

DISCUSSION

Our study provides male-female and age-specific distributions of changes in ascending and descending aortic diameters based on longitudinal data in an ageing general population. Changes in ascending and descending aortic diameters were clearly lower than expected (< 1 mm/decade). Males showed faster change in absolute thoracic aortic diameters than females, although relative change in thoracic aortic diameters was not significantly different. Furthermore, age, DBP and BMI were associated with more change in thoracic aortic diameters, with some differences between males and females. Whereas use of serum lipid lowering agents was associated with less change in DA diameter, specifically in males.

Changes in thoracic aortic diameters

Although longitudinal data on changes in aortic diameters in the general population is scarce, a gradual increase of the thoracic aortic diameter with advancing age has been reported[3,7]. In this study we found a thoracic aortic diameter growth rate of about 0.7 mm/decade. These findings are in accordance with those of Lam et al., who reported an thoracic growth rate of 0.7-0.9 mm/decade at the level of the Sinuses of Valsalva in the general population using echocardiography (n=4542, mean follow-up duration of 16 years)[3]. Bons et al. reported higher thoracic aortic change up to 1.3 mm/decade, which might be explained by the fact that this study was performed in a smoking population[7]. Our study shows that the 95th percentiles of changes in thoracic aortic diameters in an aged general population were below three mm/decade, indicating faster thoracic aortic expansion rates could be appreciated as pathological. This suggests that the currently used definition of fast thoracic aortic dilatation, which is three or more millimetres per year, is much too high for the general population. Especially since we used non-contrast CT images for our study, which do not allow visualizing the aortic wall. We believe changes in aortic diameters might be partially attributable to an increase in aortic wall thickness, which has been reported to be 0.032-0.15 mm/year in studies using Magnetic Resonance Imaging[12,13]. Therefore, a cut off value of three millimetres per decade seems more appropriate. However, it is important to keep in mind that our study included relatively younger participants with less comorbidities due to mortality and loss-to follow-up. Further research is needed to illuminate the clinical implications of this threshold and its potential association with thoracic aortic aneurysm or dissection.

Male-female differences in changing thoracic aortic diameters

Since thoracic aortic diameters are found to be larger in males than in females[10,14], we hypothesized males might show larger absolute changes in aortic diameters, as can be explained by LaPlace's law which predicts more wall tension when the aortic diameter is larger[15]. Although changes in aortic diameters were small, we indeed found significantly

faster change in absolute aortic diameter in males than in females. Moreover, male sex was an independent risk factor for faster change rate of aortic diameter. Lam et al. also reported male sex to be associated with faster growth rate at the level of the aortic sinuses over a 16 year period[3]. Notably, changes in aortic diameters seemed to decline in females aged 75 years or older. To our knowledge, this has not previously been reported. Potentially this finding could be influenced by the very small number of participants in this group (n= 23). However, all these male-female differences are very small and presumably not relevant in clinical practice. More importantly, relative change of aortic diameters was not significantly different between males and females. This indicates male-female differences in absolute aortic changes, might indeed be attributable to differences in aortic diameter at baseline. Therefore, relative aortic dilatation might be an important and more relevant parameter to consider using in clinical practice. Although the value of this parameter remains to be determined in studies investigating short and long term clinical outcomes of thoracic aortic changes.

Determinants of change in thoracic aortic diameters

Higher diastolic blood pressure was found to be independently associated with faster change in aortic diameter of the ascending and descending aorta, especially in females. Bons et al., found the same association with higher AA and DA diameters at baseline[10]. Potentially this is caused by persistent diastolic hypertension even after medication is prescribed. Our results suggest diastolic hypertension to be an independent risk factor for faster aortic change. Current guidelines promote the treatment of both diastolic and systolic blood pressure[5]. However, diastolic hypertension does not seem associated with more cardiovascular events[16]. Nevertheless, careful attention concerning diastolic blood pressure seems advisable, especially in females and patients with a predisposition to thoracic aortic aneurysm formation.

Another determinant strongly associated with faster AA and DA dilatation was higher BMI, which has been described before[3,7]. There has been much discussion about the importance of height versus weight. When examined more closely we concluded that height and weight separately were not significantly associated with faster change in aortic diameters. This was in contrast to absolute aortic diameter at baseline, which was found to be strongly associated with height[10]. Although, this finding is in line with the findings of Lam et al., who reported an association between obesity and expansion of the Sinuses of Valsalva[3]. Presumably BMI is a better representation of participants degree of obesity, and might therefore shows a stronger correlation with thoracic aortic dilatation compared to absolute height and weight.

Furthermore, we found an association between the use of serum lipid reducing agents and lower change in DA diameter. This positive effect has previously been described in patients

with thoracic aortic aneurysm[17]. Although changes in DA diameter in our population were small, this might suggest a role for serum lipid reducing agents in the prevention of DA dilatation. The descending aorta is known to be more prone to atherosclerosis and therefore, to risk factors of atherosclerosis. Another risk factor associated with change in DA diameter is current smoking, which seems especially associated with faster change of DA diameter in females. Smoking was also found to be associated with a larger aortic diameter at baseline and observed in abdominal aortic aneurysm studies as well[10,18]. However, male-female differences were not reported. Further research is needed to explore the specific impact of these risk factors. Including male-female specific analyses in future research would contribute to a better understanding of specific risk factors for fast changing thoracic aortic diameters.

Limitations

The use of ECG-gated CT scans allowed high accuracy of the aorta measurements. The use of contrast-enhanced CT might have made the measurements even more accurate, although reproducibility of our measurement was found to be very good. However, differences between aortic diameters at baseline and follow-up were very small (median change during follow-up 1 mm). Therefore measurement error due to the spatial resolution (0.4 mm) and a small inter observer variability (mean 0.29 mm for AA diameter and 0.10 for DA diameter, Supplemental file 1), could have had a limited effect on the aortic dilatation rate reported in this study. Second, not all participants of the original baseline cohort participated in the follow-up. Among survivors the response rate was 54%, a comparison between the follow-up cohort and the participants who were lost to follow-up is shown in supplemental file 2. Non-responders and non-survivors were older, more often female, had more cardiovascular risk factors and cardiovascular diseases and had slightly larger thoracic aortic diameters at baseline. This indicates older participants with more comorbidities might be underrepresented in our study population and therefore the dilatation might be underestimated.

Third, the Rotterdam Study only included inhabitants aged 55 years or older. Although there were no significant differences in rate of change in thoracic aortic diameters between the age groups, our multivariable analysis suggests an independent association between age and more rapid changes in AA and DA diameters. Therefore, rate of change in AA and DA diameters might be even lower in a younger population.

Last, our study provides information on changes in thoracic aortic diameters of the ascending and descending aorta. Therefore, changes in diameters of the Sinuses of Valsalva, sinotubular junction and aortic arch remain unknown. The ascending and descending aorta might be most clinically relevant, since thoracic aortic dissection seems

to occur most often at these locations. However, we recommend future research should include measurements at multiple locations of the thoracic aorta.

Conclusions

Some degree of increase in thoracic aortic diameters seems typical in both males and females of the aging population. Our data suggest that changes in absolute aortic diameters faster than three mm per decade should be considered abnormal. Cardiovascular risk factors associated with faster change in ascending and descending aortic diameters were BMI, smoking and hypertension, especially diastolic blood pressure. Therefore, these factors might play a role in the primary prevention of thoracic aortic dilatation. The possible positive effects of lipid-lowering medication and male-female specific risk factors warrant further study.

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SUPPLEMENTAL FILE 1

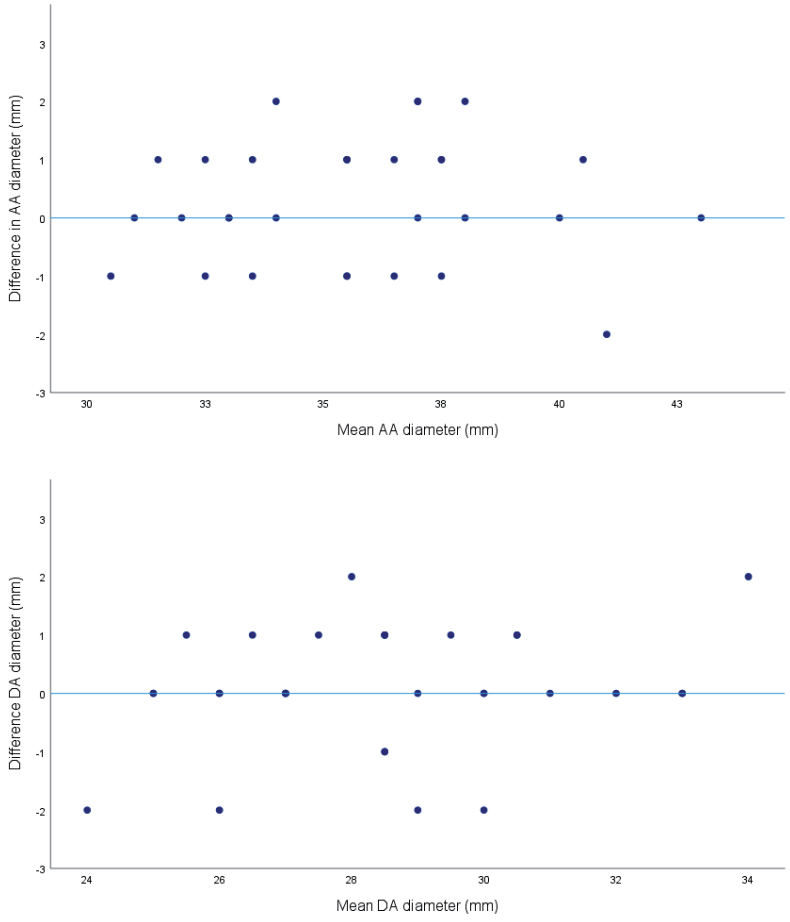

Figure 1. Bland-Altman plots presenting inter-observer variability of measurements of the ascending and descending aorta on non-contrast enhanced CT-imaging.

AA= Ascending aorta; DA= Descending aorta.
Images show the variability of the ascending and descending aortic measurements between two observers on 30 follow-up CT-scans.

SUPPLEMENTAL FILE 2

Table 1. Baseline characteristics of follow-up participants compared to loss-to follow-up.

	Total (n= 2505)	Cohort follow-up (n= 943)[1]	Loss-to-follow-up (n= 1561)	P-value
Age - y	67.0 (64.0-73.0)	65.0 (62.0-68.0)	71.0 (66.0-76.0)	<0.00
Sex (%female)	1297 (51.8)	490 (51.9)	807 (51.7)	0.952
Height - cm	168.0±9.5	168.4±9.5	167.7±9.5	0.097
Weight - kg	78.4±13.7	78.8±13.0	78.1±14.0	0.276
BSA – m^2	1.9±0.2	1.9±0.2	1.9±0.2	0.107
SBP - mmHg	146.7±20.4	142.8±17.7	149.1±21.5	<0.001
DBP - mmHg	80.1±10.4	81.0±10.0	79.5±11.3	0.001
Hip circumference - cm	102.5 (98.5-107.5)	102.6 (99.0-107.4)	102.4 (98.1-107.5)	0.118
Smoking				0.001
Never	718 (28.7)	300 (31.8)	418 (26.8)	
Past	1363 (54.4)	514 (54.4)	849 (54.4)	
Current	424 (16.9)	130 (13.8)	294 (18.8)	
Alcohol consumption				0.164
Never	154 (6.1)	56 (5.9)	98 (6.3)	
Past	182 (7.3)	57 (6.0)	125 (8.0)	
Current	2169 (86.6)	831 (88.0)	1338 (85.7)	
Total cholesterol – mmol/L	5.7±1.0	5.8±1.0	5.6±1.0	<0.001
HDL cholesterol – mmol/L	1.4 (1.2-1.7)	1.4 (1.2-1.7)	1.4 (1.2-1.7)	0.482
Diabetes Mellitus	338 (13.5)	101 (10.7)	237 (15.2)	0.002
Aortic diameter at baseline – mm				
Ascending aorta	36.4±3.6	36.0±3.6	36.7±3.6	<0.001
Descending aorta	28.7±2.7	28.1±2.6	29.0±2.7	<0.001
History of cardiovascular disease				
Myocardial infarction	143 (5.7)	32 (3.4)	111 (7.1)	<0.001
PCI	80 (3.2)	25 (2.6)	55 (3.5)	0.276
CABG	89 (3.6)	21 (2.2)	68 (4.4)	0.005
Stroke	102 (4.1)	18 (1.9)	84 (5.4)	<0.001
Medication				
Beta-blocking agents	549 (22.2)	178 (19.1)	371 (24.2)	0.004
Calcium blockers	216 (8.8)	67 (7.2)	149 (9.7)	0.039
ACE-inhibitors	482 (19.5)	136 (14.6)	346 (22.5)	<0.001
Antithrombotic agents	608 (24.3)	149 (15.8)	459 (29.4)	<0.001
Serum lipid-reducing agents	625 (25.0)	209 (22.1)	416 (26.6)	0.013

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.

BSA= Body Surface Area; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; HDL= High Density Lipoprotein; PCI= Percutaneous Coronary Intervention; CABG= Coronary Artery Bypass Grafting; ACE= Angiotensin Converting Enzyme.

[1] Minus participants excluded from follow-up cohort (n=3)

SUPPLEMENTAL FILE 3

Changes in absolute and relative thoracic aortic diameters by sex and age

Table 2. Absolute changes in aortic diameters per decade (mm/decade) by sex and age

		Ascending aorta				Descending aorta			
Age group		**Total**	**Males**	**Females**	**p-value**	**Total**	**Males**	**Females**	**p-value**
Total	N	943	453	490		932	444	488	
	Median	0.71	0.72	0.70	0.006	0.70	0.71	0.69	0.008
	IQR	0.00-1.42	0.00-1.43	0.00-1.41		0.00-1.39	0.00-1.42	0.00-1.36	
55-64	N	437	203	234		435	201	234	
	Median	0.71	0.72	0.70	0.059	0.71	0.71	0.71	0.688
	IQR	0.00-1.42	0.00-1.43	0.00-1.41		0.00-1.42	0.00-1.42	0.00-1.41	
65-74	N	467	234	233		458	227	231	
	Median	0.71	0.72	0.70	0.114	0.69	0.71	0.68	0.018
	IQR	0.00-1.42	0.00-1.42	0.00-1.42		0.00-1.38	0.00-1.40	0.00-0.72	
≥ 75	N	39	16	23		39	16	23	
	Median	0.70	0.72	0.00	0.141	0.68	0.72	0.00	0.001
	IQR	0.00-1.44	0.00-2.07	0.00-1.38		-0.71-0.72	0.69-1.60	-0.73-0.69	
p-value		0.525	0.397	0.484		0.332	0.062	<0.001	

Table 3. Relative changes in aortic diameters per decade (in%) by sex and age

		Ascending aorta				Descending aorta			
Age group		**Total**	**Males**	**Females**	**p-value**	**Total**	**Males**	**Females**	**p-value**
Total	N	943	453	490		932	444	488	
	Median	1.95	1.97	1.94	0.145	2.38	2.37	2.44	0.395
	IQR	0.00-3.95	0.00-3.93	0.00-4.02		0.00-4.66	0.00-4.66	0.00-4.69	
55-64	N	437	203	234		435	201	234	
	Median	1.96	1.99	1.94	0.306	2.45	2.37	2.59	0.293
	IQR	0.00-3.94	0.00-3.92	0.00-3.95		0.00-5.02	0.00-4.77	0.00-5.24	
65-74	N	467	234	233		458	227	231	
	Median	1.95	1.95	1.96	0.524	2.32	2.36	2.21	0.246
	IQR	0.00-3.96	0.00-3.88	0.00-4.21		0.00-4.51	0.00-4.60	0.00-3.08	
≥ 75	N	39	16	23		39	16	23	
	Median	1.89	2.02	0.00	0.239	2.26	2.65	0.00	<0.001
	IQR	0.00-4.15	0.00-5.78	0.00-3.54		-2.62-2.86	2.26-6.53	-2.98-2.31	
p-value		0.627	0.364	0.580		0.145	0.098	<0.001	

CHAPTER 2

2

Novel biomarkers associated with thoracic aortic disease

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International Journal of Cardiology, 2023

ABSTRACT

Background

Biomarkers might help to improve diagnosis, surveillance and risk stratification of thoracic aortic disease (TAD). We explored the association between a broad spectrum of cardiovascular biomarkers with clinical characteristics and thoracic aortic diameter in TAD patients.

Methods

Venous blood-samples were obtained in 158 clinically stable TAD patients visiting our outpatient clinic (2017-2020). TAD was defined as a thoracic aortic diameter ≥40 mm, or genetic confirmation (hereditary TAD). The cardiovascular panel III of the Olink multiplex platform was used for batch analysis of 92 proteins. A comparison was made between biomarker levels in patients with and without previous aortic dissection and/or surgery, and with and without hereditary TAD. Linear regression analyses were applied to identify (relative, normalized) biomarker concentrations associated with the absolute thoracic aortic diameter (AD_{max}), and thoracic aortic diameter indexed for body surface area (ID_{max}).

Results

Median age of study patients was 61.0 (IQR 50.3-68.8) years, 37.3% females. Mean AD_{max} and ID_{max} were 43.3±5.4 mm and 21.3±3.3 mm/m^2. After multivariable adjustment, Matrix Metalloproteinase-3 (MMP-3) and Insulin-like growth factor binding protein 2 (IGFBP-2) showed a significant positive association with AD_{max} and ID_{max}, respectively. Patients with previous aortic surgery/dissection had higher N-terminal-pro hormone BNP (NTproBNP) (median 3.67 [IQR 3.01-3.99] vs 2.84 [2.32-3.26], p= <0.001). Patients with hereditary TAD had higher Trem-like transcript protein 2 (TLT-2) (median 4.64 [IQR 4.45-4.84]) than those with non-heriditary TAD (4.40 [4.17-4.64]; p=0.00042).

Conclusions

Among a broad range of biomarkers, MMP-3 and IGFBP-2 were associated with disease severity in TAD patients. The pathophysiological pathways uncovered by these biomarkers, and their potential clinical use warrants further research.

INTRODUCTION

Thoracic aortic disease (TAD) including thoracic aortic aneurysm and thoracic aortic dissection have an estimated incidence of 9/100,000 per year in females, and 16/100,000 per year in males[1]. An inherited pattern of TAD is found in about 20% of cases, also referred to as hereditary thoracic aortic disease[2]. Patients with (hereditary) TAD are at risk of thoracic aortic dissection, which has a high mortality and morbidity[3,4]. To prevent aortic dissection and sudden death, timely intervention is warranted. Currently, the timing of preventive surgery for TAD patients is almost solely based on the aortic diameter, since this has been associated with the risk of acute thoracic aortic dissection[5]. However, most aortic dissections occur at aortic diameters below the threshold for elective aortic surgery. Therefore, there might be an important role for other predictors of events such as blood biomarkers to improve the risk prediction of aortic dissection[6]. Biomarkers can have potential diagnostic and prognostic value relevant for minimally invasive follow-up assessment and clinical decision making in TAD patients. Ideally, biomarkers could be used to provide a more precise estimate of the risk of aortic complications for individual patients, leading to improved and more personalized treatment strategies.

Currently, no biomarkers have been found that can accurately predict the presence, severity or prognosis of TAD[7]. Several circulating markers have been investigated for diagnosis and localization of TAD, among which mediators of collagen and elastin degradation such as matrix metalloproteinases (MMP's). Overall, finding a disease specific biomarker for TAD is not easy, since many biomarkers are not very specific for TAD. There is a need for more evidence on potential biomarkers for the surveillance and prognosis of TAD.

Recently, the proximity extension assay, has enabled the screening of 92 proteins simultaneously with high sensitivity and specificity in small biological sample volumes[8]. This technique has already been investigated in patients with abdominal aortic aneurysm (AAA), were plasma levels of 21 proteins were found to be significantly different in patients with AAA compared to controls[9]. However, different biomarkers might be associated with TAD, since TAD has a different etiology than AAA and is less strongly associated with risk factors of atherosclerosis[10].

With the use of this technology, we aimed to identify biomarkers associated with clinical characteristics and thoracic aortic diameter in patients with TAD, which is the first step in finding biomarkers for clinical use in diagnosis, surveillance and prognosis of TAD.

METHODS

Study population

All consecutive patients who visited the specialized TAD outpatient clinic of our center between October 2017 and January 2020, were eligible for inclusion. A flowchart of patient inclusion is shown in figure 1. The TAD outpatient clinic is a specialized outpatient clinic in which patients are seen by a cardiologist and/or specialized physician assistant for cardiovascular family screening or TAD surveillance, including referral from primary care and secondary care. Our tertiary care center is a referral center for patients with (suspected) hereditary thoracic aortic disease, especially Loeys-Dietz syndrome. Inclusion criteria for our study were: adult age (≥ 18 years) and thoracic aortic diameter ≥ 40 mm and/or a genetically confirmed hereditary TAD (with normal or abnormal aortic diameter). All eligible patients were invited to participate in this prospective cross-sectional study. For comparison of clinical characteristics, all TAD patients were divided into patients with and without previous aortic surgery and / or dissection. A second comparison was made between patients with and without hereditary TAD. This study was approved by the local ethics committee (METC Erasmus MC, MEC-2017-057), and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines. Written and signed informed consent was obtained from all participants.

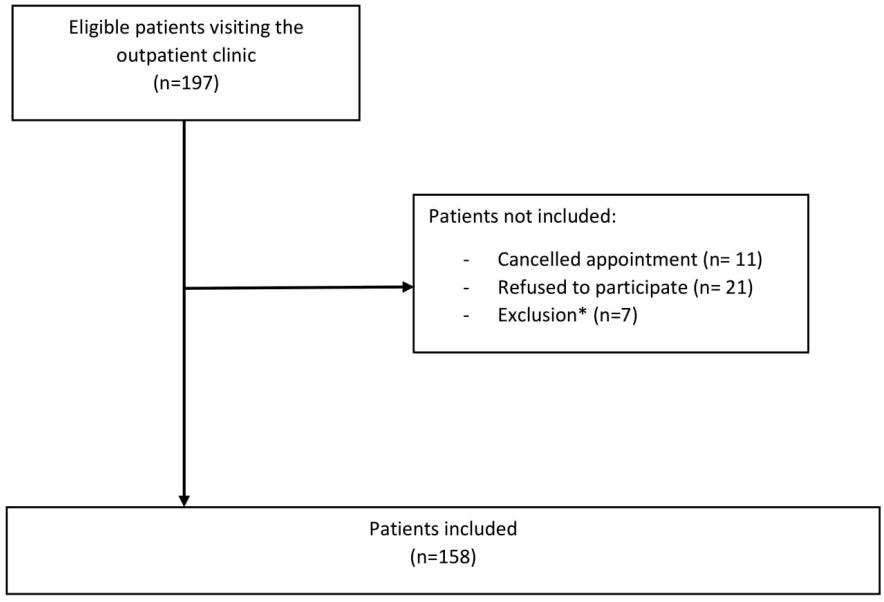

Figure 1. Flowchart of patient inclusion

*Exclusion was mostly due to patients failing to show up for venous blood sampling, or lab-related problems.

Data collection

All patients underwent standard care at the outpatient clinic by their treating physician. Additional data was collected from the hospitals patient files using a standardized case report form, and was documented using a secured web-based application (GEneric Medical Survey Tracker, Erasmus MC and Equipe Zorgbedrijven, latest release 2019, version 1.8.6, open source). Body Surface Area (BSA) was calculated using the DuBois and DuBois formula[11]. Indexed thoracic aortic diameter was calculated by dividing absolute thoracic aortic diameter by BSA for each individual patient.

Biomarker measurement

Fasting venous blood (6 ml) was collected in vacuum tubes containing ethylenediaminetetraacetic acid (EDTA). Blood samples were centrifuged and the plasma was then aliquoted and stored at -80°C within two hours after withdrawal, until batch analysis was performed. The cardiovascular panel III of the Olink Multiplex platform (Olink Proteomics AB, Uppsala, Sweden) was used for a batch-wise analysis. This panel was selected for its well-balanced inclusion of proteins with already established associations with cardiovascular disease and abdominal aortic aneurysm, and because it has a high performance among other Olink panels. The panel is a high-throughput, multiplex immunoassay enabling simultaneous quantification of 92 CVD-related proteins by Proximity Extension Assay (PEA) technology[12]. The assay uses two oligonucleotide-labelled antibodies to bind to their respective target proteins in the sample. When the two antibodies are in close proximity, a new polymerase chain reaction target sequence is formed. The resulting sequence is detected and quantified using standard real-time polymerase chain reaction testing (PCR).

The proteins/biomarkers are presented as Normalized Protein Expression (NPX) units, which are relative units that result from the polymerase chain reaction. The NPX units are expressed on a log2 scale. This arbitrary unit can thus be used for relative quantification of proteins and a comparison of (two)fold changes between groups. We analyzed the NPX units as standardized Z-scores, which enables direct comparisons of the strength of the associations between the 92 biomarkers and the study endpoints.

Imaging

The endpoints of this study were maximal absolute thoracic aortic diameter (AD_{max}) and maximal indexed thoracic aortic diameter (ID_{max}). The maximal thoracic aortic diameter was obtained using contrast enhanced and electrocardiography gated Computed Tomography imaging (CT). Thoracic aortic measurements were performed by a radiologist of the Erasmus Medical Center using a standardized protocol. The radiologist was blinded to the biomarker results. Imaging was performed on the same day the blood samples were obtained. Diameters of the Sinuses of Valsalva were measured from the cusp to

commissure, ascending aorta and descending aorta were measured in two directions at the level of the pulmonary bifurcation using the double-oblique method in a reconstruction, perpendicular to the vessel axis. Additionally, the largest ascending and descending aortic diameters were measured (if not at any standardized location). The largest diameter of the measurements was used for the analysis. If no CT scan was performed on the date of inclusion, transthoracic echocardiography (TTE) measurements were used. On TTE measurements were performed using the parasternal long axis view during late diastole with the leading edge to leading edge method. CT imaging was not available in 52 patients (32.9%). Indexed aortic diameter was calculated by dividing each patients' absolute maximal thoracic aortic diameter by their body surface area (BSA).

Statistical analysis

Baseline characteristics were studied and described in relation to sex. Biomarker levels were studied in relation to TAD type (hereditary versus non) and TAD history (aortic dissection or surgery versus non). The normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Students t-tests were used to evaluate between group differences in normally distributed continuous data which are presented as mean ± standard deviation (SD). The Mann-Whitney U-test was used to study between group differences in skewed continuous data, which are presented as median and interquartile range (IQR). For categorical data, Chi-square test or Fisher exact test were used, and the data were presented as percentages or frequencies. The statistical significance level of the statistical tests on baseline characteristics was set at $p < 0.05$.

Linear regression analyses were performed to study the association between the biomarkers on the selected multiplex-assay and the study endpoints (AD_{max} and ID_{max}). Sub-analyses were performed to study the association between the biomarkers and ascending or descending aortic diameter separately. Stratified analyses were performed in patients with connective tissue disease and patients with a history of thoracic aortic dissection. We performed crude, unadjusted analyses, and analyses with adjustment for the potential confounders age and sex, with additional analyses for previous aortic dissection and previous aortic surgery. These analyses were performed for the total population, and stratified analyses were performed for males and females. This is an exploratory analysis of a multiplex-assay with 92 biomarkers. We therefore adjusted for inflation of the type I error due to multiple statistical testing by applying Bonferroni's correction, and the statistical significance level was set at $p < 0.00055$ for univariable analysis. Since only four biomarkers were selected for further analysis the statistical significance level was set at $p < 0.05$ for multivariable analysis.

The data-analysis was performed with statistical and computing programme *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 3.6.1).

RESULTS

In total, 99 males and 59 females with TAD were included, with a median age of 61.0 (50.3-68.8) years (Table 1). The biomarker SPON1 was excluded from analysis because 98% of the measurements were below the limit of detection. The remaining 91 biomarkers were included in the analyses. Ascending aortic diameter was obtained in 150 patients (95%), whereas descending aortic diameter was obtained in 104 patients (66%). Left ventricular ejection fraction (LVEF) was normal or only slightly reduced in 101 patients (63.9%), and moderately or severely reduced in 2 patients (1.2%).

Table 1. Baseline characteristics

	Total (n=158)	Males (n=99)	Females (n=59)	P-value	Missing (%)
Age - y	61.0 (50.3-68.8)	62.0 (52.0-69.0)	57.0 (47.5-66.0)	0.257	0.0
Height - cm	179±11	185±9	170±7	<0.001*	0.0
Weight - kg	86.1±15.2	92.0±13.2	76.3±13.3	<0.001*	0.6
BSA	2.1±0.2	2.2±0.2	1.9±0.2	<0.001*	0.6
Hypertension	91 (57.6)	60 (60.6)	31 (52.5)	0.419	0.0
Hyperlipidaemia	50 (31.6)	40 (40.4)	10 (16.9)	0.005*	0.0
Smoking	15 (12.9)	7 (9.6)	8 (18.6)	0.266	26.6
Diabetes	6 (3.8)	5 (5.1)	1 (1.7)	0.412ᵗ	0.0
Renal dysfunction	5 (3.2)	3 (3.0)	2 (3.4)	1.000ᵗ	0.0
LVEF[1]				0.359	0.0
Normal	91 (57.6)	62 (62.6)	29 (49.2)		
Slightly reduced	10 (6.3)	5 (5.1)	5 (8.5)		
Moderately reduced	1 (0.6)	1 (1.0)	0 (0.0)		
Severely reduced	1 (0.6)	1 (1.0)	0 (0.0)		
Medication					0.0
Beta blocker	55 (34.8)	40 (40.4)	15 (25.4)	0.082	
ACEi	34 (21.5)	26 (26.3)	8 (13.6)	0.093	
ARB	27 (17.1)	20 (20.2)	7 (11.9)	0.259	
Diuretics	27 (17.1)	17 (17.2)	10 (16.9)	1.000	
Cholesterol	46 (29.1)	35 (35.4)	11 (18.6)	0.040*	
Antithrombotics	63 (39.9)	48 (48.5)	15 (25.4)	0.007*	
Hereditary TAD diagnosis				0.160	0.0
Marfan syndrome	11 (7.0)	9 (9.1)	2 (3.4)		
Loeys-Dietz syndrome	18 (13.4)	7 (7.1)	11 (18.7)		
Ehlers-Danlos syndrome	3 (1.9)	1 (1.0)	2 (3.4)		
Other	4 (2.5)	3 (3.0)	1 (1.7)		
Bicuspid aortic valve	6 (3.8)	6 (6.1)	0 (0.0)		
Genetic mutation					
SMAD3	11 (7.0)	5 (5.1)	6 (10.2)		
VUS	9 (5.7)	6 (6.1)	3 (5.1)		
TGFB3	4 (2.5)	2 (2.0)	2 (3.4)		
TGFB2	1 (0.6)	0 (0.0)	1 (1.7)		
Other	5 (3.2)	3 (3.0)	2 (3.4)		

Table 1. Continued

	Total (n=158)	Males (n=99)	Females (n=59)	P-value	Missing (%)
Abdominal aortic aneurysm	11 (7.0)	9 (9.1)	2 (3.4)	0.212	0.0
Other arterial aneurysm	18 (11.4)	9 (9.1)	9 (15.3)	0.357	0.0
AD_{max} (mm)	43.3±5.4	44.0±5.4	42.0±5.1	0.021*	3.8
ID_{max} (mm/m^2)	21.3±3.3	20.6±3.0	22.5±3.5	0.001*	4.4
Previous aortic surgery	30 (19.0)	20 (20.2)	10 (16.9)	0.768	
Previous dissection	16 (10.1)	8 (8.1)	8 (13.6)	0.412	0.6

Data are expressed as mean ± SD or as absolute and percentage. BSA=Body Surface Area; ARB= Angiotensin II receptor blocker; ACEi= Angiotensin Converting Enzyme inhibitor; LVEF= left ventricular ejection fraction; AD_{max}= Maximal absolute diameter thoracic aorta; ID_{max}= Maximal indexed diameter thoracic aorta.

ᵠ Fishers Exact test

[1] Only available in patients who received echocardiography at baseline visit n=104.

* Significant at the 0.05 level

Figures 2a and 2b show the association between the selected biomarkers and the study endpoints. Matrix Metalloproteinase-3 (MMP-3; strongest association) and Chitinase-3-like protein 1 (CHI3L1) showed a significant positive association with AD_{max}, but not with ID_{max}. One SD difference in ^{2}log(CHI3L1) and ^{2}log(MMP-3) was associated with a mean difference of 1.74 mm (95% CI 0.92-2.56) and 1.48 mm (95% CI 0.66-2.30) in AD_{max}, respectively. Insulin-like growth factor binding protein 2 (IGFBP-2) and metalloproteinase inhibitor 4 (TIMP4) showed a significant positive association with ID_{max}, but not AD_{max}. One SD difference in ^{2}log(IGFBP-2) and ^{2}log(TIMP4) was associated with a mean difference of 1.04 mm/m^2 (95% CI 0.53-1.56) and 1.01 mm/m^2 (0.50-1.52) in ID_{max}, respectivelySupplemental file 1 shows the results of univariable and multivariable analysis of the four biomarkers associated with the study endpoints AD_{max} or ID_{max}. Higher CHI3L1 and MMP-3 levels were significantly associated with AD_{max} in univariable analysis. Multivariable adjustment for age and sex blunted the association between CHI3L1 and AD_{max}. MMP-3 remained significantly associated with AD_{max}, even after additional adjustment for previous aortic dissection and previous aortic surgery. Higher IGFBP-2 and Tissue Inhibitor of Metalloproteinases 4 (TIMP4) levels were significantly associated with ID_{max} in univariable analysis. Multivariable adjustment for age and sex blunted the association between TIMP4 and ID_{max}, whereas IGFBP-2 remained significantly associated with ID_{max}. In supplemental file 2, a visualization is represented of the association between the four abovementioned biomarkers and the study endpoints. Stratified univariable analyses for males and females are shown in supplemental file 3. Which shows IGFBP-2 is significantly associated with ID_{max} in females but not in males. Whereas the other previously mentioned biomarkers: TIMP4, MMP-3 and CHI3L1 were only significant in the total population, and seem equally associated with AD_{max} and ID_{max} in males and females in univariable analysis.

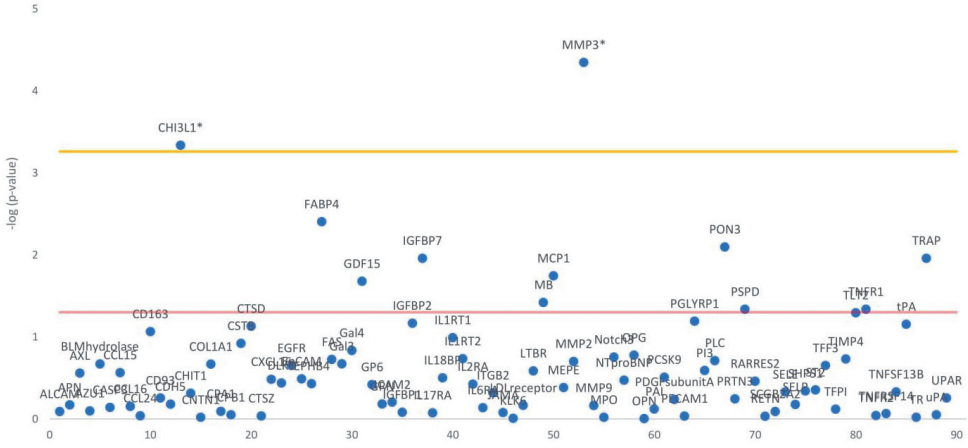

Figure 2a. Univariable analysis of 91 biomarkers with absolute thoracic aortic diameter.

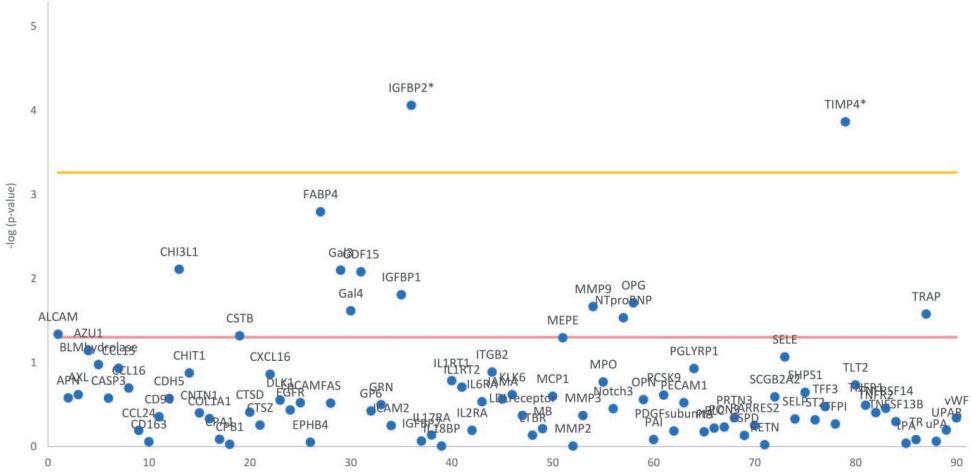

Figure 2b. Univariable analysis of 91 biomarkers with indexed thoracic aortic diameter.

The yellow line represents the Bonferroni corrected p-value. Biomarkers above the yellow line showed a statistically significant association with AD_{max} (figure 1a) or ID_{max} (figure 1b) in univariable linear regression analysis.

When analyzing the maximal ascending and descending thoracic aortic diameters separately, no biomarkers showed a significant association with maximal ascending aortic diameter. However, Fatty-acid binding protein 4 (FABP4) showed a significant association with absolute maximal descending aortic diameter, even after correction for age, sex, dissection and surgery (supplemental file 4). Comparison of biomarkers in different subgroups of TAD patients is shown in figures 3a and 3b. All biomarkers with a p-value <0.05 are presented in these figures. After Bonferroni correction, N-terminal-pro hormone BNP (NT-proBNP) was significantly higher in TAD patients with previous surgery and/or dissection (3.67 [3.01-3.99] vs 2.84 [2.32-3.26], p= <0.001). The median time between previous surgery and study inclusion was 52 months (IQR 12-90). In patients with known hereditary TAD (Figure 3b), Trem-like transcript protein 2 (TLT-2) was significantly higher than in patients without confirmed hereditary TAD (4.64 [4.45-4.84] vs 4.40 [4.17-4.64], p=0.00042). Hereditary TAD remained associated with higher TLT-2 levels after correction for sex, age, previous surgery, previous dissection and absolute TAD diameter (β [95%CI]: 0.27 [0.06-0.48], p=0.013). Tables corresponding with figures 3a and 3b are shown in supplemental file 5.

From all patients with a history of thoracic aortic dissection (n=16) four patients (2.5%) had Stanford type A aortic dissections, and 12 patients (7.5%) had type B aortic dissections. In this subgroup of patients with thoracic aortic dissection, no biomarkers were significantly associates with either AD_{max} or ID_{max} after Bonferroni correction. However, there was a trend towards a significant association between AD_{max} and FABP4 (p=0.00418) and between ID_{max} and FABP4 (p=0.00106). In the subgroup analyses for HTAD patients, no biomarkers were significantly associated with AD_{max} or ID_{max} after Bonferroni correction.

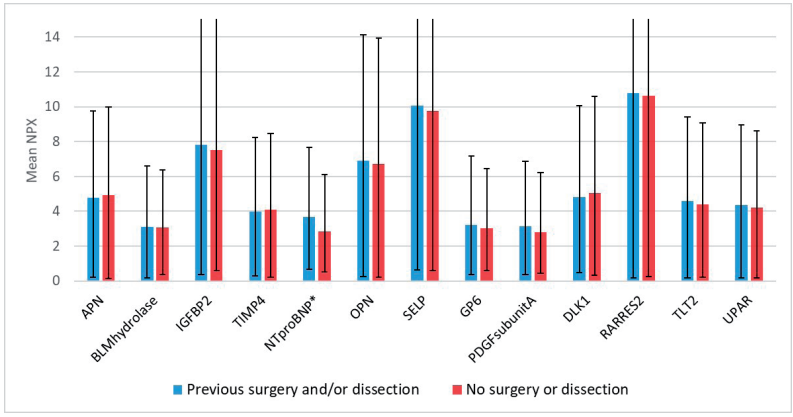

Figure 3a. Comparison of biomarkers between TAD patients with and without previous surgery and/or dissection.

TAD= Thoracic Aortic Disease; APN= aminopeptidase; NPX=Normalized Protein Expression units; IGFBP2= Insulin-like growth factor binding protein 2; TIMP4= Metalloproteinase inhibitor 4; NTproBNP= N-terminal prohormone brain natriuretic peptide; OPN= Osteopontin; SELP= P-selectin; GP6= Pletelet glycoprotein VI; PDGF subunit A= Platelet-derived growth factor subunit A; DLK1= Protein delta homolog 1; RARRES2= Retinoic acid receptor responder protein 2; TLT2= Trem-like transcript 2 protein; UPAR= Urokinase plasminogen activator surface receptor.
*= Significant after Bonferroni correction

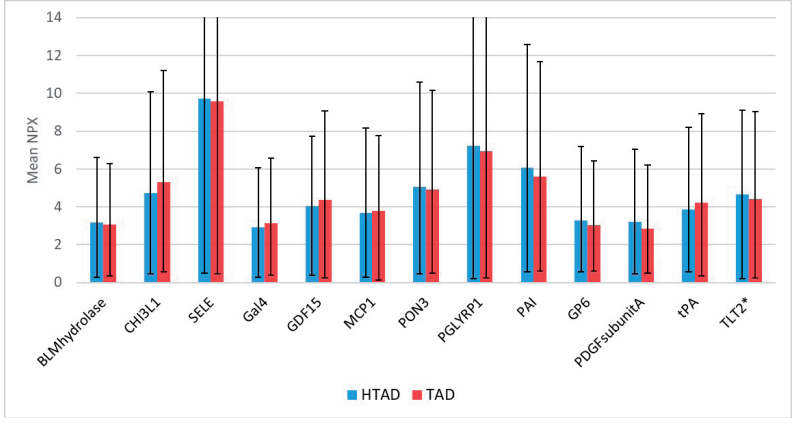

Figure 3b. Comparison of biomarkers between Hereditary TAD patients and non-hereditary TAD patients.

TAD= Thoracic Aortic Disease; NPX=Normalized Protein Expression units; CHI3L1= Chitinase-3-like protein 1; SELE= E-selectin; Gal4= Galectin-4; GDF15= Growth/differentiation factor 15; MCP1= Monocyte chemotactic protein 1; PON3= Paraoxonase; PGLYRP1= Peptidoglycan recognition protein 1; PAI= Plasminogen activator inhibitor 1; GP6= Pletelet glycoprotein VI; PDGF subunit A= Platelet-derived growth factor subunit A; tPA= Tissue-type plasminogen activator; TLT2= Trem-like transcript 2 protein.
*= Significant after Bonferroni correction

DISCUSSION

In this study, we evaluated the potential association of 91 biomarkers related to cardiovascular disease, with thoracic aortic diameter in TAD patients. Although several proteins involved in proteolysis and inflammation were found to be associated with aortic diameter, it is important to keep in mind that this kind of analysis is merely hypothesis generating. More research is needed to establish the actual relation between these biomarkers and TAD severity. MMP-3 was found to be associated with AD_{max}. IGFBP-2 was significantly associated with ID_{max} in females. Furthermore, TLT-2 was found to be significantly higher in patients with hereditary TAD.

This study shows a positive association between AD_{max} and plasma levels of MMP-3. Matrix metalloproteinases (MMP's) regulate the degradation of elastin and collagen. Plasma levels of several MMP's have been reported to be elevated in TAD patients[13]. Additionally, some MMP's in the thoracic aortic wall were found to be higher in patients with TAD and aortic dissection than in controls[14]. MMP-3 has not previously been reported as elevated or decreased in TAD patients or in association to the thoracic aortic diameter[13]. However, an inverse association between MMP-3 expression in the aortic wall and elasticity of the TAD wall has been reported[15]. Reduced aortic wall elasticity could potentially promote aneurysm formation. Therefore it is not surprising that we found circulating MMP-3 levels to be positively associated with thoracic aortic diameters. The tissue inhibitors of MMP's are TIMP's. We found a positive association between ID_{max} and TIMP-4 in univariable analysis, which was not significant anymore after adjustment for sex and age. Previous studies using gene expression profiling show decreased rather than elevated expression of TIMP4 in aortic specimens of patients with aortic dissection, which seems logical since this would lead to higher MMP levels and more degradation of elastin and collagen weakening the aortic wall. Therefore we are indeed not convinced of a true association between TIMP4 and aortic dilatation[16].

CHI3L1 was positively associated with AD_{max} in univariable analysis. CHI3L1 seems to plays a major role in tissue injury, inflammation, tissue repair, and remodeling responses[17]. CHI3L1 has been associated with various diseases among which AAA, coronary- and carotid atherosclerosis, cancer and several neurological disorders[17,18]. So far, no studies investigated plasma measurements of CHI3L1 in TAD patients. Our study showed no significant association between AD_{max} or ID_{max} after adjustment for sex and age. This suggests CHI3L1 is not a potential plasma biomarker for diagnosis of TAD.

IGFBP2 showed a significant positive association with ID_{max} in females with TAD. IGFBP-2 is a protein that regulates transport and bioavailability of Insulin-like Growth Factor 1 (IGF-1). In the heart, IGF-1 regulates several cellular processes including metabolism, apoptosis,

ageing, and growth[19]. In the circulation, IGFBP-2 predominately has an inhibitory effect on IGF-1. In cardiovascular research IGFBP-2 is regarded a rather novel biomarker, which has shown potential for diagnosis and prognosis of heart failure, and for use of risk prediction in patients needing transcatheter aortic valve implantation[20,21]. Circulating IGFBP-2 has not previously been reported in association to TAD. Our finding suggests IGFBP-2 might also have an association with TAD severity, especially in females with TAD, warranting further male-female specific research.

We found plasma TLT-2 was associated with the presence of hereditary TAD, even after correction for thoracic aortic diameter. TLT-2 is expressed in cells of the immune system, such as T-cells and B-cells, neutrophils and macrophages[22]. TLT-2 is involved in leukocyte activation, and expression of TLT-2 is up-regulated in response to inflammatory stimuli[23]. Evidence suggests inflammatory responses are involved in TAD pathogenesis, and therefore it has been claimed that TAD should be seen as an inflammatory disease[24]. Moreover, among patients with Loeys-Dietz Syndrome (LDS), a rare hereditary TAD, there is a high prevalence of immunologic features including osteoarthritis, asthma, food allergy, eczema and allergic rhinitis[25]. Also in Marfan Syndrome contribution of inflammation in the development of aortic dilatation and many of the other clinical features has been reported[26]. Several aspects of the Triggering receptor expressed on myeloid cells (TREM) cascade, which includes TLT-2, have been linked to these clinical features[27]. Elevated TLT-2 levels in hereditary TAD patients might be another indication of inflammatory involvement in thoracic aortic disease and connective tissue disorders. However, it remains unclear why TLT-2 is the only inflammatory biomarker which was significantly higher in hereditary TAD patients. Indeed also other factors involved in inflammation were expected to be higher. Such as monocyte chemotactic protein 1 (MCP-1) which has been found to be associated with cerebral and abdominal aneurysm formation and aortic dissection in mice[28]. This might be explained by the fact that we included a small and heterogeneous sample of hereditary TAD patients, or TLT-2 could be a more specific biomarker for hereditary TAD patients. The exact role of TLT-2 in the processes of different connective tissue diseases causing hereditary TAD needs further attention.

FABP4, also known as adipocyte FABP (A-FABP), is a fatty-acid binding protein which regulates lipid trafficking and responses in cells. FABP4 is highly expressed in adipocytes, but also in macrophages and dendritic cells. FABP4 has been associated with various cardiovascular diseases, including diabetes mellitus, hypertension[29], adiposity and atherosclerosis[30]. In a recent study by Memon et al., which used the same Olink panel for analyzing biomarkers, FABP4 was found to correlate with absolute abdominal aortic aneurysm diameter[9]. In our cohort FABP4 was associated with absolute descending aortic diameter and showed a trend towards significance in a subgroup of patients with thoracic aortic dissection. It seems FABP4 could be a potential prognostic marker for descending

thoracic aortic pathology. Although elevated FABP4 levels do not seem very specific for aortic pathology, agents capable of modifying FABP4 function could become a new class of therapeutic agents against several metabolic and cardiovascular diseases. Since these agents have already been developed, and have shown beneficial for preventing atherosclerosis and outcome of ischemic stroke in mouse model studies[31,32].

This is the first study that used a relatively new technology, the proximity extension assay, to evaluate a large amount of biomarkers associated with cardiovascular diseases and their association with TAD. We identified several promising biomarkers which originate from proteolysis and inflammation pathways. Further studies should evaluate the potential clinical use of these biomarkers for diagnosis and surveillance of TAD. Moreover, these biomarkers can help reveal biochemical pathways in pathogenesis of TAD, which could provide options for pharmaceutical therapies.

Limitations

Our study has several limitations. First, this study was performed in TAD patients only, which means we were unable to compare biomarkers between TAD patients and a population without TAD. Therefore we assessed only the biomarkers associated with thoracic aortic diameter as an indication of TAD severity. A sample size calculation was performed using nQuery[33], which showed a sample size of 400 is necessary to reproduce most of our results. However, we believe it might be more valuable to compare biomarker levels in TAD patients to control population in future studies. In this case, a smaller sample size will be sufficient. Second, we used biomarker values in Normalized Protein Expression (NPX) Units, i.e., relative units. While these values can be used for comparing patients and changes over time within a patient, for clinical applications absolute concentrations are recommended. Third, CT imaging was not available in 52 patients (32.9%), in these patients aortic diameter was measured using TTE, which might be slightly less accurate. However, this variability in imaging modalities allowed us to perform blood sampling and imaging on the same day. Last, our tertiary care facility is a referral center for patients with hereditary thoracic aortic disease. This might have resulted in a relatively large amount of patients with HTAD in our cohort, which could have influenced our results. As information on biomarkers is extremely limited in patients with aortic disease, it is not known whether biomarkers differ between HTAD patients and non-syndromic TAD patients.

Conclusions

We identified MMP-3, IGFBP-2 and FABP4 as plasma biomarkers associated with thoracic aortic diameter in TAD patients. Elevated TLT-2 levels might indicate inflammatory involvement in hereditary TAD patients. These biomarkers and their corresponding biochemical pathways seem to play a role in assessing TAD severity. The potential clinical use of these biomarkers and their biochemical pathways warrants further research.

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SUPPLEMENTAL FILE 1

Table 2a. Biomarkers associated with AD_{max}

	Univariable analysis			Multivariable analysis *Sex, age*			Multivariable analysis *Sex, age, dissection, surgery*		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
CHI3L1	1.48	0.66;2.30	<0.001*	0.56	-0.34;1.46	0.223	0.52	-0.39;1.42	0.261
MMP3	1.74	0.92;2.56	<0.001*	1.06	0.06;2.06	0.038*	1.21	0.21;2.21	0.019*

95% CI= 95% Confidence Interval; AD_{max}= Maximal absolute diameter thoracic aorta.
* Significant at the 0.05 level

Table 2b. Biomarkers associated with ID_{max}

	Univariable analysis			Multivariable analysis *Sex, age*			Multivariable analysis *Sex, age, dissection, surgery*		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
IGFBP2	1.04	0.53;1.56	<0.001*	0.61	0.12;1.11	0.016*	0.72	0.19;1.24	0.007*
TIMP4	1.01	0.50;1.52	<0.001*	0.23	-0.34;0.79	0.433	0.27	-0.32;0.85	0.367

95% CI= 95% Confidence Interval; ID_{max}= Maximal indexed diameter thoracic aorta
* Significant at the 0.05 level

SUPPLEMENTAL FILE 2

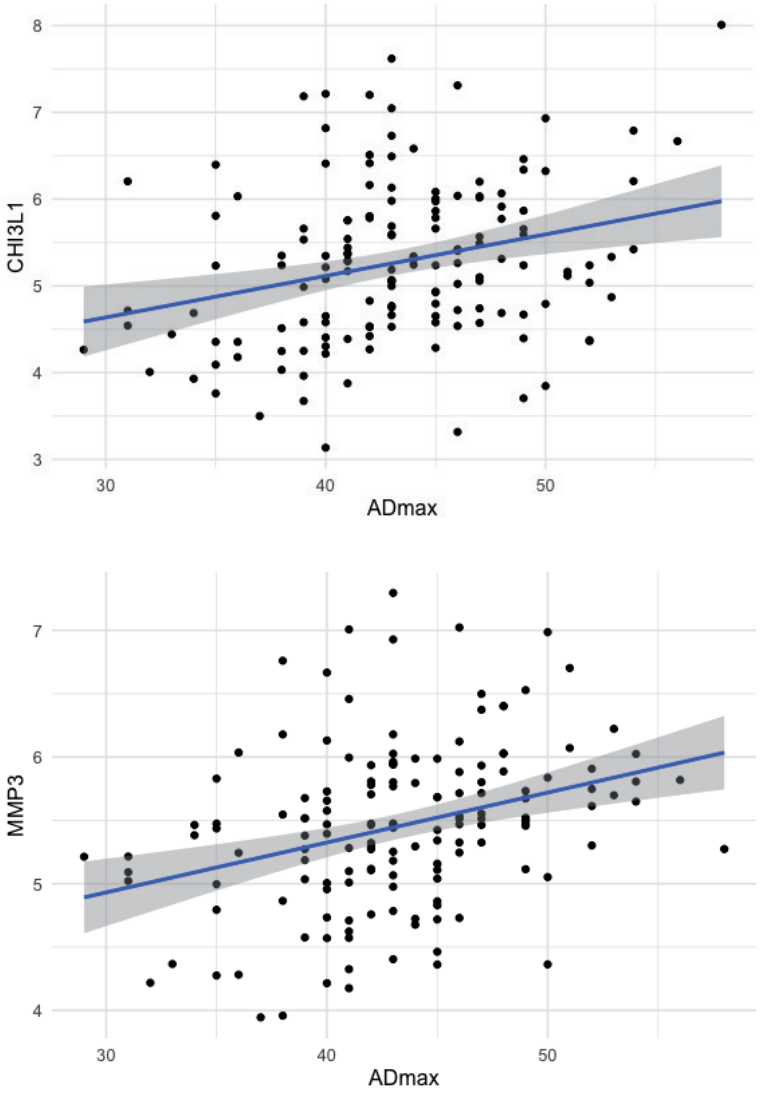

Figure 4a . Biomarkers associated with AD_{max}

AD_{max}= Maximal thoracic aortic diameter (in millimetres); CHI3L1= chitinase 3-like-1 (Z-score); MMP3= Matrix metalloproteinase 3 (Z-score).
Figures are displayed as scatterplot with linear regression line.

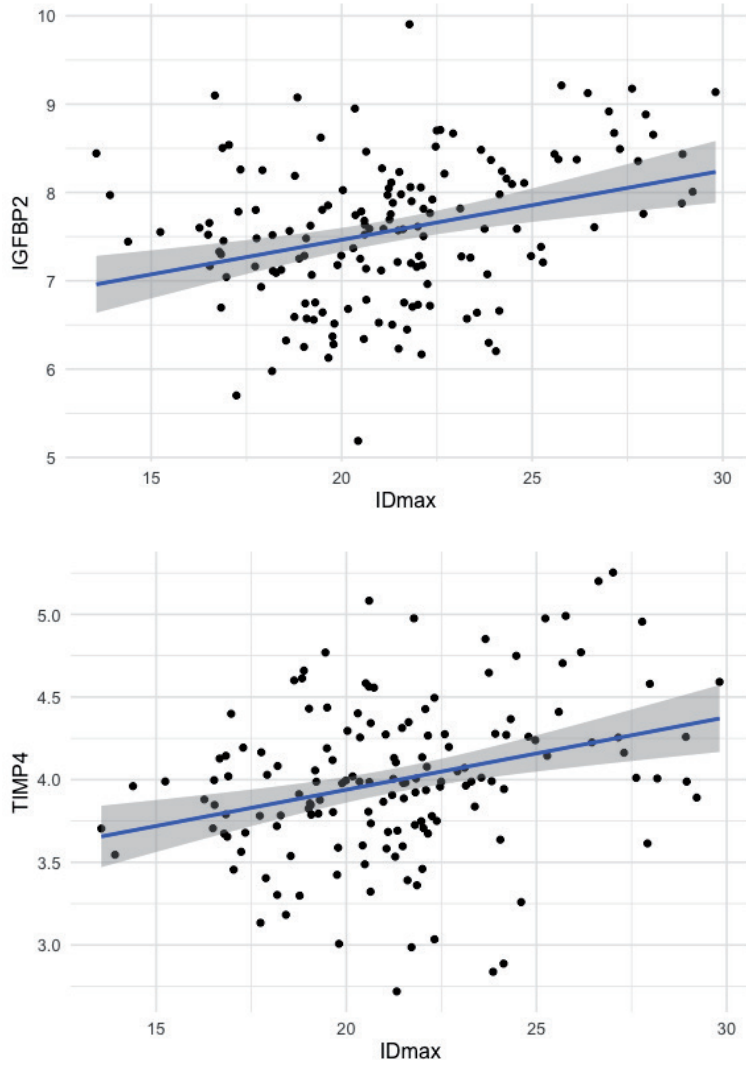

Figure 4b. Biomarkers associated with ID_{max}

ID_{max}= Indexed maximal thoracic aortic diameter (in millimetres per m^2); IGFBP2= insulin like growth factor binding protein 2 (Z-score); TIMP4 Metalloproteinase inhibitor 4 (Z-score).
Figures are displayed as scatterplot with linear regression line.

SUPPLEMENTAL FILE 3

Table 3a. Stratified Univariable analyses AD_{max}

	Total population n=158			Males n=99			Females n=59		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
CXCL16	0.424	0.18; 1.20	0.329	-0.095	-1.19; 1.00	0.863	1.330	0.02; 2.64	0.047
CTSD	0.772	-0.08; 1.62	0.074	-0.131	-1.31; 1.05	0.826	1.620	0.45; 2.79	0.008
CHI3L1	1.481	0.66; 2.30	<0.001*	1.095	0.05; 2.14	0.041	1.932	0.62; 3.25	0.005
COL1A1	-0.542	-1.40; 0.32	0.215	-1.199	-2.30; -0.10	0.033	0.493	-0.83; 1.82	0.459
FABP4	1.235	0.40; 2.07	0.004	1.852	0.71; 3.00	0.002	1.450	0.19; 2.71	0.025
Gal4	0.638	-0.22; 1.50	0.146	0.267	-0.75; 1.28	0.604	1.821	0.24; 3.40	0.025
GRN	-0.192	-1.05; 0.66	0.658	-1.327	-2.55; -0.10	0.035	0.876	-0.24; 1.99	0.122
GDF15	0.993	0.15; 1.83	0.021	0.903	-0.24; 2.05	0.122	1.083	-0.12; 2.28	0.076
IGFBP2	0.805	-0.06; 1.67	0.068	0.012	-1.19; 1.17	0.984	2.067	0.90; 3.23	0.001
IGFBP7	1.087	0.25; 1.93	0.011	0.115	-1.04; 1.27	0.843	2.175	0.78; 3.57	0.003
ITGB2	-0.304	-1.15; 0.54	0.480	-1.193	-2.24; -0.14	0.027	1.126	-0.20; 2.45	0.095
IL1RT1	-0.715	-1.57; 0.14	0.102	-1.533	-2.62; -0.44	0.006	0.178	-1.18; 1.54	0.794
IL18BP	0.436	-0.42; 1.29	0.315	-0.553	-1.64; 0.53	0.314	1.803	0.45; 3.16	0.010
MMP3	1.739	0.92; 2.56	<0.001*	1.680	0.32; 3.04	0.016	1.776	0.31; 3.24	0.018
MCP1	1.016	0.17; 1.86	0.018	0.706	-0.45; 1.86	0.227	1.182	-0.05; 2.41	0.059
PRTN3	0.249	-0.61; 1.11	0.568	-0.678	-1.81; 0.45	0.236	1.459	0.22; 2.70	0.022
MB	0.896	0.05; 1.74	0.038	0.473	-0.70; 1.64	0.424	0.867	-0.58; 2.31	0.234
OPN	-0.005	-0.87; 0.86	0.991	-0.787	-1.83; 0.26	0.140	1.568	0.14; 3.00	0.032
PON3	-1.131	-1.97; -0.30	0.008	-1.302	-2.32; -0.29	0.013	-0.161	-1.73; 1.41	0.839
PSPD	0.878	0.02; 1.74	0.046	0.574	-0.43; 1.57	0.258	0.990	-1.13; 3.11	0.353
CD163	0.744	-0.11; 1.60	0.086	-0.091	-1.18; 1.00	0.869	2.100	0.84; 3.37	0.002
TRAP	1.163	0.27; 2.05	0.011	0.331	-0.96; 1.62	0.611	1.787	0.61; 2.97	0.004
TFPI	0.131	-0.72; 0.98	0.761	-0.589	-1.65; 0.47	0.271	1.459	0.11; 2.81	0.034
tPA	0.782	-0.06; 1.63	0.070	-0.173	-1.31; 0.96	0.763	1.853	0.65; 3.06	0.003
TNFR1	0.861	0.01; 1.71	0.046	0.188	-0.91; 1.29	0.736	1.662	0.35; 2.97	0.014
FAS	0.592	-0.29; 1.48	0.188	-0.293	-1.36; 0.77	0.587	0.332	0.74; 3.93	0.005
AXL	0.470	-0.38; 1.32	0.276	-0.296	-1.35; 0.76	0.5782	1.592	0.09; 3.09	0.038
uPA	0.060	-0.79; 0.91	0.889	-0.434	-1.38; 0.51	0.364	2.081	0.21; 3.95	0.030
vWF	0.526	-0.33; 1.38	0.224	-0.077	-1.24; 1.08	0.895	1.233	0.04; s2.43	0.044

All biomarkers with a p-value ≤ 0.05 for the either the total population, males or females are displayed in this table.
AD_{max}= Maximal absolute thoracic aortic diameter; 95%CI= 95% Confidence interval.
* Significant after Bonferroni correction

Table 3b. Stratified univariable analyses ID_{max}

	Total population n=158			Males n=99			Females n=58		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
AZU1	-0.477	-0.97;0.04	0.072	-0.660	-1.19;-0.13	0.016	0.902	-0.34;2.14	0.150
CCL16	-0.346	-0.88;0.19	0.201	-0.634	-1.24;-0.03	0.039	0.509	-0.46;1.48	0.298
CXCL16	0.400	-0.13;0.93	0.138	-0.004	-0.63;0.62	0.989	1.024	0.14;0.91	0.024
CPA1	0.061	-0.47;0.59	0.820	-0.447	-1.03;0.13	0.129	1.052	0.09;2.01	0.032
ALCAM	0.535	0.01;1.06	0.046	-0.037	-0.72;0.65	0.914	0.786	-0.05;1.62	0.064
CHI3L1	0.711	0.19;1.23	0.008	0.716	0.12;1.32	0.020	1.066	0.14;1.99	0.024
CHIT1	0.407	-0.13;0.94	0.133	0.251	-0.34;0.84	0.404	1.020	0.02;2.02	0.046
CSTB	0.528	0.00;1.05	0.048	0.361	-0.24;0.96	0.235	0.798	-0.14;1.74	0.095
SELE	-0.463	-0.99;0.07	0.086	-0.789	-1.38;-0.19	0.010	0.143	-0.81;1.09	0.764
EGFR	-0.243	-0.77;0.29	0.366	-0.780	-1.47;-0.09	0.028	0.220	-0.57;1.01	0.579
FABP4	0.830	0.32;1.34	0.002	0.515	-0.15;1.18	0.128	0.766	-0.11;1.64	0.086
Gal3	0.702	0.19;1.22	0.008	0.242	-0.43;0.91	0.474	1.026	0.24;1.81	0.012
Gal4	0.607	0.08;1.13	0.024	0.324	-0.25;0.89	0.262	1.308	0.24;2.38	0.018
GRN	-0.266	-0.79;0.26	0.317	-1.001	-1.67;-0.33	0.004	0.337	-0.44;1.11	0.387
GDF15	0.697	0.18;1.21	0.008	0.793	0.16;1.43	0.015	0.610	-0.22;1.44	0.145
IGFBP1	0.651	0.13;1.18	0.016	0.258	-0.37;0.88	0.415	0.797	-0.22;1.81	0.121
IGFBP2	1.044	0.53;1.56	<0.001*	0.446	-0.21;1.10	0.177	1.676	0.92;2.43	<0.001*
IGFBP7	0.048	-0.49;0.58	0.858	-0.045	-0.71;0.62	0.894	1.338	0.37;2.31	0.008
ITGB2	-0.401	-0.92;0.12	0.130	-0.859	-1.44;-0.28	0.004	0.462	-0.46;1.38	0.319
IL1RT1	-0.376	-0.91;0.16	0.164	-0.648	-1.27;-0.02	0.042	0.332	-0.59;1.26	0.473
MMP3	0.213	-0.32;0.74	0.428	1.251	0.51;1.99	0.001	0.766	-0.27;1.80	0.143
MMP9	-0.608	-1.13;-0.09	0.022	-0.583	-1.14;-0.02	0.041	0.024	-1.15;1.20	0.968
TIMP4	1.012	0.50;1.52	<0.001*	0.674	-0.00;1.35	0.051	1.019	0.17;1.87	0.020
PRTN3	-0.201	-0.73;0.33	0.454	-0.630	-1.25;-0.01	0.048	0.479	-0.40;1.36	0.280
MPO	-0.369	-0.90;0.16	0.170	-0.664	-1.27;-0.06	0.032	0.538	-0.42;1.50	0.265
NTproBNP	0.586	0.06;1.11	0.029	0.206	-0.41;0.82	0.506	1.110	0.19;2.03	0.019
OPN	0.294	-0.24;0.82	0.276	-0.061	-0.65;0.53	0.839	1.133	0.16;2.10	0.023
OPG	0.634	0.10;1.16	0.020	0.264	-0.35;0.88	0.395	0.997	0.02;1.97	0.046
PON3	-0.145	-0.67;0.38	0.586	-0.636	-1.21;-0.06	0.030	0.351	-0.72;1.42	0.514
TRAP	0.623	0.07;1.17	0.027	0.367	-0.35;1.08	0.312	1.188	0.38;2.00	0.005
TFPI	0.163	-0.36;0.69	0.539	-0.447	-1.04;0.14	0.135	1.327	0.44;2.21	0.004
TFF3	0.256	-0.27;0.78	0.334	1.388	0.30;2.48	0.013	-0.270	-0.92;0.38	0.405
FAS	0.285	-0.26;0.83	0.304	0.265	-0.33;0.86	0.382	1.153	0.02;2.29	0.046

All biomarkers with a p-value ≤ 0.05 for the either the total population, males or females are displayed in this table.
ID_{max}= Maximal thoracic aortic diameter indexed for body surface area; 95%CI= 95% Confidence interval.
* Significant after Bonferroni correction

SUPPLEMENTAL FILE 4

Supplemental table 4a. Biomarkers associated with ascending aortic diameter

	Univariable analysis			Multivariable analysis *Sex, age*			Multivariable analysis *Sex, age, dissection, surgery*		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
MMP3	1.70	0.85;2.56	<0.001**	0.86	-0.20;1.92	0.111	0.83	-0.17;1.82	0.105

95% CI= 95% Confidence Interval, MMP3= Matrix Metalloproteinase-3, MB= myoglobin.
** Significant after Bonferroni correction

Supplemental table 4b. Biomarkers associated with descending aortic diameter

	Univariable analysis			Multivariable analysis *Sex, age*			Multivariable analysis *Sex, age, dissection, surgery*		
Biomarker	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
FABP4	2.13	1.04;3.22	<0.001**	2.05	0.80;3.31	0.002*	1.86	0.61;3.12	0.004*

95% CI= 95% Confidence Interval; FABP4= Fatty acid-binding protein 4
** Significant after Bonferroni correction
* Significant at the 0.05 level

SUPPLEMENTAL FILE 5

Supplemental table 5a. Comparison between TAD patients with and without previous surgery and/or dissection

Biomarker	Previous surgery and/or dissection n= 38	No surgery or dissection n= 120	p-value
APN	4.79 (4.59-4.97)	4.91 (4.77-5.08)	0.030
BLMhydrolase	3.12 (2.95-3.49)	3.07 (2.71-3.29)	0.041
IGFBP2	7.81 (7.46-8.33)	7.52 (6.92-8.03)	0.029
TIMP4	3.98 (3.69-4.26)	4.11 (3.88-4.34)	0.039
NTproBNP	3.67 (3.01-3.99)	2.84 (2.32-3.26)	<0.001*
OPN	6.90 (6.64-7.22)	6.73 (6.50-7.2)	0.041
SELP	10.04 (9.41-10.60)	9.75 (9.14-10.28)	0.033
GP6	3.21 (2.85-3.95)	3.02 (2.42-3.41)	0.024
PDGFsubunitA	3.14 (2.78-3.72)	2.80 (2.35-3.41)	0.027
DLK1	4.80 (4.32-5.25)	5.04 (4.72-5.55)	0.027
RARRES2	10.78 (10.59-10.96)	10.63 (10.37-10.87)	0.017
TLT2	4.58 (4.42-4.82)	4.41 (4.19-4.67)	0.026
UPAR	4.36 (4.19-4.60)	4.21 (4.05-4.41)	0.004

TAD= Thoracic Aortic Disease; APN= aminopeptidase; IGFBP2= Insulin-like growth factor binding protein 2; TIMP4= Metalloproteinase inhibitor 4; NTproBNP= N-terminal prohormone brain natriuretic peptide; OPN= Osteopontin; SELP= P-selectin; GP6= Pletelet glycoprotein VI; PDGF subunit A= Platelet-derived growth factor subunit A; DLK1= Protein delta homolog 1; RARRES2= Retinoic acid receptor responder protein 2; TLT2= Trem-like transcript 2 protein; UPAR= Urokinase plasminogen activator surface receptor.
*= Significant after Bonferroni correction

Supplemental table 5b. Comparison between Hereditary TAD patients and non-hereditary TAD patients

Biomarker	Hereditary TAD N= 36	TAD N=122	p-value
BLMhydrolase	3.17 (2.88-3.43)	3.06 (2.72-3.21)	0.020
CHI3L1	4.72 (4.26-5.35)	5.32 (4.76-5.87)	0.006
SELE	9.72 (9.21-9.98)	9.57 (9.11-9.74)	0.042
Gal4	2.90 (2.61-3.15)	3.13 (2.76-3.44)	0.024
GDF15	4.04 (3.64-4.49)	4.36 (4.13-4.71)	0.004
MCP1	3.68 (3.42-3.68)	3.79 (3.67-3.98)	0.043
PON3	5.07 (4.62-5.52)	4.91 (4.42-5.23)	0.030
PGLYRP1	7.22 (7.01-7.43)	6.92 (6.67-7.18)	0.001
PAI	6.06 (5.48-6.50)	5.60 (4.98-6.07)	0.009
GP6	3.28 (2.73-3.89)	3.01 (2.41-3.40)	0.012
PDGFsubunitA	3.21 (2.76-3.84)	2.84 (2.36-3.37)	0.023
tPA	3.86 (3.30-4.35)	4.21 (3.85-4.70)	0.010
TLT2	4.64 (4.45-4.84)	4.40 (4.17-4.64)	<0.001*

TAD= Thoracic Aortic Disease; BLMhydrolase= B-aminoalaninamide moiety hydrolase; CHI3L1= Chitinase-3-like protein 1; SELE= E-selectin; Gal4= Galectin-4; GDF15= Growth/differentiation factor 15; MCP1= Monocyte chemotactic protein 1; PON3= Paraoxonase; PGLYRP1= Peptidoglycan recognition protein 1; PAI= Plasminogen activator inhibitor 1; GP6= Pletelet glycoprotein VI; PDGF subunit A= Platelet-derived growth factor subunit A; tPA= Tissue-type plasminogen activator; TLT2= Trem-like transcript 2 protein.
*= Significant after Bonferroni correction

CHAPTER 3

3

Neurovascular abnormalities in patients with Loeys-Dietz Syndrome type III

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European Journal of Medical Genetics, 2022

ABSTRACT

The aim of this article is to describe neurovascular findings in patients with Loeys Dietz syndrome type III and their possible clinical impact. Loeys Dietz syndrome type III, caused by pathogenic *SMAD3* variants, is an autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with osteoarthritis. Neurovascular abnormalities have been described in other heritable aortic syndromes, however, reliable data in Loeys Dietz syndrome type III is missing.

In our tertiary center, all adult patients with confirmed Loeys Dietz syndrome type III are followed in a standardized aorta outpatient clinic including Computed Tomography Angiography (CTA) of the head and neck region at baseline and (tri) yearly during follow-up. We performed an analysis of the neurovascular imaging findings and clinical follow-up. The primary outcome was a combined endpoint of mortality, dissection, cerebral vascular event and intervention. In addition, tortuosity and vascular growth were assessed. In total 26 patients (mean age 38.4 years, 38.5% males) underwent 102 (mean 3.9 (1-8) per patient) neurovascular Computed Tomography Angiography scans between 2010 and 2021. In 84.6% some form of neurovascular abnormality was found. The abnormalities at baseline were aneurysm (26.9%) dissection flap (7.7%), arterial tortuosity (61.5%), arterial coiling (23.1%) and arterial kinking (3.8%). During follow up (mean 8.85 (1-11) years) one patient suffered from sudden death and one patient needed a neuro-radiological intervention. No cerebral bleeding or stroke occurred.

In conclusion, neurovascular imaging in Loeys Dietz syndrome type III patients revealed abnormalities such as aneurysm, tortuosity, coiling and kinking in the vast majority of patients, but clinical events were rare. Neurovascular screening and follow up is advised in all Loeys Dietz syndrome type III patients.

INTRODUCTION

The Aneurysms-Osteoarthritis Syndrome (AOS) was first described in 2011, and was caused by pathogenic variants in the *SMAD3* gene. The syndrome was classified as Loeys Dietz syndrome type III (LDSIII)[1]. This syndrome has an autosomal dominant inheritance pattern with variable clinical expression[2]. The *SMAD3* gene is located on chromosome 15q22.2-24.2 and encodes for a protein of the *TGF*-β pathway that is essential for *TGF*-β signal transmission[3]. Heterozygous *SMAD3* variants lead to increased aortic expression of several key players in the *TGF*-β pathway, such as phosphorylated *SMAD2*, *SMAD3* and *TGF*-β*1*[3]. Activation of the *TGF*-β pathway has also been observed in other diseases with arterial wall anomalies, such as Marfan Syndrome (MFS), bicuspid aortic valve and degenerative aneurysmal aortic disease[4]. LDS exhibits a more aggressive course than the other disorders, with morbidity and mortality typically resulting from complications of aortic/arterial dissections[5].

Aneurysms, dissections and tortuosity throughout the arterial tree are the main features of LDS III. These features may potentially cause serious complications such as dissection and rupture, which explain the reported high mortality rates of up to 34%[2]. Early diagnosis, short-interval follow-up imaging and prophylactic surgical intervention have proven beneficial in preventing catastrophic vascular complications or death[6].

Neurovascular abnormalities such as tortuosity or aneurysms of the carotid and vertebrobasilar arteries have been described in patients with heritable thoracic aortic diseases. Van de Laar (2012) described tortuosity in cerebral arteries in 50% of 45 patients with a S*MAD3* mutation[4]. Although arterial tortuosity is not a classical feature of MFS, vertebral tortuosity is found significantly more often in MFS and LDS patients compared to controls (9).

Moreover, in MFS, a higher percentage of vertebral arterial tortuosity was associated with earlier age at first cardiovascular surgery and increased rates of surgical interventions (10, 11). Since there are different types of LDS, with variable clinical symptoms, it is important to report in which type neurovascular abnormalities are more prevalent. Evidence about neurovascular abnormalities in patients with a *SMAD3* gene-variant is limited, with mostly retrospective studies and without information about the clinical follow-up of these neurovascular abnormalities[7-9].

The aim of this study is to assess the prevalence of neurovascular abnormalities and to investigate their clinical impact in LDS III patients, evaluate changes of cerebral vasculature and abnormalities over time and identify factors associated with these neurovascular abnormalities.

METHODS

Study population

In 2010 a standard protocol for assessment and follow-up of patients with LDS III was initiated (Fig. 1) at the dedicated outpatient clinic for adult patients with aorta pathology in our tertiary center. Patients were routinely investigated and underwent electrocardiogram, echocardiography and CTA of the thorax and abdomen every year and CTA of the head and neck arteries at baseline and at least every three years. All adult patients with confirmed LDS III, were invited to participate in this observational study between April 2010 and January 2020, with clinical follow-up until September 2020. The study was approved by the medical ethics committee, and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines. Written informed consent was obtained from all patients.

The primary endpoint was any neurovascular event, defined as neurovascular related mortality (proven or high suspicion), neurovascular dissection or rupture, ischemic stroke or cerebral bleeding or need for preventive neurovascular intervention.

The secondary endpoint was presence of neurovascular abnormalities on CT and neurovascular changes over time.

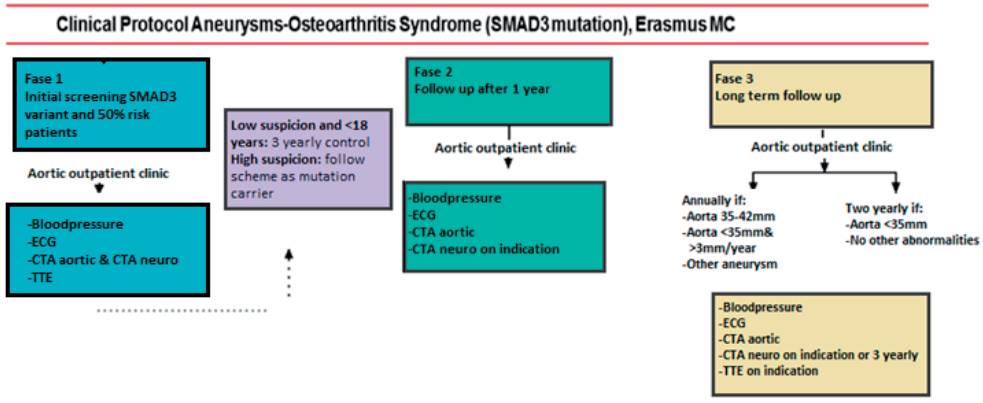

Figure 1. Clinical protocol of aneurysm-osteoarthritis syndrome (*SMAD3* variant)

CTA aortic= computed tomography angiography of the total aorta, CTA head/neck arteries= computed tomography angiography of the neurovascular arteries, ECG=electrocardiogram, TTE=transthoracic echocardiography

Data collection

For this observational study, the following information was registered at baseline: medical history, neurovascular abnormalities, neurovascular interventions, aorta- and small vessel abnormalities and interventions, other vascular abnormalities or interventions.

The body surface area (BSA) was calculated using the DuBois and DuBois formula: BSA (m2) =0.007184×height (m)$^{0.725}$×weight (kg)$^{0.425}$. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg or 'requiring medical therapy'. Dyslipidemia was defined as 'Cholesterol total ≥ 6.5 and/or LDL ≥ 4.12' or 'requiring medical therapy'. Smoking was defined as never, current or former. The age at first neurovascular CTA was defined as the baseline of the study. The follow up CTA was defined as the last CTA the patient received. Baseline measurement of the thoracic, abdominal and cerebral vascular diameters was performed using CTA. Cross sectional aortic diameter was evaluated at the aortic annulus, the sinus of Valsalva, the sino-tubular junction, and the ascending aorta using the double oblique measurement method perpendicular to the vessel axis [10]. A thoracic aorta ≥ 40 mm was defined as thoracic aortic aneurysm (TAA). An abdominal aorta ≥ 25 mm was defined as abdominal aortic aneurysm (AAA). A common internal artery ≥ 25 mm, an iliac internal artery ≥ 8 mm, a splenic artery ≥ 6 mm, a hepatic/gastric artery ≥ 6 mm, a renal artery ≥ 6 mm, a coeliac artery ≥ 6mm, a left internal mammary artery (LIMA) ≥ 5mm and a right internal mammary artery (RIMA) ≥ 5mm were defined as small vessel aneurysm. In the patients with an aneurysm in the intra- and extracranial vasculature the change in diameter in mm's was measured and divided by the number of years between the scans.

Assessment of cerebral vasculature

See supplemental data: file 1

Statistical analyses

Continuous data were presented as mean and standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when skewed. Categorical data were presented as frequencies with percentages. Differences were assessed between patients with and without neurovascular abnormalities. For categorical variables including thoracic aortic aneurysm, abdominal aneurysm, age, height, BSA, hypertension, hypercholesterolemia and smoking the Chi-square test was used. Analyses were performed using IBM SPSS Statistics Viewer (version 25) software. A p-value ≤ 0.05 was defined to be statistically significant.

RESULTS

Baseline characteristics

In total, 26 patients with confirmed pathogenic or likely pathogenic *SMAD3* genetic variants were included. These variants in our group were documented in the Leiden Open Variation Database (LVOD), the access numbers are as follows: 0000308567; 0000308566; 0000615471; 0000308563; 0000308554; 0000308555; 0000831232; 0000308564; 0000399285; 29907982; 0000399300. (See supplemental file 2)

The mean age was 38.4 $\pm$ 12.7 years (38.5% males) (Table 1). In total 102 CTA's of the head and neck arteries were performed (mean 3.9 (1-8) per patient). Four patients had only one CTA due to short follow up. The mean follow up between the first and last CTA of the 23 patients with multiple CT scans was mean 8.85 (1-11) years.

The median height was 177.5 cm (IQR 173.3-187.0), weight 83.3 kg (IQR 72.5-92.8) and BSA 2.0 m2 (IQR 1.9-2.1). The median systolic blood pressure was 123.0 mmHg (IQR116.0-134.5), diastolic blood pressure 75.5 mmHg (IQR 71.8-82.8), median of the mean arterial blood pressure 93.0 mmHg (IQR 87.0-100.8). Hypertension was found in 12 (46.2%) of the patients. Of the 26 patients 6 (23.0 %) were treated with a beta blocker, 6 (23.0 %) with an Angiotensin-converting enzyme (ACE) inhibitor, 1 (3.7 %) with an Angiotensin II receptor blockers (ARB), 1 (3.8 %) with a calcium blocker and in 14 (53.8 %) no medication was used. Seven (26.9 %) were current, 3 (11.5 %) former and 16 (61.5 %) never smokers. Cholesterol panel was normal in 19 (73.1 %), without use of cholesterol lowering medication. In 4 patients (15.4 %) hypercholesterolemia was present of whom 1 (3.8 %) received medication. In three patients no information on cholesterol was available.

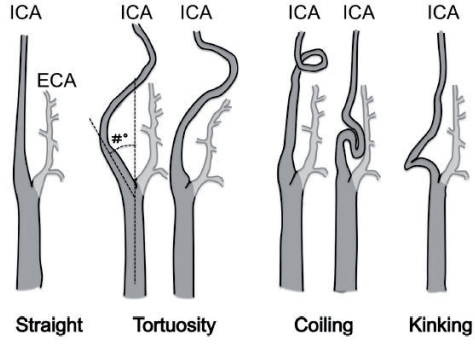

Figure 2 Overall tortuosity of intracranial vasculature

Schematic drawing of morphological classification of the carotid artery, viewed from the right lateral side. ICA=internal carotid artery; ECA=external carotid artery. Obtained permission for publication from Elsevier, Journal of Cranio-Maxillofacial surgery, 'Three-dimensional computed tomographic analysis of variations of the carotid artery', Authors: Tetsuji Nagata, Kazuma Masumoto, Yutaro Hayashi, Yoshiko Watanabe, Yuta Kato, Fuminori Katou.

Table 1. Baseline characteristics and neurological findings of adult patients with proven SMAD3 gene variant

patient	sex	BSA@	Hyper-tension*	Age diag-nosis(y)	Gene variants	Age first CTA head neck (y)	Follow up (y)	Amount of neuro CT's	Neurovascular findings		Neurovascular intervention	Thoracic aorta Findings/ intervention		Abdominal aorta Findings/intervention		Small vessel findings	Small vessel intervention
									Aneurysm/ shape (1,2)**	Overall tortuosity#		TAA@	Aortic surgery	AAA ##	AAA## Intervention	Small vessel aneurysm	Small vessel intervention
1	F	1,74	No	29	c.861delG, p.Arg288fs	29	7	5	aneurysm ICA left (1) 2mm	1	No	No	No	No	No	Saccular aneurysm splenic artery	coiling splenic artery
2	F	1,87	Yes	54	c.861delG, p.Arg288fs	54	22	5	No	3	No	Yes	Yes	No	No	Aneurysm distal splenic artery Aneurysm proximal splenic artery	coiling distal splenic artery
3	F	1,71	Yes	59	c.859C>T, p.Arg287Trp	59	8	3	No	1	No	Yes	No	No	No	No	
4	M	2,10	Yes	31	c.859C>T, p.Arg287Trp	31	8	4	aneurysm ICA left (1) and right (1)	1	Yes	Yes	Yes	No	No	No	
5	F	1,88	Yes	46	c.859C>T, p.Arg287Trp	46	11	8	No	2	No	Yes	No	Chronic dissection distal aortic	No	Aneurysm splenic artery Aneurysm coeliac artery, iliac communis artery right, splenic artery, hepatic artery left	coiling splenic artery
6	M	1,96	No	19	c.859C>T, p.Arg287Trp	22	9	3	No	0	No	Yes	Yes	No	No	No	
7	F	1,82	No	66	c.859C>T, p.Arg287Trp	66	8	6	aneurysm MCA left (1)	2	No	No	No	No	No	No	
8	F	2,08	No	40	c.859C>T, p.Arg287Trp	40	12	6	No	1	No	Yes	Yes	No	No	No	
9	M	2,04	Yes	63	c.859C>T, p.Arg287Trp	63	9	4	No	1	No	Yes	Yes	No	No	Aneurysm gastroduodenal artery, renal artery right	No
10	M	2,42	Yes	31	c.859C>T, p.Arg287Trp	36	11	3	No	2	No	Yes	Yes	No	No	No	
11	F	2,14	No	35	c.859C>T, p.Arg287Trp	40	12	4	No	0	No	Yes	Yes	No	No	Aneurysm thoracic internal artery right	Coiling thoracic internal artery right
12	F	2,17	No	30	c.401-6G>A, r.400_401insACAG	30	5	2	aneurysm ICA left 3mm (1)	1	No	No	No	No	No	Aneurysm splenic artery, one saccular, one fusiform	No
13	F	1,74	Yes	36	c.859C>T, p.Arg287Trp	43	8	1	Pseudo aneurysm and dissection flap VA left	2	No	No	No	No	No	No	
14	F	1,83	Yes	45	c.859C>T, p.Arg287Trp	46	12	5	No	1	No	Yes	Yes	No	No	No	
15	F	1,95	No	42	c.859C>T, p.Arg287Trp	42	11	4	No	1	No	No	No	No	No	aneurysm CIA	No

Table 1. Continued

patient	sex	BSA@	Hyper-tension*	Age diag-nosis(y)	Gene variants	Age first CTA head neck (y)	Follow up (y)	Amount of neuro CT's	Neurovascular findings		Neurovascular intervention	Thoracic aorta Findings/ intervention		Abdominal aorta Findings/intervention		Small vessel findings	Small vessel intervention
16	M	1,99	No	20	c.859C>T, p.Arg287Trp	18	7	4	No	0	No	Yes	Yes	No	No	No	
17	M	2,33	No	28	c.859C>T, p.Arg287Trp	28	11	4	No	2	No	No	No	No	No	No	
18	M	2,33	No	28	c.859C>T, p.Arg287Trp	31	12	5	No	1	No	Yes	No	No	No	No	
19	M	2,17	Yes	40	c.859C>T, p.Arg287Trp	42	11	6	aneurysm ICA right 6mm (2)	2	No	Yes	Yes	No	No	Aneurysm splenic artery, hepatic artery, gastric artery, LIMA, mesenteric superior artery, thoracic intercostal artery	Stenting splenic artery, hepatic artery, gastric artery. Coiling LIMA, thoracic intercostal artery
20	F	2,06	Yes	45	c.741-742delAT, p.Thr247fs	49	12	6	No	1	No	Yes	Yes	No	No	Aneurysm coeliac artery	No
21	F	1,84	No	41	c.1045G>C, p.Ala349Pro	42	7	5	Dissection flap VA right	1	No	No	No	No	No	Aneurysm RIMA and LIMA	No
22	M	2,06	No	30	exon 6 deletion, c.659_871del	32	12	2	No	1	No	Yes	Yes	No	No	No	
23	F	2,01	No	25	c.1102C>T, p.Arg368*	29	6	2	No	1	No	No	No	No	No	No	
24	M	2,28	Yes	48	c.1102C>T, p.Arg368*	54	7	1	No	1	No	Yes	No	No	No	No	
25	F	1,91	No	23	15q22.3q23 microdeletion including SMAD3	30	8	1	No	0	No	Yes	No	No	No	No	
26	F	2,00	Yes	45	c.76C>T, p.Gln26*	45	1	1	No	1	No	No	No	No	No	No	
Total 26	38,5% men	Mean BSA 2.0 m^2 (+ ,2)	46.2% Hyper-tension or medical therapy	Mean age 38.4 (+ 12.7) years		Mean age first CTA 40,1 (+ 12,4)	Median follow up 9,0 years IQR[7.0-12.0]	Median amount of CTA's head/ neck 4.0 IQR[2,0-5,3]	7 (26.9%) patients with neuro (pseudo) aneurysms/ dissections	22 (84.6%) patients with neuro vascular tortuosity	1 neuro-vascular interven tion	17 (65.4%) patients with TAA	12 (46,2%) patient with aortic surgery	1 (3.8%) patients with abdominal aneurysm	0 (0%) patients with abdominal interven-tion	10 (38,5%) patients with small vessel aneurysm	5 (19,2%) patients with small vessel intervention

@BSA (body surface area in m2), *hypertension (systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg or 'requiring medical therapy'); **aneurysm shape (1=saccular, 2=fusiform), ICA=internal carotid artery; MCA=middle cerebral artery; PCOM=posterior communis artery; VA=vertebral artery; #overall tortuosity (0=straight, 1=tortuosity, 2=coiling, 3=kinking); @TAA=thoracic aortic aneurysm, if aorta diameter is > 40mm; ##AAA=abdominal aneurysm, if aorta diameter is > 25mm; Small vessel aneurysm if a common internal artery ≥ 25 mm, an iliac internal artery ≥ 8 mm, a splenic artery > 6 mm, a hepatic/gastric artery > 6 mm, a renal artery > 6 mm, a coeliac artery is > 6mm, a LIMA/RIMA > 5mm; CIA=common iliac artery; LIMA=left internal mammary artery, RIMA=right internal mammary artery.

Prevalence of abnormalities in cerebral vasculature

At baseline 22 of the 26 patients (84.6 %) showed neurovascular abnormalities. Neurovascular aneurysms were diagnosed in 6 patients (23.1 %), of whom one patient had 2 aneurysms. The aneurysms were located in the internal carotid artery (5), the vertebral artery (1) and the middle cerebral artery (1) (Fig. 3). In terms of shape, 5 were saccular, 1 was fusiform and 1 was a pseudo aneurysm (vertebral artery). One patient had two aneurysms bilateral of the internal carotid arteries. Arterial dissection of the vertebral artery was diagnosed in 2 (7.7%) patients at baseline. None of these patients had any symptoms.

The patients having a chronic neurovascular dissection, were both female and had no intervention. The first patient underwent only one CTA of the head and neck arteries at the age of 43 years, due to late inclusion with short follow-up. There was tortuosity of the left internal carotid artery with a focal dilatation, possible because of an earlier dissection. The right internal carotid artery had a small torturous course. The proximal vertebral artery had dilatations, narrowing and on more places a suggestion of dissection flaps on both sides and a suggestion of a small pseudo aneurysm on the left side. More distally a strong tortuous course on both sides of the vertebral artery was found. The intracranial arteries all showed tortuosity. This patient was known to have a normal diameter of the thoracic- and abdominal aorta, a BSA of 1.74m^2, hypertension without medical treatment, no dyslipidemia and never smoked.

The second patient who had a neuro-vascular dissection underwent 5 neurovascular CTA's in total and her age at baseline was 42 years. The neurovascular findings were stable over time. The CTA's described a normal diameter of the carotid artery, fusiform dilatation of the V1 segment of the right vertebral artery, with a dissection of a short segment. Normal diameter of the left vertebral artery and the intracerebral arteries. This patient was known with a normal diameter of the thoracic aorta, an aneurysm of the right internal mammary artery of 6mm, a BSA of 1.84m^2, no hypertension, no dyslipidemia and never smoked.

The most prevalent neurovascular abnormality in our patient population was neurovascular arterial tortuosity, which was found in 61.5% of all the patients. In 23.1% arterial coiling and in 3.8% arterial kinking was found. A distribution in categories of the tortuosity was made on the different arteries, the bilateral internal carotid artery, the bilateral vertebral artery and the basilar artery, see Table 2.

Change of neurovascular abnormalities over time

During a mean of mean 8.85 (1-11) years follow up, in 4 (15.4%) patients there was progression in the neurovascular abnormalities. In one patient, who was already known with 2 aneurysms of the carotid artery on both sites, a new aneurysm of 3 mm in the left

carotid artery was observed after 2 years of follow-up. Two patients had a change of the vertebral artery, one from straight to tortuosity and the other from tortuosity to coiling. One patient had a change from tortuosity to coiling in the overall view. No change in diameters was observed in the patients known with an aneurysm.

Table 2. Overall tortuosity of neurovascular arteries in adult patients with proven *SMAD3* gene variant divided in straight (normal), tortuosity, coiling and kinking.

	Overall	ICA left	ICA right	VA left	VA right	BA
Straight	4 (15.4)	5 (19.2)	9 (34.6)	4 (15.4)	6 (23.1)	9 (34.6)
Tortuosity	16 (61.5)	18 (69.2)	13 (50.0)	11 (42.3)	10 (38.5)	17 (65.4)
Coiling	6 (23.1)	3 (11.5)	5 (19.2)	8 (30.8)	7 (26.9)	1 (3.8)
Kinking	1 (3.8)	1 (3.8)	0 (0.0)	4 (15.4)	4 (15.4)	0 (0.0)

Data is displayed as frequency and (percentage), ICA=internal carotid artery, VA=vertebral artery, BA=basilar artery

Prevalence of clinical events

During follow-up, there were 2 clinical events: one patient needed a neurovascular intervention, and one patient suffered from sudden death of unknown cause, no autopsy was performed. Below we will describe these cases in further detail.

The patient who needed a neurovascular intervention, was a male of 35 years with a Tyron David (valve sparing aortic root replacement) operation at the age of 32. He had a BSA of 2.10m^2, no dyslipidemia, was current smoker and used ACE- inhibition for hypertension. At baseline, the patient was known with two asymptomatic aneurysms of the carotid siphon on both sites, measuring both 7 mm. These aneurysms remained stable during two years of follow-up. However, a third aneurysm of 3 mm occurred and was located also at the left side of the carotid artery in a different part. The left vertebral artery showed coiling, but there was a normal course of the vertebral artery on the right site and the basilar artery. Because there was progression noticed of the third aneurysm, 2 flow diverters were placed in the carotid artery on both sides. No complications occurred.

The patient who died suddenly, was a female patient of 67 years, she was found death lying in front of her bed, no autopsy was performed and the cause of death remains unknown. This patient was known to have a stable aorta sinus of Valsalva of 40 mm and a stable aorta ascending of 38 mm during 8 years of follow-up. The last CTA of head and neck arteries showed a sharp angle at the entrance of the left vertebral artery, with a further normal aspect of the vertebral arteries and on both sides a normal aspect of the carotid arteries. She was known with an unchanged fusiform dilatation of the basilar artery of 7 mm, no signs of a basilar artery aneurysm and no signs of an intracranial aneurysm. Furthermore this patient had a normal BSA (1.88 m^2), was known with hypertension

treated with a beta blocker, had no dyslipidemia and never smoked. The cardiovascular history revealed atrial fibrillation for which 2 electro-cardioversions in the past and use of apixaban for stroke prevention. Other relevant medical history included arthrosis of the cervical vertebral column.

Factors associated with neurovascular abnormalities.

In our study population there was no difference in the amount of neurovascular aneurysms between males (30.8%) and females (30.8%). No significant difference was found in patients with and without neurovascular aneurysm in having TAA (7.7% vs 57.7%, p=.028), AAA (0.0% vs 3.8%, p=1.0), or small vessel aneurysm (15.4% vs 23.1%, p=.369). Osteoarthritis was present in 16 (61.5%) patients and 3 (11.5%) of them had a neurovascular aneurysm. There was no significant difference (p=0.369) in osteoarthritis in patients with or without neurovascular abnormalities. There was also no significant difference in sex, age, hypertension, dyslipidaemia, smoking, BSA or BMI, as is shown in Table 3.

Table 3 Prevalence of neurovascular aneurysms in adult patients with *SMAD3* gene variant

	With cerebral aneurysm n= 6	Without cerebral aneurysm n= 21	p-value
TAA, n(%)	2 (7.7)	15 (57.7)	0.302
AAA, n(%)	0 (0.0)	1 (3.8)	1.00
Small vessel aneurysm, n(%)	4 (15.4)	6 (23.1)	0.369
Osteoarthritis, n(%)	3 (11.5)	13 (50.0)	0.369
Hypertension, n (%)	3 (11.5)	11 (42.3)	1.000
Dyslipidemia, n(%)	0 (0.0)	4 (15.4)	1.000
Smoking			
current, n(%)	2 (7.7)	5 (19.2)	0.755
former, n(%)	1 (3.8)	2 (7.7)	
never, n(%)	3 (11.5)	13 (50.0)	
BSA* (m2)	1.9 (1.74-2.17)	1.9 (1.71-2.42)	0.206
BMI* (kg/m2)	25.2 (20.2-30.6)	26.1 (±4.2)	0.408
Age*(years)	40.3 (29-68)	40.1 (18-63)	0.419
Gender* male, n(%)	2 (7.7)	8 (30.8)	0.668
female, n(%)	5 (19.2)	11 (42.3)	

Data is displayed as frequency (percentages) or mean (SD).
TAA= thoracic aortic aneurysm, AA=abdominal/iliac aneurysm. Hypertension: systolic blood pressure ≥ 140mmHg and/or a diastolic blood pressure ≥ 90mmHg or 'requiring medical therapy'. Dyslipidemia: 'Cholesterol total ≥6.5 mmol/L and/or LDL ≥4.12mmol/L' or 'requiring medical therapy'. Smoking: never, current or former. Age of the first CTA head and neck arteries was defined as the baseline of the study.

In 15 (57.7%) patients of the same family, the same pathogenic variant on chromosome *R287W, 859C>T (SMAD3 ex 9)* (heterozygous form) was found. Only 2 patients with this pathogenic variant had a neurovascular aneurysm. No difference was found between specific pathogenic variant and neurovascular aneurysm.

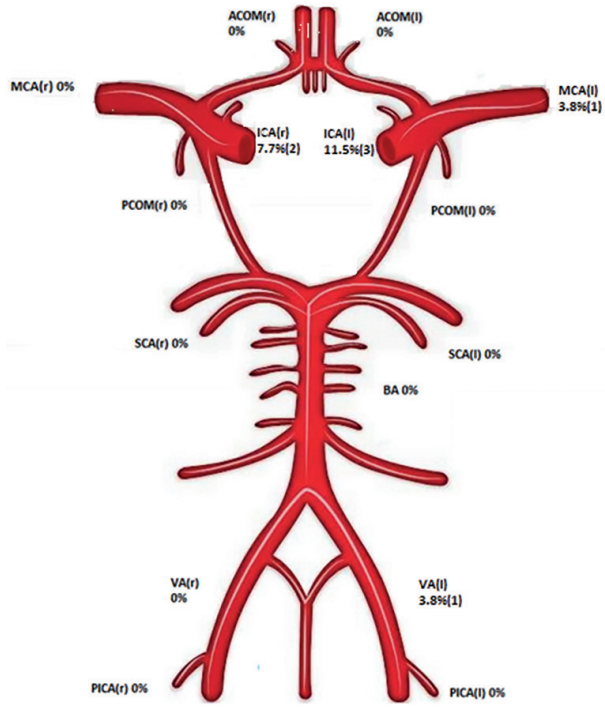

Figure 3 Occurrence of aneurysms per neurovascular artery, the circle of Willis in adult patients with proven *SMAD3* gene mutation

Percentage of occurrence per neurovascular artery.
ICA(l/r)-internal carotid artery(left/right); ACOM(l/r)=anterior communicating artery (left/right); MCA (l/r)=middle cerebral artery(left/right); PCOM(l/r)=posterior communicating artery (left/right); SCA(l/r)=superior cerebellar artery(left/right); BA=basilar artery

DISCUSSION

To the best of our knowledge, we conducted the first prospective study with clinical and imaging evaluation on neurovascular abnormalities in LDS III patients. We found at a mean age of 38.5 years in 84.6% of the patients neurovascular imaging abnormalities, including two dissections. During a mean follow-up of 8.85 years, two patients (7.7%) suffered from an event: one unexplained sudden death and one progression of aneurysm formation needing preventive neurovascular intervention. However, no cerebrovascular hemorrhage or ischemic stroke occurred.

Intra- and extracranial aneurysms were found in 26.9% of our patients. Previous studies on neurovascular aneurysms in Loeys–Dietz Syndrome, described different percentages of aneurysms. In a cohort of 62 LDS III patients [8], 13% had an intra- and extracranial

aneurysm, while in a cohort of 25 LDS type I patients [9] 32% had an intra- and cranial aneurysm. In a retrospective study [11] the prevalence of intra- and extracranial aneurysms in patients with different connective tissue diseases was described: 14% in MFS patients, 12% in different types of EDS patients and 28% in different types of LDS patients. Although no differentiation in types of LDS was mentioned in this study, the percentage of cerebral aneurysms seems similar to our study. Furthermore, a higher prevalence of aneurysm is found in LDS compared to Marfan- and Ehlers Danlos syndrome. With a prevalence of almost one third of the LDS type III patients, it seems advisable to screen for these abnormalities at diagnosis.

In our study, asymptomatic cerebral dissection was seen in 7.7% of LDS III patients. In a cohort of LDS type I patients [9] this was reported to be 12% (3/25). Kim et al [11] found cerebral dissections in 2% (2/99) of Marfan syndrome patients and in 2% (1/47) of EDS patients. Notably they reported no cerebral dissection in LDS at selection and there was no follow-up. In a cohort of 62 LDS III patients, one patient suffered from a neurovascular hemorrhage due to dissection [8]. Overall, neurovascular dissections in LDS III occur in 7-12% but only rarely seems associated with actual clinical impact.

Diedrich et al [12] reported higher arterial tortuosity in the familial aneurysm and connective tissue syndromes cases than the negative controls. In our study the vast majority of LDS III patients (84.6%) had neurovascular arterial tortuosity, while this is not commonly observed in the general population[13]. Rodrigues et al [9] even reported arterial tortuosity in all 25 LDS type I patients. Arterial tortuosity seems more prevalent in LDS than in patients with Marfan syndrome [12].

During a mean of 8.85 (1-11) years follow up, in 15.4% of our patients there was progression in the neurovascular abnormalities, from changes in arterial tortuosity to developing a new aneurysm. No change of the diameters was observed in the patients known with an aneurysm. It was to be expected that extreme tortuosity in the shape of kinking, could develop into an aneurysm or a dissection. We did not see extreme tortuosity developing in an aneurysm during follow up. A novel finding from our study is that arterial tortuosity, although prevalent in this population, remained reasonable stable over time.

A neurovascular clinical event was found in 7.7% during follow up, one patient needed a neurovascular intervention and one patient died of unknown cause. Of course we cannot prove this event was of neurovascular origin. It could also be caused by an aortic rupture, knowing that this patient had a stable aorta dilatation for 8 years. No proven neurovascular hemorrhage or ischemic stroke was observed in our patient group. In a retrospective study of LDS III patients of Regalado et al [7] 9.5% of the patients had a neurovascular event, such as rupture, or hemorrhage but they also included an aneurysm as an event.

A retrospective review of Hostetler et al [8] found at baseline in 6.5% of LDS III patients a neurovascular event, three individuals who underwent surgical repair of intracranial aneurysms and one individual died at the age of 56 years from subarachnoid hemorrhage. All the study groups are small, with less events if the studies contained more patients, pointing towards possible bias in including more severally ill patients. Larger prospective multicenter studies are clearly warranted.

It was to be expected that patients with TAA, AAA or small vessel aneurysm caused by a defective *SMAD3* gene, would also develop aneurysms in the neurovascular arteries. Therefore, we sought to investigate possible associations with the prevalence of TAA / AAA/small vessel aneurysm. However, we found no difference in prevalence of TAA, AAA or small vessel aneurysm, which is in concordance with the study of Regalado [7] et al, who described that *SMAD3* variants were not found in patients with a combination of TAA and intracerebral aneurysms or a combination of TAA, intracerebral aneurysms and AAA. On the other hand Loeys et al [14] described that vertebral and carotid artery dissection and cerebral bleeding have been observed in LDS III patients who had dilatation of the aortic root.

We did not find any significant difference in baseline characteristics between LDS III patients with and without neurovascular abnormalities. The difference in the amount of patients with a neurovascular aneurysm and TAA (11.5%) and without neurovascular aneurysm and TAA (57.7%) was not significant, probably because of our small study group and also here it is clear that larger studies are warranted. There was also no statistical difference in patients with (0.0%) and without (3.8%) neurovascular aneurysm and an AAA or with (23.0%) and without (15.4%) neurovascular aneurysm and small vessel aneurysm. Miyazawa [15] et al also found only 7% of patients known with an intracranial aneurysm to have AAA. Age, multiplicity of intracranial aneurysms, size of intracranial aneurysms, and current smoking were the independent risk factors they found, of having AAA and an intracranial aneurysm. We did not find these risk factors, maybe this was influenced by the higher mean age of the patients of Miyazawa et al of 76.7 years, whereas in our study the mean age was 38.4 years.

Since the clinical implications with possible risk of these abnormalities is yet unknown, we believe it is important to follow up these patients. Therefore, at least one CTA of the head and neck arteries should be done at the time of diagnosis and since our study did show development of new aneurysms, in our opinion, CTA's of the head and neck arteries should be repeated every 2-5 years, depending on the initial findings. Preferably the imaging surveillance is performed by specialized neurologists or neuro-radiologists. More research and longer follow-up is needed to investigate the clinical relevance of these

imaging findings and have better information on when to perform preventive treatment to reduce the risk for possible cerebral hemorrhage or ischemic stroke.

Study limitations

The main limitation of this study is the small sample size of patients with LDS type III (*SMAD3*). That was inevitable, as this syndrome is only recently discovered and relatively unknown. In our outpatient clinic we have another group of 14 patients (mean age of 23 years) with a high suspicion of LDS III. They decided not to do genetic testing yet, because of possible problems with their life insurance. These patients are relatives of patients in our study group (often children). Of these 14 patients, nine do have clinical features of LDS III. Neurovascular abnormalities were seen in five and thoracic aortic dilatation in 4 of these 9 patients, of whom 2 already underwent ascending aorta replacement. In the future hopefully we can include these patients in our cohort. Although the follow-up period is not short with 8.85 years, a longer follow-up is clearly needed to get better insight in the clinical relevance of our imaging findings.

Conclusion

The vast majority of LDS III patients have neurovascular tortuosity and a quarter has developed a neurovascular aneurysm or dissection, however clinical events were relatively rare. Larger prospective follow-up studies are warranted to determine progression over time and the clinical relevance of the observed neurovascular abnormalities.

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SUPPLEMENTAL FILE 1

Assessment of cerebral vasculature

All patients received CTA's of the head and neck arteries at baseline and every 3 years thereafter, or more often when clinically indicated. Baseline and follow up of neurovascular abnormalities were assessed by two dedicated radiologists. For all CT's Siemens 128 slice scanners were used. For all CTA's a standardized imaging protocol was used, all Multi-Detector-Row CTA images were transferred into a workstation equipped with dedicated 3D analysis software. Using the CT vascular package, a centerline was automatically obtained along the long axis of the blood vessel of interest and manually corrected when needed. The vessel lumen diameter was automatically calculated perpendicular to the centerline at the point of interest. The volume rendering 3-D reconstruction was automatically done for the whole carotid and vertebral artery with bone removal option.

The objective morphological measurements were extracted for the Internal Carotid Artery (ICA).

1. The actual vessel length (mm) along centerline was established for the ICA from the carotid bifurcation to the entrance in the skull base.
2. The ICA diameter (mm) at two points:
   - at midpoint of extracranial segment of ICA (between carotid bifurcation and skull base).
   - at point directly before the entrance in the skull base
3. The shortest distance (mm) of the extracranial ICA was measured as the straight line between the carotid bifurcation to the ICA entrance in the skull base (on three-dimensional multiplanar [coronal] plane view).
4. Tortuosity index (TI) calculated as the shortest distance between the ICA divided by real length of the ICA. Thus, a higher TI represents a more tortuous vessel.

The radiologists performed the ICA morphological classification on 3-D reconstructions proposed by Weibel and Fields [1]. The classification was as follows: tortuosity: S- or C-shaped course of the ICA; coiling: an exaggerated S-shaped curve or a circular configuration of the course of ICA; kinking: angulation of one or more segments of the ICA associated with stenosis (see Fig. 2). The extracranial internal carotid artery was classified as straight if the course of artery was straight and if none of the above-mentioned abnormality was seen. The degree of lumen stenosis in the carotid bifurcation was measured according to the European Carotid Surgery Trial (ECST) [2] and North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [2], perpendicular to the central lumen line.

To determine the abnormalities of the neuro-vasculature, the following arteries were analyzed: Bilateral internal carotid arteries (ICA); Bilateral anterior communicating arteries (ACOM); Bilateral middle cerebral arteries (MCA); Bilateral posterior communicating arteries (PCOM); Bilateral vertebral arteries (VA); Bilateral posterior inferior cerebellar arteries (PICA); Bilateral superior cerebellar arteries (SCA) and basilar artery (BA).

SUPPLEMENTAL FILE 2

Table 1a. Genetic Data

Patient	Published as	Transcript ID	Variant ID
1	c.861delG, p.Arg288fs	NM_5902.3	0000308567
2	c.861delG, p.Arg288fs	NM_5902.3	0000308567
3	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
4	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
5	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
6	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
7	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
8	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
9	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
10	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
11	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
12	c.401-6G>A, r.400_401insACAG	NM_5902.3	0000308566
13	c.859C>T, p.Arg287Trp	NM_5902.3	0000615471
14	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
15	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
16	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
17	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
18	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
19	c.859C>T, p.Arg287Trp	NM_5902.3	0000308566
20	c.741-742delAT, p.Thr247fs	NM_5902.3	0000308563
21	c.1045G>C, p.Ala349Pro	NM_5902.3	0000308554
22	exon 6 deletion c.659_871del	NM_5902.3	0000399285
23	c.1102C>T, p.Arg368*	NM_5902.3	0000308555
24	c.1102C>T, p.Arg368*	NM_5902.3	0000308555
25	15q22.3q23 microdeletion including SMAD3	NM_5902.3	0000399300
26	c.76C>T, p.Gln26*	NM_5902.3	0000831232

PART II

Thoracic aortic dissection and surgery

CHAPTER 4

Male-female Differences in contemporary elective ascending aortic surgery: Insights from the Netherlands Heart Registration

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Annals of Cardiothoracic Surgery, 2023

ABSTRACT

Background

Scientific research regarding male-female differences in ascending aortic surgery is scarce. The objective of this study was to identify male-female differences in presentation, treatment and peri-operative outcome in elective ascending aortic surgery.

Methods

Elective ascending aortic surgery procedures that took place in the Netherlands between 01/01/2013-31/12/2017 were identified from the Netherlands Heart Registration. Male-female differences in presentation, treatment characteristics, and in-hospital mortality and morbidity were explored.

Results

The study population consisted of 887 females (31%) and 1972 males (69%). Females were older (median age 67 versus 62 years, $p<0.001$), more often had chronic lung disease (12.3% versus 9.1%, $p=0.011$), NYHA class III-IV (21.5% versus 15.5%, $p=0.003$), and less often a history of PCI (3.2% versus 5.0%, $p=0.033$). Isolated supracoronary aortic replacement was performed in 47.7% of females versus 30.6% of males ($p<0.001$), and ascending aorta with root replacement in 40.6% of females versus 56.7% of males ($p<0.001$). Females more often underwent concomitant interventions of the aortic arch (33.1% versus 20.2%, $p<0.001$) and the mitral valve (8.2% versus 5.2%, $p=0.002$), and less often concomitant CABG (14.4% versus 19.1%, $p=0.002$). Overall in-hospital mortality was significantly higher in females (5.1% versus 2.7%, $p=0.003$). In multivariable regression analysis, being female was an independent risk factor for in-hospital mortality (OR 1.55, 95% confidence interval 1.02-2.37).

Conclusions

This nation-wide cohort shows clear differences between females and males in patient presentation, procedural characteristics, in-hospital outcomes, and risk factors for in-hospital mortality in elective ascending aortic surgery. Further exploration of these differences, and of modifiable within-male and within-female risk factors, may offer great opportunities in improving treatment and thereby outcomes for both males and females.

INTRODUCTION

The exact incidence of thoracic aortic aneurysm (TAA) remains uncertain because of its asymptomatic character, but is estimated to be 6-10 per 100,000 person years [1, 2]. The death rate due to aortic aneurysm in Western Europe in 2010 was estimated to be 7.68 per 100,000 [3]. As a result of improved diagnosis, monitoring and treatment options, morbidity and mortality have improved in recent years [4]. While there has been a lot of attention to male-female differences in diagnosis and surgical treatment of coronary artery disease, little is known about potential male-female differences in presentation, treatment and outcomes in TAA and current guidelines acknowledge the lack of male-female specific literature regarding aortic disease [5]. The scarcely available published evidence, often single center with a limited sample size, provides contradicting insights [6-8].

Knowledge of the differences between men and women in determinants of outcome is important to provide patient-tailored treatment decision-making. With this knowledge, hopefully, outcomes in both men and women can be improved. Therefore, the aim of this study was to identify male-female differences in diagnosis, treatment and in-hospital mortality and morbidity in contemporary (2013-2017) elective ascending aortic aneurysm surgery, using data from the Netherlands Heart Registration.

METHODS

Study design and patient selection

A retrospective analysis of data from the Netherlands Heart Registration (NHR) was performed. The NHR is a Dutch nationwide prospective registry that contains anonymized peri-operative patient data of all cardiothoracic surgical procedures and percutaneous cardiac interventions performed in the Netherlands. Approval from the board of the NHR was obtained on 18-01-2019 to analyze the requested dataset. The study was reported following the STROBE statement [9].

The NHR database was queried for all adult patients (≥18 years) undergoing thoracic aortic surgery between 01-01-2013 and 31-12-2017, totaling 6114 procedures. Exclusion criteria were isolated descending aortic surgery or isolated thoracic endovascular aortic repair (N=536 and N=14 respectively), isolated aortic arch surgery (N=85), no aortic surgery performed or type of surgery could not be determined (N=15 and N=14 respectively), cardiac transplant (N=1), duplicate patient (N=2), and non-elective surgery (urgent N=685, emergency/salvage N=1133, missing N=770). A total of 2859 patients undergoing elective

ascending aortic surgery, with or without concomitant cardiac or aortic surgery, were included.

Endpoints and definitions

The primary endpoint of this study was in hospital mortality stratified by sex. Secondary endpoints were patient characteristics, procedural characteristics, in-hospital morbidity, and risk factors for in-hospital mortality stratified by sex. The definitions of the NHR variables are available in Supplementary Table S1.

Statistical analysis

Descriptive statistical analyses

Normally distributed continuous variables were presented as mean ± standard deviation and compared using the Student's *t*-test. Skewed continuous variables were presented as median and interquartile range and compared using the Mann-Whitney U test. Normality of the distributions was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as counts and percentages and compared using the χ^2-test or the Fisher's exact test, as appropriate. The descriptive statistical analyses were performed on the original dataset.

Imputation of missing values

An imputed dataset was used for the exploration of risk factors for in-hospital mortality, using multivariable logistic regression modelling. The missing values were presented in tables 1-3. Missing values were assumed to be missing at random: inspection of missing data pattern plots was performed, and for variables with >5% missing associations between the missing values and the other variables eligible for the logistic regression analyses were investigated by student's t-tests and cross tabulation inspection. Assuming missing at random, multiple imputation was performed to impute missing covariate values for the logistic regression analyses[10]. Covariates exceeding 15% missing values were omitted from imputation and the logistic regression analysis. To prevent the induction of bias, we excluded for imputation those variables that are present after a treatment decision is made (e.g. procedural characteristics). The imputed variables were: age, sex, BMI, creatinine level, LVEF (categorized), chronic pulmonary disease, arterial pathology, prior cardiac or aortic surgery, neurological dysfunction, active endocarditis, recent myocardial infarction, prior PCI, pulmonary artery pressure and diabetes. Five imputed datasets were generated using 5 iterations each. The imputations were visually checked by strip plots and density plots.

Logistic regression analyses

The imputed datasets were used to develop the multivariable logistic regression models. Preoperative and procedural variables were eligible as covariates if they did not exceed 15% missing values, and if there were at least 10 events due to in-hospital mortality (for categorical variables: at least 10 events per category). Correlations between covariates were checked using Pearson and Spearman correlation coefficients, as appropriate. In the case of high correlation (between ±0.50 and ±1.0) the clinically most relevant variable was chosen. Variables with a p-value < 0.1 in univariate modelling were selected for inclusion in the multivariable model. A full multivariable model was chosen to be presented. The analyses were performed on all five imputed datasets and the results were aggregated. Odds ratio's (OR's) with corresponding 95% confidence intervals (95%-CI's) were reported.

To further explore male-female differences in risk factors for in-hospital mortality, multivariable logistic regression models for the male and female subpopulation were developed. These models were developed to explore male-female differences in both the independent risk factors, as well as in the weight of these risk factors for in-hospital mortality. For these models subsets of the imputed datasets were used: one subset was created of the female population and one subset of the male population. These subsets of the imputed datasets were then used to develop multivariable logistic regression models, as described above for the complete study population: preoperative and procedural variables were eligible as covariates if they did not exceed 15% missing values, if there were at least 10 events due to in-hospital mortality, and in the case of highly correlated covariates the clinically most relevant variable was chosen. Variables with a p-value < 0.1 in univariate modelling were selected for inclusion in the multivariable model, and a full multivariable model was presented. The analyses were performed on all five imputed datasets and the results were aggregated. Odds ratio's (OR's) with corresponding 95% confidence intervals (95%-CI's) were reported. Supplementary Figures S2-6 show missing data pattern plots and imputed data plots for the variables that were used in the multivariable logistic regression model.

All statistical analyses were performed in computing and statistical program *R* (The R foundation for Statistical Computing, Vienna, Austria. Version 3.6.1.) using packages "*glm*" and "*MICE*". A p-value < 0.05 was considered significant for all statistical tests.

Table 1 Patient characteristics of patients undergoing elective ascending aortic surgery

	Overall (N 2859)	Female (N 887, 31%)	Male (N 1972, 69%)	p-value	Missing F/M (%)
Age	64.00 [54.00-71.00]	67.00 [59.00-73.00]	62.00 [53.00-70.00]	<0.001	0/0
Body mass index (kg/m^2)	26.14 [23.85-29.04]	25.66 [22.79-29.00]	26.31 [24.30-29.04]	<0.001	5.3/4.2
Creatinine level (µmol/L)	84.00 [73.00-97.00]	72.00 [63.00-83.00]	88.00 [79.00-100.00]	<0.001	1.1/0.8
Creatinine (> 200µmol/L)	25 (0.9)	4 (0.5)	21 (1.1)	0.129	0/0
Logistic EuroSCORE	10.60 [6.35-17.19]	14.74 [9.35-21.68]	8.82 [4.79-14.48]	<0.001	0.3/0.3
Diabetes Mellitus	189 (6.8)	60 (7.0)	129 (6.7)	0.807	3.4/2.7
LVEF				0.205	0.6/0.8
- LVEF < 30%	62 (2.2)	13 (1.5)	49 (2.5)		
- LVEF 30-55%	2052 (72.3)	638 (72.3)	1414 (72.3)		
- LVEF > 55%	725 (25.5)	231 (26.2)	494 (25.2)		
Chronic pulmonary disease	289 (10.1)	109 (12.3)	180 (9.1)	0.011	0.5/0.2
Chronic arterial pathology	274 (9.6)	94 (10.6)	180 (9.1)	0.216	0.3/0.1
Neurological dysfunction	63 (2.2)	17 (1.9)	46 (2.3)	0.582	0.3/0.1
Active endocarditis	41 (1.4)	7 (0.8)	34 (1.7)	0.082	0.5/0.2
Recent myocardial infarction	34 (1.2)	7 (0.8)	27 (1.4)	0.061	0.3/0.2
PA pressure (mmHg)	25.00 [25.00-25.00]	25.00 [25.00-25.00]	25.00 [25.00-25.00]	0.812	1.2/1.5
Prior CVA	89 (4.6)	20 (3.3)	69 (5.1)	0.099	32.2/31.7
Dialysis	6 (0.3)	2 (0.3)	4 (0.3)	1	31.6/27.7
NYHA class				0.003	39.6/37.0
- I-II	1471 (82.7)	421 (78.5)	1050 (84.5)		
- III-IV	307 (17.3)	115 (21.5)	192 (15.5)		
CCS class IV	18 (0.9)	3 (0.5)	15 (1.0)	0.303	30.4/26.2
Prior PCI	118 (4.4)	26 (3.2)	92 (5.0)	0.033	7.6/6.9
Prior aortic surgery	246 (10.0)	80 (10.4)	166 (9.8)	0.663	13.5/14.1
Prior cardiac surgery	502 (17.6)	153 (17.3)	349 (17.7)	0.832	0.2/0.1

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. CCS: Canadian Cardiovascular Society. CVA: cerebrovascular accident. F = female. LVEF: left ventricular ejection fraction. M = male. NYHA: New York Heart Association. PA: pulmonary artery. PCI: percutaneous coronary intervention.

RESULTS

Patient characteristics

Table 1 displays preoperative patient characteristics for the entire cohort, and the female and male subcohorts. Females presented at an older age (median 67 [IQR 59-73] versus median 62 [IQR 53-70] years old, p <0.001), with a higher EuroSCORE (median 14.74 [IQR 9.35-21.68] versus median 8.82 [IQR 4.79-14.48], p<0.001), with more often chronic pulmonary disease (12.3% versus 9.1%, p=0.011), and a higher New York Heart Association (NYHA) class (class III-IV 21.5% versus 15.5%, p=0.003) compared to males. Males presented with a higher body mass index (BMI, median 26.3 [IQR 24.3-29.0] versus median 25.7 [IQR 22.8-29.0], p<0.001) and creatinine level (median 88 [IQR 79-100] versus median 72 [IQR 63-83], p<0.001).

Procedural characteristics

Table 2 displays procedural characteristics for the entire cohort, and the female and male subcohorts. Female patients underwent supracoronary ascendens replacement significantly more often (47.7% versus 30.6%, p<0.001), whereas male patients underwent aortic root and aorta ascendens replacement significantly more often (56.7% versus 40.6%, p<0.001). Female patients received concomitant aortic arch surgery (33.1% versus 20.2%, p<0.001) and mitral valve surgery (8.2% versus 5.2%, p=0.002) significantly more often, whereas male patients received concomitant CABG significantly more often (19.1% versus 14.4%, p=0.002).

In-hospital mortality and morbidity

Table 3 displays postoperative in-hospital mortality and morbidity. In-hospital mortality was significantly higher in female patients (5.1% versus 2.7%, p=0.003). Furthermore, female patients had a longer admission duration (median days 8 [IQR 6-12] versus median days 7 [IQR 5-10], p<0.001), more often had extended intubation (>24 hours, 7.7% versus 4.9%, p=0.004), and more often had urinary tract infections (3.2% versus 1.2%, p<0.001).

Risk factors in-hospital mortality

Table 4 shows the uni- and multivariable risk factor analysis for in-hospital mortality for the entire study population. Independent risk factors for in-hospital mortality were: older age (OR 1.04, 95%-CI 1.02-1.06), being female (OR 1.55, 95%-CI 1.02-2.37), chronic lung disease (OR 2.65, 95%-CI 1.64-4.30), previous cardiac or aortic surgery (OR 2.05, 95%-CI 1.25-3.35), and concomitant CABG and/or valve surgery (other than the aortic valve)(OR 2.82, 95%-CI 1.85-4.31).

Table 2 Procedural characteristics of patients undergoing elective ascending aortic surgery

	Overall (N 2859)	Female (N 887, 31%)	Male (N 1972, 69%)	p-value	Missing (% F/M)
Surgery type				<0.001	0/0
- Aortic root and ascendens replacement	1479 (51.7)	360 (40.6)	1119 (56.7)		
- Supracoronary ascendens replacement	1027 (35.9)	423 (47.7)	604 (30.6)		
- Ascendens replacement (location unknown)	353 (12.3)	104 (11.7)	249 (12.6)		
Aortic root and ascendens replacement	1479 (51.7)	360 (40.6)	1119 (56.7)	<0.001	
- without valve intervention	146 (5.1)	34 (3.8)	112 (5.7)		
- with biological prosthesis	650 (22.7)	190 (21.4)	460 (23.3)		
- with mechanical prosthesis	488 (17.1)	94 (10.6)	394 (20.0)		
- with homograft	10 (0.3)	4 (0.5)	6 (0.3)		
- with autograft	7 (0.2)	4 (0.5)	3 (0.2)		
- valve-sparing root replacement	178 (6.2)	34 (3.8)	144 (7.3)		
Supracoronary ascendens replacement	1027 (35.9)	423 (47.7)	604 (30.6)	<0.001	
- without valve intervention	481 (16.8)	236 (26.6)	245 (12.4)		
- with aortic valve plasty	56 (2.0)	26 (2.9)	30 (1.5)		
- with biological prosthesis	344 (12.0)	122 (13.8)	222 (11.3)		
- with mechanical prosthesis	145 (5.1)	38 (4.3)	107 (5.4)		
- with homograft	1 (0.0)	1 (0.1)	0 (0.0)		
Ascendens replacement (location unknown)*	353 (12.3)	104 (11.7)	249 (12.6)	0.001	
- without valve intervention	37 (1.3)	12 (1.4)	25 (1.3)		
- with aortic valve plasty	35 (1.2)	19 (2.1)	16 (0.8)		
- with biological prosthesis	183 (6.4)	56 (6.3)	127 (6.4)		
- with mechanical prosthesis	80 (2.8)	12 (1.4)	68 (3.4)		
- with homograft	1 (0.0)	0 (0.0)	1 (0.1)		
- with valve replacement, type unknown	17 (0.6)	5 (0.6)	12 (0.6)		
Concomitant arch surgery	692 (24.2)	293 (33.1)	399 (20.2)	<0.001	0.1/0
Concomitant descending aortic surgery	77 (2.7)	31 (3.5)	46 (2.3)	0.081	0/0
Concomitant CABG	505 (17.7)	128 (14.4)	377 (19.1)	0.002	0/0
Concomitant mitral valve surgery	176 (6.2)	73 (8.2)	103 (5.2)	0.002	0/0
Concomitant pulmonary valve surgery	13 (0.5)	4 (0.5)	9 (0.5)	1.000	0/0
Concomitant tricuspid valve surgery	59 (2.1)	25 (2.8)	34 (1.7)	0.064	0/0
Other concomitant surgery	209 (7.3)	87 (9.8)	122 (6.2)	0.001	0/0
Circulatory arrest performed	766 (26.8)	320 (36.2)	446 (22.6)	<0.001	0.3/0.1

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. CABG: coronary artery bypass grafting. CPB: cardiopulmonary bypass. F = female. M = male. *In the database it was unknown which parts of the ascending aorta were replaced exactly.

Table 5 shows the uni- and multivariable risk factor analysis for in-hospital mortality for the female and male subpopulations. For the female subpopulation, chronic lung disease (OR 3.00, 95%-CI 1.51-5.99) and concomitant CABG and/or valve surgery (other than the aortic valve)(OR 3.74, 95%-CI 1.97-7.10) were independent risk factors. For the male subpopulation, older age (OR 1.04, 95%-CI 1.01-1.07), chronic lung disease (OR 2.10, 95%-CI 1.05-4.18), arterial pathology (OR 2.34, 95%-CI 1.20-4.57), concomitant aortic arch surgery (OR 2.01, 95%-CI 1.08-3.71) and concomitant CABG and/or valve surgery (other than the aortic valve)(OR 2.08, 95%-CI 1.17-3.67) were independent risk factors.

Table 3 Mortality and morbidity outcome of patients undergoing elective ascending aortic surgery

	Overall (N 2859)	Female (N 887, 31%)	Male (N 1972, 69%)	p-value	Missing (% F/M)
In-hospital mortality	99 (3.5)	45 (5.1)	54 (2.7)	0.003	0/0
Admission in days	7.00 [5.00-11.00]	8.00 [6.00-12.00]	7.00 [5.00-10.00]	<0.001	0.2/0.4
Perioperative myocardial infarction				0.475	36/33.6
- One criterion	86 (4.6)	21 (3.7)	65 (5.0)		
- Two or more criteria	34 (1.8)	11 (1.9)	23 (1.8)		
Pneumonia	131 (5.2)	31 (4.0)	100 (5.8)	0.065	11.7/12.7
Urinary tract infection	46 (1.8)	25 (3.2)	21 (1.2)	<0.001	11.7/12.7
Reintubation during admission	83 (3.3)	34 (4.3)	49 (2.8)	0.070	11.6/12.8
Extended intubation (exceeding 24 hours)	165 (5.8)	68 (7.7)	97 (4.9)	0.004	0.6/0.4
Readmission to ICU	135 (4.8)	49 (5.6)	86 (4.4)	0.183	0.9/1.1
CVA with permanent damage	68 (2.4)	27 (3.1)	41 (2.1)	0.143	0.6/0.5
CVA without permanent damage	20 (0.8)	9 (1.2)	11 (0.6)	0.225	12.4/13.6
Renal failure	79 (2.8)	26 (3.0)	53 (2.7)	0.712	0.7/0.5
Gastrointestinal complications				0.832	0.6/0.4
- Unknown	2 (0.1)	0 (0.0)	2 (0.1)		
- Yes, type unknown	4 (0.1)	1 (0.1)	3 (0.2)		
- Bleeding	11 (0.4)	4 (0.5)	7 (0.4)		
- Yes, Other	23 (0.8)	9 (1.0)	14 (0.7)		
Vascular complications	18 (0.6)	6 (0.7)	12 (0.6)	0.802	0.9/0.5
Heart rhythm complications	964 (34.8)	313 (36.3)	651 (34.1)	0.282	2.7/3.3
Rethoracotomy				0.805	33.8/33.8
- Bleeding/tamponade	203 (10.7)	57 (9.7)	146 (11.2)		
- Cardiac	37 (2.0)	12 (2.0)	25 (1.9)		
- Other	8 (0.4)	2 (0.3)	6 (0.5)		
Deep sternal wound infection	7 (0.4)	1 (0.2)	6 (0.5)	0.445	37.8/38.4

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. CVA: cerebrovascular accident. F = female. ICU: intensive care unit. M = male.

Table 4 Uni- and multivariable logistic regression results of in-hospital mortality in the entire study population

	Univariate		Multivariable	
Risk factors	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (years)	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.06)	0.001
Female	1.90 (1.27-2.83)	0.002	1.55 (1.02-2.37)	0.041
Body mass index (kg/m^2)	0.99 (0.94-1.04)	0.656		
Creatinine (µmol/l)	1.00 (1.00-1.01)	0.263		
Left ventricular ejection fraction 30-55%*	1.22 (0.75-1.99)	0.427	1.18 (0.71-1.97)	0.530
Left ventricular ejection fraction < 30%*	2.92 (1.06-8.00)	0.039	2.51 (0.87-7.21)	0.089
Chronic lung disease	3.56 (2.25-5.64)	<0.001	2.65 (1.64-4.30)	<0.001
Arterial pathology	2.48 (1.51-4.14)	<0.001	1.51 (0.88-2.59)	0.135
Previous cardiac or aortic surgery	1.73 (1.12-2.72)	0.021	2.05 (1.25-3.35)	0.005
Aortic root replacement*	0.79 (0.51-1.25)	0.317		
Aortic ascendens replacement, location unspecified*	1.32 (0.73-2.36)	0.357		
Concomitant aortic arch surgery	1.84 (1.21-2.77)	0.005	1.53 (0.98-2.40)	0.061
Concomitant CABG and/or valve surgery (other than aortic valve)	3.35 (2.23-5.00)	<0.001	2.82 (1.85-4.31)	<0.001

*reference category is left ventricular ejection fraction >55%
**reference category is supracoronary replacement
CABG: coronary artery bypass surgery

DISCUSSION

This nation-wide cohort shows clear male-female differences in patient presentation, procedural characteristics, in-hospital mortality and morbidity, and risk factors for in-hospital mortality in contemporary elective ascending aortic surgery in The Netherlands.

Patient and procedural characteristics

Patient characteristics were significantly different between male and female patients, including known risk factors for cardiovascular surgery. It is obvious from the observed differences in patient characteristics that female patients are older, tend to present in a worse clinical condition with a higher NYHA class and more often chronic pulmonary disease, while male patients more often had a previous percutaneous coronary intervention (PCI). These differences are also reflected in the higher logistic EuroSCORE found in female patients.

The older age at the time of surgery has been found in previous studies [6, 7, 11] and can be attributed to biological factors, such as the protective effect of estrogen on cardiovascular diseases, causing a delayed aortic aneurysm incidence in female patients [12]. However, socio-cultural factors related to gender such as a delayed presentation due to patient and/or physician delay may also be a contributing factor , and remains to be explored as

Table 5 Uni- and multivariable logistic regression results of in-hospital mortality in the female and male subcohorts

	Female population				Male population			
	Univariate		Multivariable		Univariate		Multivariable	
Risk factors	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (years)	1.04 (1.00-1.07)	0.023	1.03 (1.00-1.06)	0.096	1.06 (1.03-1.09)	<0.001	1.04 (1.01-1.07)	0.005
Body mass index (kg/m^2)	1.01 (0.96-1.07)	0.619			0.96 (0.90-1.03)	0.328		
Creatinine (µmol/l)	1.01 (1.00-1.01)	0.094	1.01 (1.00-1.01)	0.103	1.00 (1.00-1.01)	0.347		
Left ventricular ejection fraction 30-55%*	1.39 (0.66-2.94)	0.389	1.38 (0.64-2.97)	0.418	1.12 (0.58-2.14)	0.748		
Left ventricular ejection fraction <30%*	4.53 (0.87-23.57)	0.073	2.72 (0.46-16.12)	0.272	2.59 (0.70-9.39)	0.154		
Chronic lung disease	3.97 (2.05-7.61)	<0.001	3.00 (1.51-5.99)	0.002	2.97 (1.54-5.75)	0.001	2.10 (1.05-4.18)	0.035
Arterial pathology	1.31 (0.54-3.19)	0.553			3.71 (1.97-6.96)	<0.001	2.34 (1.20-4.57)	0.013
Previous cardiac or aortic surgery	1.80 (0.92-3.53)	0.104			1.68 (0.91-3.10)	0.101		
Aortic root replacement**	1.46 (0.77-2.77)	0.242			0.58 (0.32-1.08)	0.088	0.93 (0.49-1.79)	0.840
Ascending aorta replacement, location unspecified**	1.14 (0.41-3.13)	0.805			1.48 (0.71-3.06)	0.295	1.99 (0.90-4.35)	0.086
Concomitant aortic arch surgery	1.25 (0.67-2.32)	0.492			2.20 (1.25-3.90)	0.007	2.01 (1.08-3.71)	0.027
Concomitant CABG and/or valve surgery (other than aortic valve)	4.76 (2.59-8.76)	<0.001	3.74 (1.97-7.10)	<0.001	2.61 (1.51-4.48)	<0.001	2.08 (1.17-3.67)	0.012

*reference category is left ventricular ejection fraction >55%

**reference category is supracoronary replacement

CABG: coronary artery bypass surgery

no evidence in the context of thoracic aortic aneurysm surgery is available in this regard. However, a delayed recognition by physicians in female patients has been observed in aortic dissection [13].

In the current study, aortic diameter at surgery was not available. However, as the study comprised elective surgical patients, we can assume the 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases were followed regarding timing of surgery [5]. However, in published literature, it has been shown that female patients undergo surgery at a larger body size indexed aortic diameter than male patients [7], and aortic dilatation rates in female patients are higher [14], both of which are risk factors for aortic dissection. Furthermore, population based studies show that female patients have higher out of hospital deaths caused by acute aortic dissection than male patients [15, 16]. Considering the above, it is possible worse outcomes due to aortic disease in female patients unfortunately remain undocumented. In the light of elective surgery, it is important to be aware of these differences, to prevent dissections through timely interventions.

The differences observed in the procedural characteristics might indicate different underlying pathophysiology of aneurysm development, as male patients more often underwent a procedure including the root, whereas female patients more often underwent a procedure without root replacement and with arch replacement. Sokolis et al. found differences between male and female patients in ascending thoracic aortic aneurysms in mechanics and matrix, which supports the possibility of different underlying pathophysiology [17]. Furthermore, male patients more often underwent concomitant CABG surgery which indicates more atherosclerotic disease in male patients, as observed by previous studies [6, 11].

Mortality and morbidity

We observed a higher unadjusted in-hospital mortality in female patients. Published literature on ascending aortic surgery shows contradicting estimates of male-female post-operative mortality differences [6-8, 11, 18]. However, these studies are usually single center with a limited sample size and concern diverging patient populations, for example including emergency surgery [7, 8, 18], or focusing on a specific surgical technique [11]. Beller et al. found a comparable short-term mortality between male and female patients undergoing elective ascending aortic aneurysm surgery, whereas Chung et al. found a higher mortality in female patients undergoing thoracic aortic surgery with deep hypothermic circulatory arrest [6, 18]. Beller and colleagues had a comparable population to ours, and although they did not find a significant difference in 30-day mortality, they had a smaller population, a smaller number of events, and there was a trend towards a significant difference (30-day mortality rate in males of 3.5%, in females 7.9%, p-value of 0.058) [6].

Female patients experienced more morbidity post-surgery: a longer admission time, more often extended intubation, and more urinary tract infections. Other adverse in-hospital outcomes were comparable. Awareness of the differences is important, in order to take preventative measures wherever possible (e.g. removing bladder catheters as soon as possible).

Risk factor differences between male and female patients for in-hospital mortality

Previous studies utilizing the NHR data in isolated mitral valve surgery, tricuspid valve surgery and combined aortic valve and CABG surgery have shown differences between male and female patients in risk factors and the weights of risk factors for in-hospital mortality [19-21]. This demonstrates the presence of differences and the importance to investigate these differences in an aortic surgery population.

The added value of our study is that it allows, due to its national multicenter character with a large sample size and a sufficient number of events to provide adequate power for a meaningful in-hospital mortality risk factor analysis. In multivariable testing, being female was an independent risk factor for in-hospital mortality. Older age, chronic pulmonary disease, previous cardiac or aortic surgery, and concomitant CAGB and/or valve surgery proved to be independent risk factors. Older age, chronic pulmonary disease, and concomitant mitral valve surgery were also more prevalent in female patients. Regardless of the causative factors underlying the higher observed mortality, we urge clinicians to be aware of these associations.

In this study, we indeed found that the risk factors and weights of the risk factors for in-hospital mortality differ between male and female patients. Beller et al. also found that the relevant risk factors for short-term mortality in ascending aortic aneurysm surgery differed between males and females (e.g. age and myocardial infarction in males, arch involvement and renal insufficiency in females) [6]. As the data used in our study was registered patient data, not all possible modifiable risk factors could be included in these analyses, especially aortic diameter at surgery and cardiovascular risk factors such as hypertension and hypercholesterolemia would be valuable to include in the analyses. However, it underlines the importance of further investigating modifiable risk factors to improve personalized clinical care for both male and female patients.

Relevance to patient centered clinical decision making and recommendations

It is likely that there are underlying pathophysiological differences in male and female patients, because comorbidities differ, location of aneurysms differ, and risk factors differ. We recommend more fundamental and translational science to investigate these

underlying pathophysiological differences, to aid in (preventive) clinical interventions and decision-making.

Furthermore, investigating the different clinical risk factors for male and female patients is equally important to aid *in* (preventive) clinical interventions and shared decision-making. Knowledge of specific risk factors can help clinicians to better inform patients of their risks and help patients make an informed decision fitting to their personal values. In this light, we recommend large dedicated multicenter prospective databases specifically set up for patients with thoracic aortic disease, regardless of their treatment trajectory, in order to follow patients over time. Such databases could aid in the further investigation of male-female differences in this specific patient group, including diagnoses, treatment, prognosis, time-to-event data, and include both clinical and non-clinical risk factors (such as aortic diameters before surgery, socio-cultural and economic factors).

Aside from important adverse clinical outcomes, health related quality of life (HRQOL) is an outcome important to the patient undergoing surgery. Prior to surgery, patients with thoracic aortic disease experience a lower health related quality of life, especially the female patients [22]. Furthermore, in-depth interviews showed that determinants of HRQOL included physical symptoms, coping strategies, impact on social and professional life, and disease-related knowledge. We recommend clinicians to be aware of these factors influencing HRQOL, in order to aid in shared decision-making for the individual patient.

Finally, good scientific practice includes the use of standardized terms and definitions. The terms sex and gender are often used interchangeably or incorrectly. We recommend the proper use of these terms [23].

Limitations

This study was a retrospective analysis of registered data. Missing values and mistakes could not be corrected for. Some variables had many missing values and this should be taken into account when interpreting data, e.g. 12.3% of the study population for whom it was not registered whether they received a supracoronary ascending aorta replacement or an ascending aorta replacement including the aortic root. Valuable information regarding aortic diameter and detailed disease etiology was not present in the registered data.

CONCLUSION

This nation-wide cohort shows clear male-female differences in patient presentation, procedural characteristics, in-hospital outcomes, and risk factors for mortality in contemporary elective ascending aortic surgery. Further exploration of these male-female

differences, and of modifiable within-male and within-female risk factors, offers great opportunities in improving treatment and thereby outcomes for both men and women.

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SUPPLEMENTARY TABLE S1

Data specification

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
4	CHIR-ID-60	Sex	1 = Male, 2 = Female, -1 = Unknown
6	CHIR-PAT-10	Height	Last known height in centimeters. Integer, 20 t/m 270, -1 = Unknown
7	CHIR-PAT-20	Weight	Last known weight in kilograms. Decimal, 0,3 t/m 250,0, -1 = Unknown
8	CHIR-PAT-30	Serum creatinine level	Last known creatinine level prior to surgery in µmol/l. Integer, 1 t/m 2000, -1 = unknown
9	CHIR-PAT-40	Diabetes	Diabetes mellitus. 0 = No 1 = Diabetes, treatment unknown 2 = Diabetes, No treatment 10 = Diabetes, treatment with diet 20 = Diabetes, oral medication 30 = Diabetes, treatment with insuline 90 = Diabetes, other -1 = Unknown
10	CHIR-PAT-50	Left ventricular ejection fraction	Last known LVEF prior to surgery. Integer, 1 t/m 99 (%) -1 = unknown
11	CHIR-PAT-60	Systolic arteria pulmonalis pressure	Integer, 10 t/m 120 (mmHg) -1 = unknown
12	CHIR-PAT-70	Chronic lung disease	Long-term use of bronchus dilation medication or steroids. 0 = No, 1 = Yes, -1 = unknown
13	CHIR-PAT-80	Extracardiac arterial vascular pathology	One or more of the following criteria: Claudicatio intermittens, Carotis occlusion or > 50% stenosis, Amputation due to arterial disease, prior or planned surgery of abdominal aorta, arteries of the limbs or carotid arteries. 0 = No, 1 = Yes, -1 = unknown
14	CHIR-PAT-90	Neurologic dysfunction	Neurologic dysfunction limiting daily functioning. 0 = No, 1 = Yes, -1 = Unknown
15	CHIR-PAT-100	Prior cardiac surgery	Prior cardiac surgery, requiring opening of the pericardium. 0 = No, 1 = Yes, -1 = Unknown
16	CHIR-PAT-110	Active endocarditis	Treatment with antibiotics for endocarditis at the time of surgery. 0 = No, 1 = Yes, -1 = Unknown
17	CHIR-PAT-120	Start date antibiotics for endocarditis	DD-MM-JJJJ
18	CHIR-PAT-130	Critical preoperative state	One or more of the following criteria: preoperative ventricular tachycardia or fibrillation at start of surgery, preoperative sudden death survivor, or preoperative CPR, preoperative ventilation prior to arrival at OR, preoperative administration of inotropes, preoperatively placed IABP, preoperative kidney failure (diuresis less than 10 ml/hour). 0 = No, 1 = Yes, -1 = Unknown
19	CHIR-PAT-140	Unstable angina pectoris	Angina pectoris requiring IV inotropes until arrival at OR. 0 = No, 1 = Yes, -1 = Unknown
20	CHIR-PAT-150	Recent myocardial infarction	Myocardial infarction within 90 days of surgery. 0 = No, 1 = Yes, -1 = Unknown
21	CHIR-PAT-160	Thoracic aortic surgery	Surgical intervention of the ascending aorta, aortic arch, or descending aorta. 0 = No, 1 = Yes, -1 = Unknown

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
22	CHIR-PAT-170	Post-infarction ventricle septum rupture	Surgery for post-infarction VSR, defined as a defect of the interventricular septum caused by a myocardial infarction. 0 = No, 1 = Yes, -1 = Unknown
23	CHIR-PAT-180	Logistic EuroSCORE	0,88 t/m 100,0 %
24	CHIR-PAT-190	Dialysis	Hemo- or peritoneal dialysis for kidney failure at the time of surgery, including CVVH for kidney failure. 0 = No, 1 = Yes, -1 = Unknown
25	CHIR-PAT-200	Impaired mobility	Impaired mobility due to musculoskeletal or neurological dysfunction. 0 = No, 1 = Yes, -1 = Unknown
26	CHIR-PAT-210	NYHA-class	1 = Class I;2 = Class II;3 = Class III; 4 = Class IV
27	CHIR-PAT-220	CCS- Class IV angina	0 = No, 1 = Yes, -1 = Unknown
28	CHIR-PAT-230	Urgency	10 = Elective, routine admission for surgery ;20 = Urgent, non-elective admission and requiring surgery within the same admission; 30 = Emergency, unplanned intervention within the same working day as admission;40 = Salvage, patient requiring CPR on the way to the OR or prior to anesthesia.
29	CHIR-PAT-240	Weight intervention	10 = Isolated CABG;11 = Single intervention (not CABG);20 = 2 interventions;30 = 3 or more interventions
30	CHIR-PAT-250	EuroSCORE II	0,50 t/m 100,0 %
31	CHIR-PAT-260	Prior CVA	CVA determined by a neurologist caused by an infarction of bleeding. 0 = No, 1 = Yes, -1 = Unknown
32	CHIR-PAT-270	Multiple coronary artery disease	At least 70% stenosis in two or more coronary arteries or first order side branches. 0 = No, 1 = Yes, -1 = Unknown
33	CHIR-PAT-280	Atrial fibrillation	Atrial fibrillation diagnosed in the period before surgery. 0 = No AF (sinus rhythm) 10 = Intermittend AF; 20 = Non-intermittend AF -1 = Unknown
34	CHIR-PAT-500	Prior PCI	Any PCI prior to surgery. 0 = No, 1 = Yes, -1 = Unknown
35	CHIR-PAT-510	Prior coronary artery surgery	Any coronary artery surgery prior to surgery. 0 = No, 1 = Yes, -1 = Unknown
36	CHIR-PAT-520	Prior valve surgery, including transcatheter interventions	Any valve intervention prior to surgery, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
37	CHIR-PAT-530	Prior aortic valve surgery	Any aortic valve intervention prior to surgery, including transcatheter intervention. 0 = No, 1 = Yes, -1 = Unknown
38	CHIR-PAT-540	Prior mitral valve surgery	Any mitral valve intervention prior to surgery, including transcatheter intervention.0 = No, 1 = Yes, -1 = Unknown
39	CHIR-PAT-550	Prior pulmonary valve surgery	Any pulmonary valve intervention prior to surgery, including transcatheter intervention 0 = No, 1 = Yes, -1 = Unknown
40	CHIR-PAT-560	Prior tricuspid valve surgery	Any tricuspid valve intervention prior to surgery, including transcatheter intervention 0 = No, 1 = Yes, -1 = Unknown

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
41	CHIR-PAT-570	Prior aortic surgery	Any aortic intervention prior to surgery, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
42	CHIR-PAT-580	Other prior cardiac surgery	Any other cardiac intervention that cannot be grouped into coronary, valve or aortic surgery, prior to surgery. 0 = No, 1 = Yes, -1 = Unknown
43	CHIR-INT-30	Accept date	Date at which patient was accepted for surgery during the heart team. DD-MM- YYYY; empty = missing/ unknown
44	CHIR-INT-40	Intervention date	Date of intervention, defined as moment of incision. DD-MM-YYYY; empty = missing/unknown
45	CHIR-INT-50	Planned intervention	10 = Isolated CABG, 20 = Isolated aortic valve surgery, 30 = CABG + aortic valve surgery, 90 = Other
46	CHIR-INT-60	Cessation of intervention	Cessation of intervention after incision. 0 = No, 1 = Yes, -1 = Unknown
47	CHIR-INT-70	ECC	Type of extracorporeal circulation used. 0=No ECC; 10=ECC type unknown, 20=Conventional ECC, 30=Minimal ECC
48	CHIR-INT-80	ECC cannulation	Type of cannulation used during ECC. 0 = None; 1 = Cannulation, type unknown; 10 = Classic cannulation; 20 = Left-left bypass; 90 = Other cannulation
49	CHIR-INT-90	Circulatory arrest	Temporary cessation of ECC, causing an arrest of blood circulation, including with the use of cerebral perfusion. 0 = No, 1 = Yes, -1 = Unknown
50	CHIR-INT-100	Operative approach	10 = Sternotomy 20 = Other non-minimally invasive techniques 30 = Mini-sternotomy 40 = Mini-thoracotomy 50 = Percutaneous 60 = Other minimally invasive
51	CHIR-INT-200	CABG	0 = No, 1 = Yes, -1 = Unknown
52	CHIR-INT-210	Arterial graft	Arterial graft used as bypass. 0 = No, 1 = Yes, -1 = Unknown
53	CHIR-INT-220	Distal anastomoses arterial	Total number of distal arterial anastomoses, excluding anastomoses between composite grafts (Y- and T-grafts). 0 = None; 1 t/m 9, -1 is unknown
54	CHIR-INT-230	LIMA	Use of left internal mammary artery as arterial graft. 0 = No, 1 = Yes, -1 = Unknown
55	CHIR-INT-240	RIMA	Use of right internal mammary artery as arterial graft. 0 = No, 1 = Yes, -1 = Unknown
56	CHIR-INT-250	Arteria Radialis	Use of left or right radial artery as arterial graft. 0 = No, 1 = Yes, -1 = Unknown
57	CHIR-INT-260	GEA	Use of left or right gastro-epiploic artery as arterial graft. 0 = No, 1 = Yes, -1 = Unknown
58	CHIR-INT-270	Other arterial graft	Use of other arterial graft. 0 = No, 1 = Yes, -1 = Unknown
59	CHIR-INT-280	Venous graft	Use of venous graft as bypass. 0 = No, 1 = Yes, -1 = Unknown
60	CHIR-INT-290	Number of distal venous anastomoses	Total number of distal venous anastomoses, excluding anastomoses between composite grafts (Y- and T-grafts). 0 = None; 1 t/m 9, -1 is unknown

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
61	CHIR-INT-300	Other coronary artery surgery	Other coronary artery surgery, during which no graft is used, with the intention of improving coronary blood flow, such as coronary ostium plasty. 0 = No, 1 = Yes, -1 = Unknown
62	CHIR-INT-310	Valve surgery	Surgery on any of the heart valves, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
63	CHIR-INT-320	Aortic valve surgery	Any aortic valve intervention, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
64	CHIR-INT-330	Aortic valve procedure	Type of aortic valve intervention. 0 = None;10 = Plasty;20 = Conventional replacement;21 =Transcatheter replacement type unknown;22 = Transcatheter replacement vascular;23 = Transcatheter replacement transapical;90 = Other
65	CHIR-INT-340	Aortic valve prosthesis	Type of prosthesis used. 0 = None;10 = biological prosthesis type unknown ;11 = biological prosthesis non-stented ;12 = biological prosthesis stented ;20 = Mechanical prosthesis ;30 = Homograft ;40 = Autograft
66	CHIR-INT-350	Mitral valve surgery	Any mitral valve intervention, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
67	CHIR-INT-360	Mitral valve procedure	Type of mitral valve intervention. 0 = None ;10 = Conventional plasty ;11 = Transcatheter plasty ;20 = Conventional replacement;21 =Transcatheter replacement;90 = Other
68	CHIR-INT-370	Mitral valve prosthesis	Type of prosthesis used. 0 = None ;10 = biological prosthesis type unknown ;11 = biological prosthesis stentless ;12 = Biological prosthesis stented ;20 = Mechanical prosthesis ;30 = Homograft
69	CHIR-INT-380	Pulmonary valve surgery	Any pulmonary valve intervention, including transcatheter interventions. 0 = No, 1 = Yes, -1 = Unknown
70	CHIR-INT-390	Pulmonary valve procedure	Type of pulmonary valve intervention. 0 = None ;10 = PLasty ;20 = Conventional replacement ;21 =Transcatheter replacement;90 = Other intervention
71	CHIR-INT-400	Pulmonary valve prosthesis	Type of prosthesis used. 0 = None;10 = Biological prosthesis type unkown;11 = Biological prosthesis stentless ;12 = Biological prosthesis stented ;20 = Mechanical prosthesis ;30 = Homograft
72	CHIR-INT-410	Tricuspid valve surgery	Any tricuspid valve intervention, including transcatheter interventions 0 = No, 1 = Yes, -1 = Unknown
73	CHIR-INT-420	Tricuspid valve procedure	Type of tricuspid valve intervention. 0 = None ;10 = Plasty ;20 = Replacement ;90 = Other intervention
74	CHIR-INT-430	Tricuspid valve prosthesis	Type of prosthesis used. 0 = None;10 = Biological prosthesis type unkown;11 = Biological prosthesis stentless ;12 = Biological prosthesis stented ;20 = Mechanical prosthesis ;30 = Homograft
75	CHIR-INT-440	Aortic surgery	Surgery on the ascending aorta, aortic arch, or descending aorta. 0 = No, 1 = Yes, -1 = Unknown

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
76	CHIR-INT-450	Approach aortic surgery	0 = None 10 = Open procedure 20 = simple (T)EVAR 21 = Complex (T)EVAR 30 = Combination open and (T)EVAR
77	CHIR-INT-460	Aorta ascendens	Type of surgery on ascending aorta. 0 = None ;1 = isolated aortic root ;2 = Aorta ascendens including aortic root; 3 = Aorta ascendens excluding aortic root ;9 = Aorta ascendens location unknown
78	CHIR-INT-470	Aorta ascendens pathology	0 = None 10 = Aneurysm 20 = Acute dissection 90 = Other
79	CHIR-INT-480	Aortic arch	Surgery on aortic arch, starting at arteria anonyma and ending after arteria subclavian sinistra. 0 = No, 1 = Yes, -1 = Unknown
80	CHIR-INT-490	Aortic arch pathology	0 = None 10 = Aneurysm 20 = Acute dissection 90 = Other
81	CHIR-INT-500	Aorta descendens	Surgery on descending aorta0 = No, 1 = Yes, -1 = Unknown
82	CHIR-INT-510	Aorta descendens pathology	0 = None 10 = Aneurysm 20 = Acute dissection 90 = other
83	CHIR-INT-520	Other cardiac surgery	Cardiac surgery other than coronary, aortic or valve surgery. 0 = No, 1 = Yes, -1 = Unknown
84	CHIR-INT-530	Cardiac Assist Device	0 = None;10 = VAD;20 = Total artificial heart;30 = Catheter Based Assist Device;40 = ECMO;90 = Other
86	CHIR-INT-550	Heart rhythm surgery	Including MAZE, PVI, PVISO, cryo-ablation, endocard resection. 0 = No, 1 = Yes, -1 = Unknown
87	CHIR-INT-560	Additional PM-/ICD	0 = No ;10 = Pacemaker;20 = ICD; 30 = Lead;90 = Other
88	CHIR-INT-570	Correction heart aneurysm	0 = No;10 = correction left ventricular aneurysm;90 = Other
89	CHIR-INT-580	Closure heart rupture	0 = No;10 = closure ventriular septum rupture;20 = closure free wall rupture;30 = closure ventricular septum rupture and free wall rupture.
90	CHIR-INT-590	Correction heart trauma	Such as a stab wound or during a trauma0 = No, 1 = Yes, -1 = Unknown
91	CHIR-INT-600	Removal of tumor	0 = No;10 = resection of intracardial tumor such as myxoma, lipoma or sarcoma. ;20 = Grawitz tumor;90 = Other, such as ventricular thrombosis or lead.
92	CHIR-INT-610	Myectomy or myotomy	0 = No, 1 = Yes, -1 = Unknown
93	CHIR-INT-620	Closure ventricular septum defect	0 = No, 1 = Yes, -1 = Unknown
94	CHIR-INT-630	Closure atrial septum defect	0 = No, 1 = Yes, -1 = Unknown
95	CHIR-INT-640	Congenital cardiac surgery	Not performed by a pediatric cardiac surgeon. Including bicuspid aortic valve, ASD, coronary fistula. 0 = No, 1 = Yes, -1 = Unknown
96	CHIR-INT-650	Other ventricular surgery	Non-congenital. 0 = No, 1 = Yes, -1 = Unknown
97	CHIR-INT-690	Other cardiac surgery	0 = No, 1 = Yes, -1 = Unknown
98	CHIR-INT-700	Description other cardiac surgery	Free text field

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
99	CHIR-INT-710	Non-cardiac surgery	Non.cardiac surgery performed in the same surgery, such as pulmonary or vascular surgery. 0 = No, 1 = Yes, -1 = Unknown
100	CHIR-INT-720	Pulmonary surgery	Both therapeutic as well as diagnostic. 0 = No, 1 = Yes, -1 = Unknown
101	CHIR-INT-730	Other non-cardiac surgery	0 = No, 1 = Yes, -1 = Unknown
106	CHIR-INT-3040	Preoperative haemoglobin value	Last measured Preoperative haemoglobin value 0,1 t/m 12,0 (mmol/l)
107	CHIR-INT-3210	Lowest temperature	Lowest temperature during surgery in celcius. 10,0 t/m 40,0 (°C) -1,0 = unknown
108	CHIR-INT-3220	ECC time	0 t/m 1000 (min.)
109	CHIR-INT-3230	Aortic clamp time	0 t/m 600 (min)
110	CHIR-INT-3240	Circulatory arrest time	0 t/m 120 (min.)
111	CHIR-INT-3300	Intra operative IABP	Use of an Intra-aortic balloon pump during surgery. 0 = No, 1 = Yes, -1 = Unknown
112	CHIR-INT-3340	RBC	Use of non-autologous red blood cell transfusion during hospital admission, both pre and postoperative. 0 = No, 1 = Yes, -1 = Unknown
113	CHIR-INT-3350	Blood plasma	Use of non-autologous red blood plasma transfusion during hospital admission, both pre and postoperative. 0 = No, 1 = Yes, -1 = Unknown
114	CHIR-INT-3360	Thrombocytes	Use of non-autologous red thrombocyte transfusion during hospital admission, both pre and postoperative. 0 = No, 1 = Yes, -1 = Unknown
115	CHIR-UIZ-10	In-hospital mortality	Regardless of duration of primary admission. 0 = No, 1 = Yes, -1 = Unknown
116	CHIR-UIZ-20	Mortality location	0 = Not applicable;10 = Operating room;20 = Intensive care unit;30 = Ward
117	CHIR-UIZ-40	New cardiac surgery during primary admission	0 = No, 1 = Yes, -1 = Unknown
118	CHIR-UIZ-50	Date of release	DD-MM-YYYY
119	CHIR-UIZ-60	Perioperative myocardial infarct	Using the STS definition. 0 = None 1 = One criterium 2 = Two or more criteria
120	CHIR-UIZ-70	Arm or leg wound complication	One or more of the following; surgical drainage, positive wound cultures, antibiotics use for wound infection. 0 = No, 1 = Yes, -1 = Unknown
121	CHIR-UIZ-80	Pneumonia	Pneumonia with positive cultures or lung infection. 0 = No, 1 = Yes, -1 = Unknown
122	CHIR-UIZ-90	Urinary tract infection.	UTI with positive urine culture. 0 = No, 1 = Yes, -1 = Unknown
123	CHIR-UIZ-100	Respiratory insufficiency	Respiratory insufficiency requiring reintubation. 0 = No, 1 = Yes, -1 = Unknown
124	CHIR-UIZ-110	Mechanical ventilation > 24 hours	0 = No, 1 = Yes, -1 = Unknown
125	CHIR-UIZ-120	Readmission to ICU or PACU	0 = No, 1 = Yes, -1 = Unknown

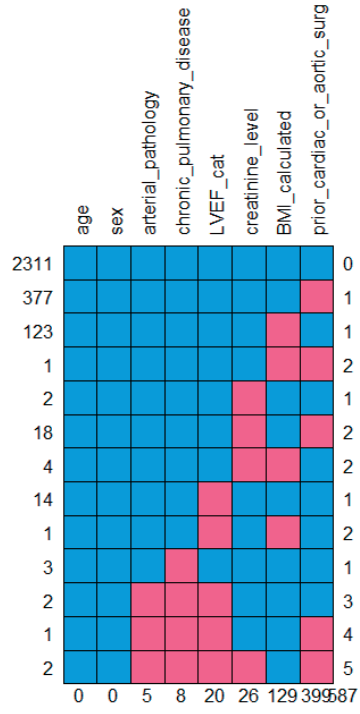
Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
126	CHIR-UIZ-130	CVA permanent	Postoperative CVA as diagnosed by a neurologist, with permanent neurological dysfunction. 0 = No, 1 = Yes, -1 = Unknown
127	CHIR-UIZ-140	CVA non-permanent	Postoperative CVA or TIA as diagnosed by a neurologist, without permanent neurological dysfunction. 0 = No, 1 = Yes, -1 = Unknown
128	CHIR-UIZ-150	Kidney failure	According to STS-criteria of kidney failure 0 = No, 1 = Yes, -1 = Unknown
129	CHIR-UIZ-160	Gastrointestinal complications	0 = No, 1 = Yes, -1 = Unknown
130	CHIR-UIZ-170	Vascular complications	According to VARC-2 definition, excluding CVA. 0 = No, 1 = Yes, -1 = Unknown
131	CHIR-UIZ-180	Heart rhythm complications	Any type of complication requiring treatment, such as AF, VF, VT. 0 = No, 1 = Yes, -1 = Unknown
132	CHIR-UIF-10	Rethoracotomy within 30 days	0 = None 10 = bleeding / heart tamponade 20 = cardiac complication 90 = other -1 = unknown
133	CHIR-UIF-20	Rethoracotomy date	DD-MM-YYYY
134	CHIR-UIF-30	Refixation sternum within 30 days	0 = No, 1 = Yes, -1 = Unknown
135	CHIR-UIF-40	Refixation sternum date	DD-MM-YYYY
136	CHIR-UIF-50	Deep sternal wound infection within 30 days	One or more of the following criteria; surgical drainage or refixation sternum. Positive wound culture. Antibiotic treatment. 0 = No, 1 = Yes, -1 = Unknown
137	CHIR-UIF-60	Deep sternal wound infection date	DD-MM-YYYY
138	CHIR-UIF-500	Mortality status	0 = Alive 1 = Deceased 2 = Lost to follow-up -1 = Unknown
139	CHIR-UIF-510	Date mortality status	DD-MM-YYYY
140	CHIR-UIF-600	Repeat myocardial infarction	A second myocardial infarction after surgery until max. 5 years after surgery. 0 = No, 1 = Yes, -1 = Unknown
141	CHIR-UIF-610	Repeat myocardial infarction date	DD-MM-YYYY
142	CHIR-UIF-620	Repeat myocardial infarction follow up date	DD-MM-YYYY
143	CHIR-UIF-630	CABG reintervention during follow-up	after surgery until max. 5 years after surgery. 0 = No, 1 = Yes, -1 = Unknown
144	CHIR-UIF-640	CABG reintervention date	DD-MM-YYYY
145	CHIR-UIF-650	CABG reintervention follow-up date	DD-MM-YYYY
146	CHIR-UIF-660	PCI reintervention during follow-up	after surgery until max. 5 years after surgery. 0 = No, 1 = Yes, -1 = Unknown
147	CHIR-UIF-670	PCI reintervention date	DD-MM-YYYY
148	CHIR-UIF-680	PCI reintervention follow-up date	DD-MM-YYYY
149	CHIR-UIF-690	Implementation new permanent pacemaker within 30 days	Including ICD. 0 = No, 1 = Yes, -1 = Unknown

Supplementary table 1. Continued

	Variable code NHR v2018.0.4	Variable name	Variable definition and values
150	CHIR-UIF-700	Aortic valve reintervention during follow up	Any type of reintervention after surgery until max. 5 years after surgery. 0 = No, 1 = Yes, -1 = Unknown
151	CHIR-UIF-710	Aortic valve reintervention date	DD-MM-YYYY
152	CHIR-UIF-720	Aortic valve reintervention follow up date	DD-MM-YYYY
153	CHIR-UIF-760	Reïntervention during follow-up	Any type of coronary reintervention or aortic valve reintervention after surgery until max. 5 years after surgery. 0 = No, 1 = Yes, -1 = Unknown
154	CHIR-UIF-770	Reïntervention date	DD-MM-YYYY
155	CHIR-UIF-780	Reïntervention follow-up date	DD-MM-YYYY

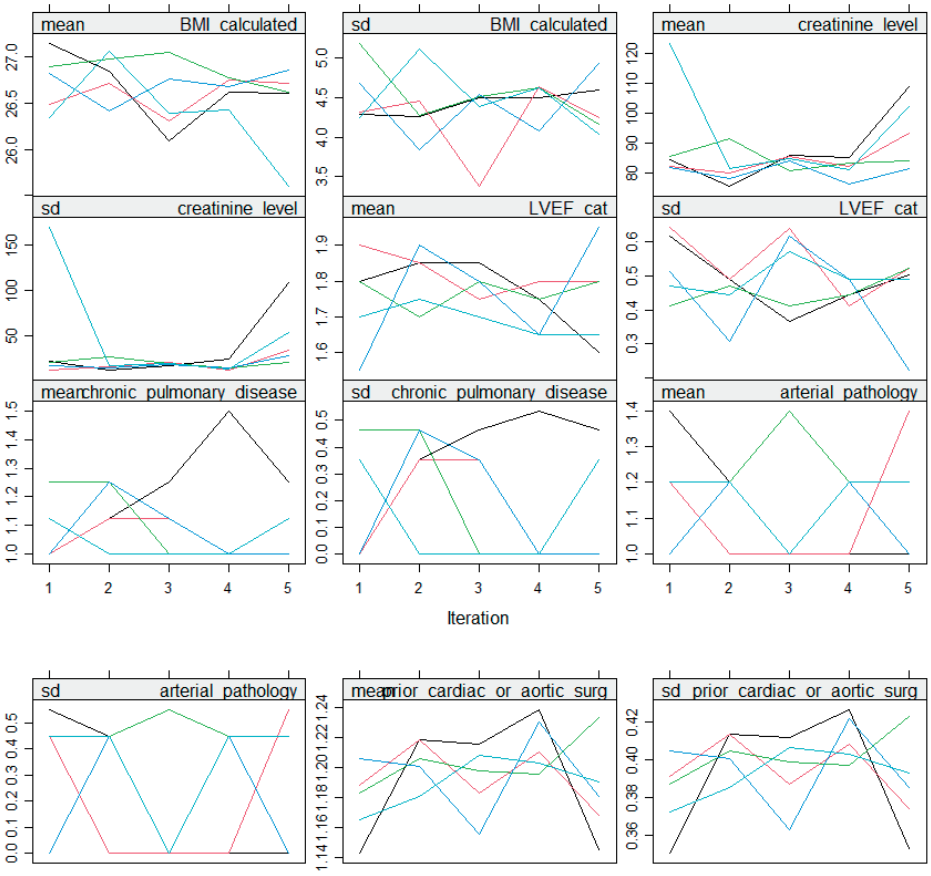
SUPPLEMENTARY FIGURE S2



Missing data pattern plot

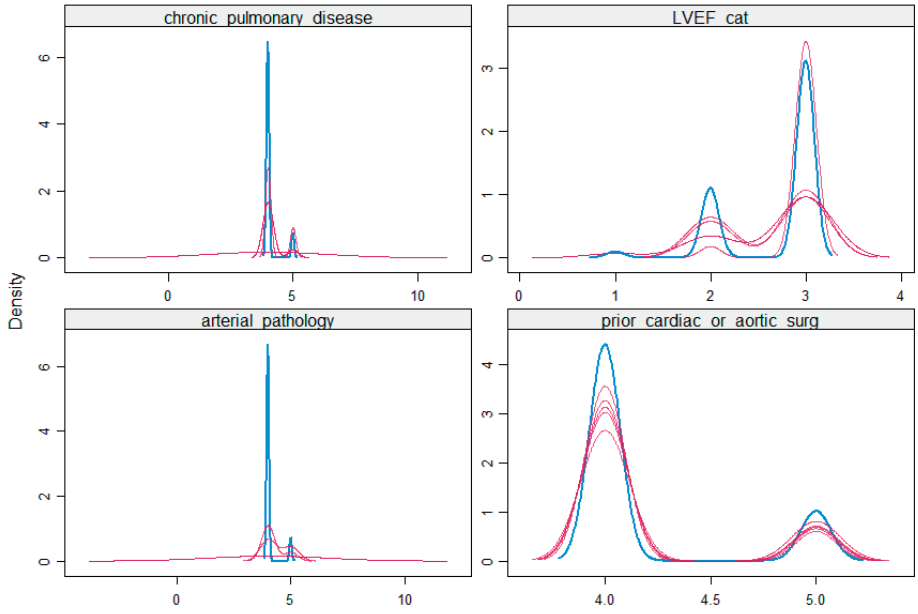
SUPPLEMENTARY FIGURE S3 AND S4

Imputation plots



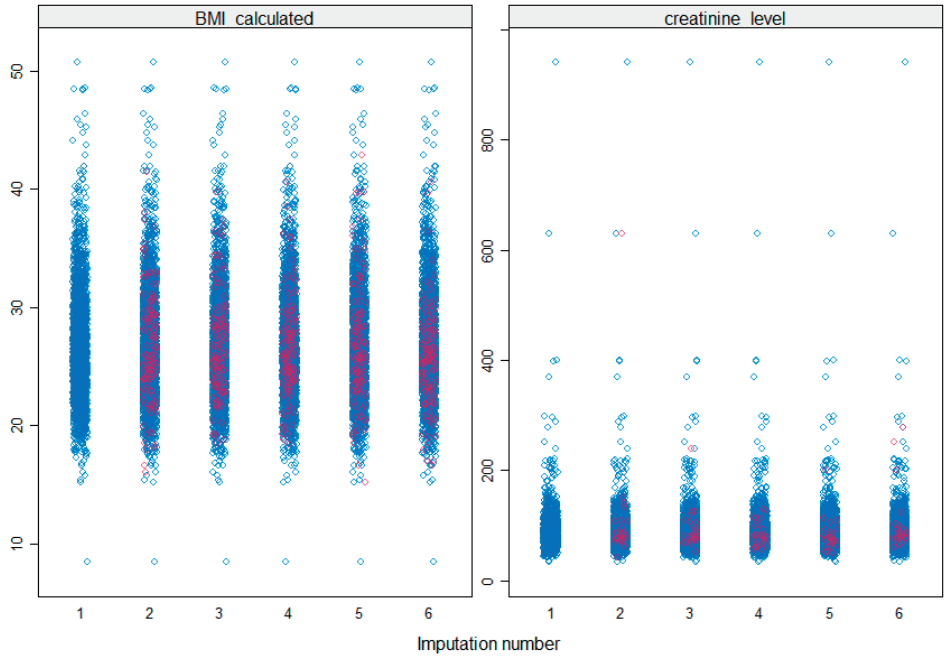
SUPPLEMENTARY FIGURE S5:

Density plot of imputed data



SUPPLEMENTARY FIGURE S6

Stripplot of imputed data



CHAPTER 5

5

Male-Female differences in presentation, management and outcome of acute type A aortic dissection: The DisSEXion Study

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ABSTRACT

Background

Acute Stanford type A aortic dissection (AD-A) is a cardiovascular emergency with a very high mortality. Male-female specific knowledge could optimize diagnosis and treatment, and reduce mortality.

Methods

We performed a multicentre retrospective cohort study including extensive information on presentation, imaging, management and outcomes of males and females diagnosed with AD-A. We collected data on all adult (≥18 years old) patients who were conservatively or surgically treated for acute Stanford type A dissection at four centres in The Netherlands (2007-2017). Clinical presentation, perioperative outcomes and mortality were compared between male and female patients. Logistic regression analysis was performed to identify factors associated with mortality.

Results

In total 893 patients were included (37.5% females). Females were significantly older at time of AD-A diagnosis (67.0 years [59.0-75.0] vs 61.0 years [53.0-69.0], p=<0.001) and more often had cardiovascular risk factors including hypertension, diabetes mellitus and chronic kidney disease (CKD). Females more often presented with severe hypotension (31.3% vs 19.4%, p<0.001), tamponade (26.0% vs 18.0%, p=0.014) and nausea (42.8% vs 28.8%, p=0.024). Data on thoracic aortic diameters was scarce (81% missing), but showed uncorrected maximal thoracic aortic diameters at presentation were not significantly different in males and females (53.0 [49.0-60.0] vs 53.0 [47.0-59.0], p=0.514). Aortic arch surgery was performed significantly more often in males (70.9% vs 62.9%, p=0.019). Logistic Euroscore was significantly higher in females compared to males (30.0 [20.1-47.4] vs 18.0 [9.3-30.3], p<0.001). Overall mortality was 19.5 %, and was not significantly different between males and females (18.5% vs 21.2%, p=0.362). Higher age, presence of chronic obstructive pulmonary disease, descending aortic surgery and concomitant surgical procedures showed a significant association with mortality in multivariable analysis.

Conclusions

Clinicians should be aware of the fact that females with AD-A are significantly older, more often present with nausea and severe hypotension. However, based on absolute aortic diameter, stage of disease progression seems comparable in males and females. Furthermore, Logistic Euroscore seems to overestimate mortality in females with AD-A, and should be used with caution.

INTRODUCTION

Acute Stanford type A aortic dissection (AD-A) is a cardiovascular emergency with an estimated incidence of about 12 cases per 100,000 inhabitants a year, with a male-female ratio of 2:1[1, 2]. The incidence has been increasing over the past decades and is often underestimated due to high numbers of pre-hospital mortality. Even after diagnosis, AD-A has a high 30-day mortality of 33-47%[3, 4]. Since emergency surgery is the treatment of choice, rapid diagnosis of AD-A is essential[5].

Patient specific knowledge on symptoms at presentation might improve fast diagnosis and reduce mortality. Thus far, there has been little attention for patient-specific factors in presentation with AD-A, especially concerning potential male-female differences. The number of females included in the majority of studies, seems comparable to the male-female ratio in population based studies[6]. Although only minimal data is available on the symptoms at presentation, so far there seem to be some differences between males and females in presentation with AD-A[6, 7]. Most importantly, females seem to present with AD-A at an older age[6, 8, 9].

Furthermore, findings on male-female differences in outcomes and mortality are contradictory. Several studies reported higher mortality rates in females with AD-A compared to males[6, 7, 10]. Higher mortality in females is also predicted by the (Logistic) Euroscore, which is a scoring system for the prediction of mortality in cardiac surgical patients on the basis of objective risk factors[11]. However, a recent systematic review and meta-analysis showed no significant difference between males and females[12].

Current guidelines do not specify any male-female or patient specific treatment options for either thoracic aortic aneurysm or dissection, and an absolute thoracic aortic diameter of 55 mm remains the threshold for preventive thoracic aortic aneurysm surgery for both males and females with non-syndromic thoracic aortic disease[5, 13]. It is uncertain whether body size should be taken into account when assessing aortic diameter. Correcting aortic diameters for height, weight or body surface area (BSA) has been proposed, especially in patients with Marfan and Turner syndrome [14, 15]. As females typically have a lower BSA it is important to know whether correcting for BSA should be done routinely.

Therefore, we performed a multicentre retrospective cohort study including extensive information of patients diagnosed with AD-A in four large centers in the Netherlands. The aim of this study was to explore male-female differences in clinical presentation, diagnostic imaging, management and outcomes after AD-A.

METHODS

Study population

We collected data on all adult (≥18 years old) patients who were conservatively or surgically treated for acute Stanford type A dissection at four secondary and tertiary care centres in The Netherlands between the 1st of January 2007 and the 31st of December 2017. "Acute" was defined as presentation within 14 days of symptom onset according to current guidelines[5]. Exclusion criteria were: chronic Stanford Type A dissections, asymptomatic patients of whom the time of symptom onset could not be determined; patients who underwent thoracic (aortic) surgery for a different indication than AD-A, iatrogenic dissection or aortic dissection secondary to trauma. Participating centres were Erasmus Medical Centre (Rotterdam, The Netherlands), Radboud University Medical Centre (Nijmegen, The Netherlands), Catharina Ziekenhuis Eindhoven (Eindhoven, The Netherlands) and St. Antonius Ziekenhuis (Nieuwegein, The Netherlands). This study was approved by the local ethics committees (MEC-2018-1535) of all participating centres, and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines.

Data collection

Patients were identified using the institutional aortic surgery databases. Additionally, an extensive search was performed using the hospitals' diagnosis registration systems. Files of all patients with diagnosis treatment codes (DBC's) related to any thoracic aortic disease were checked manually, to see if patients were eligible for inclusion. Data was collected using a standardized case report form (CRF) with an electronic Clinical Research Form application (OpenClinica, LLC, version 3.6). The CRF included information on patients' demographics, medical history, clinical presentation, imaging findings, surgical procedures, post-surgical complications and mortality. All variables and definitions are shown in supplemental file 1. Mortality and morbidity were defined as occurring within 30 days from diagnosis or before hospital discharge. Information on short-term survival was obtained from the Dutch municipal registries. Severity of valve regurgitation or valve stenosis was determined by echocardiography, and categorised as grade 1 (minimal), grade 2 (mild), grade 3 (moderate) and grade 4 (severe). BSA was calculated using the DuBois and DuBois formula[16]. Severe hypotension was defined as systolic blood pressure (SBP) <90 mmHg or medical treatment for severe hypotension at presentation or before surgery. Normal values for laboratory results were calculated using the Dutch association for Laboratory Medicine's reference values[17].

Statistical Analyses

The data-analysis was performed with statistical and computing programme *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 3.6.1). Normal distribution was assessed using the Shapiro-Wilk test. Descriptive analyses were used for the patient and procedural characteristics. The Students t-test was used to compare normally distributed continuous data and data were presented as mean and standard deviation (SD). The Mann-Whitney U-test was used to compared skewed continuous data, and the data were presented as median and interquartile range (IQR). For categorical data, the Chi-square test or Fisher exact test was used, and the data were presented as percentages or frequencies.

For the post-operative 30-day outcomes the events were presented as percentages of the total patient population and compared using the Chi-square test or the Fisher's exact test. Univariable and multivariable analysis was performed including only patients who were surgically treated for AD-A. Variables with a maximum of up to 15% of missing values were included in univariable logistic regression analysis for 30 day mortality. Collinearity was assessed using the Variance Inflation Factor. Stratified analyses were performed for females and males. Pre- and per-operative variables with a p-value < 0.20 in univariable analysis, which were considered clinically relevant, and showed low correlation with other variables were included in the multivariable model. Interaction terms were included for age and COPD, diabetes mellitus, chronic kidney disease. Multivariable logistic regression analysis was adjusted considering the four different hospitals of inclusion. Odds ratio's (OR) with their corresponding 95% confidence interval (CI) were presented. A P-value of <0.05 was considered statistically significant.

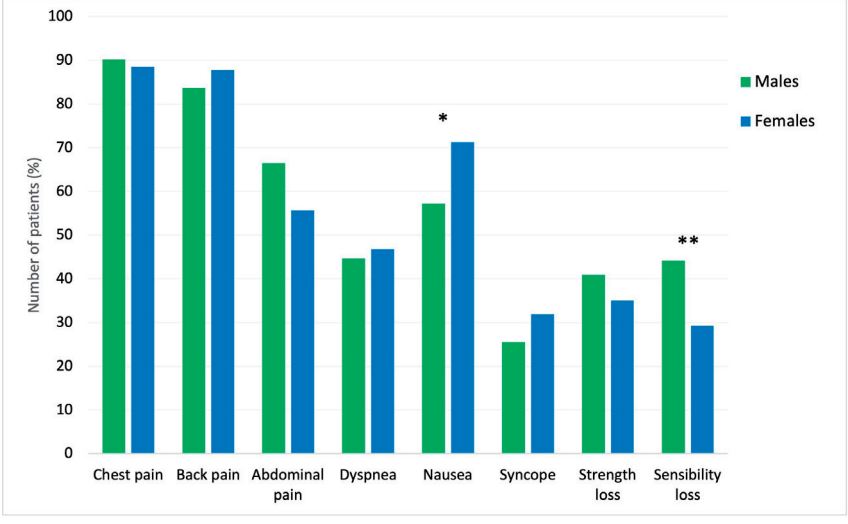

Figure 1. Male-female differences in symptoms at AD-A presentation

RESULTS

In total 893 patients were included (335 females, 37.5%). Male-female differences in baseline characteristics are shown in table 1. Females were significantly older at time of AD-A diagnosis (67.0 years IQR [59.0-75.0] vs 61.0 years IQR[53.0-69.0], p=<0.001). Females more often had cardiovascular risk factors, such as hypertension (58.5% vs 46.0%, p=0.001), diabetes mellitus (3.7% vs 1.3%, p=0.036) and chronic kidney disease (4.6% vs 1.8%. p=0.031).

Clinical presentation

Figure 1 shows symptoms reported by male and female patients at AD-A presentation. Symptoms most frequently reported were 'chest pain' and 'back pain' (80-90% of patients), which was not significantly different in males and females. Females reported nausea significantly more often (71.2% vs 57.2%, p=0.024), whereas males more often had sensibility loss (44.1% vs 29.3%, p=0.008). Time to diagnosis was not significantly different between males and females (p=0.249). Supplemental file 2 summarizes all male-female differences in symptoms and clinical presentation.

Imaging and laboratory results

Male-female differences in abnormal laboratory results at presentation are shown in figure 2. Creatinin Kinase was significantly more often elevated in males (21.5% vs 11.9%, p=0.009). Aspartate Transaminase and Alanine Transaminase were significantly more often elevated in females (15.7% vs 27.3%, p=0.001 and 11.0% vs 23.9%, p<0.001). A male-female comparison of the absolute values derived from diagnostic laboratory testing is shown in supplemental file 3. Supplemental file 4 shows a male-female comparison of diagnostic imaging results.

Surgery

As is shown in supplemental file 5, there were no significant differences in medical and surgical treatment of AD-A between males and females. With the exception of aortic arch surgery, which was performed significantly more often in males (70.9% vs 62.9%, p=0.019).

Mortality and morbidity

Post-operative mortality and morbidity is shown in table 2. We found an overall combined mortality of 19.5 % in conservatively and surgically treated patients, which was not significantly different between males and females (18.5% vs 21.2%, p=0.362). In patients who underwent surgery for AD-A (n=880, 98.5%) 30-day mortality was 18.3% (17.4% vs 19.8%, p=0.386). Results of the univariable logistic regression analysis for mortality are shown in supplemental file 6. Older age, COPD, hemi-arch replacement descending aortic surgery, concomitant procedures, post-operative myocardial infarction, bleeding and CVA

were potentially associated with higher mortality in univariable analysis. Additionally, a higher Logistic Euroscore was significantly associated with mortality (0.04 95%CI [0.03-0.05], p<0.001) in both males and females. In stratified univariable analysis hemi-arch replacement was associated with higher mortality in females only. Figure 3 shows older age, presence of COPD, descending aortic surgery and concomitant surgical procedures were associated with mortality in multivariable analysis.

Table 1. Baseline characteristics

	Total n= 893	Males n= 558	Females n= 335	P-value	Missing (%)
Age - years	63.0 [55.0-71.0]	61.0 [53.0-69.0]	67.0 [59.0-75.0]	<0.001**	0.2
Body surface area - m^2	2.0±0.2	2.1±0.2	1.8±0.2	<0.001**	30.8
History of hypertension	426 (50.7)	241 (46.0)	185 (58.5)	0.001**	5.9
History of diabetes mellitus	19 (2.2)	7 (1.3)	12 (3.7)	0.036*	3.2
History of COPD	64 (7.4)	34 (6.3)	30 (9.2)	0.147	3.0
History of CVA	43 (5.0)	23 (4.3)	20 (6.2)	0.278	3.4
History of chronic kidney disease	25 (2.9)	10 (1.8)	15 (4.6)	0.031*	3.2
Smoking ≥ 1 pack years				0.118	58.3
Currently	191 (51.3)	124 (51.5)	67 (51.1)		
In past	78 (21.0)	57 (23.7)	21 (16.0)		
History of dyslipidaemia	93 (10.9)	51 (9.5)	42 (13.1)	0.129	4.3
History of myocardial infarction	41 (4.7)	25 (4.6)	16 (4.9)	0.992	3.2
Prior aortic surgery	28 (3.2)	20 (3.7)	8 (2.5)	0.420	3.2
Prior cardiac surgery				0.276[e]	2.7
CABG	14 (1.6)	11 (2.0)	3 (0.9)		
MVR	6 (0.7)	6 (1.1)	0 (0.0)		
CABG + MVR	7 (0.8)	3 (0.6)	4 (1.2)		
PCI	14 (1.6)	10 (1.8)	4 (1.2)		
Other	7 (0.8)	4 (0.7)	3 (0.9)		
Aortic valve stenosis[1]	7 (2.5)	4 (2.5)	3 (2.5)	1.000	68.4
Aortic valve regurgitation[1]	18 (6.3)	12 (7.4)	6 (5.0)	0.565	68.2
Mitral valve regurgitation	10 (3.5)	8 (4.9)	2 (1.7)	0.257	68.3
Thoracic aortic aneurysm	70 (8.2)	37 (6.9)	33 (10.2)	0.115	4.0
Last measured aortic diameter - mm	47.4 [44.3-50.0]	47.9 [45.3-50.0]	47.0 [43.0-50.0]	0.387	93.1
Last measured diameter indexed for BSA - mm/m^2	23.7 [22.6-26.9]	22.8 [21.9-24.2]	26.8 [23.7-28.9]	<0.001**	94.4
Prior dissection or aneurysm in other arteries	35 (4.1)	26 (4.9)	9 (2.8)	0.186	3.6
Bicuspid aortic valve	21 (2.7)	15 (3.1)	6 (2.0)	0.483	13.4
Presence of connective tissue disease[a]	31 (10.1)	19 (9.6)	12 (11.0)	0.929	65.7

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.
COPD= Chronic Obstructive Pulmonary Disease; CVA= Cerebrovascular Accident including Transient Ischemic Attack; CABG= Coronary Artery Bypass Grafting; MVR= Mitral Valve Replacement; PCI= Percutaneous Coronary Intervention; BSA= Body Surface Area.
* Significant at the 0.05 level
** Significant at the 0.01 level

[e] Fishers exact test
[1] Defined as at least moderate stenosis / regurgitation.
[a] Confirmed connective tissue diseases: Marfan syndrome (7 patients), ACTA2 mutation (6 patients), Loeys-Dietz syndrome (3 patients), Turner syndrome (3 patients), Ehlers-Danlos syndrome (1 patient) and other mutations associated with connective tissue disorders (8) patients.

Table 2 Short-term mortality and morbidity.

	All N= 893	Male patients N=558	Female patients N= 335	P value	Missings (%)
Short-term mortality	174 (19.5)	103 (18.5)	71 (21.2)	0.362	0.0
Cause of death				0.244	1.5
Cardiac	46 (5.2)	31 (5.6)	15 (4.6)		
Neurologic	42 (4.8)	21 (3.8)	21 (6.4)		
Organ failure	22 (2.5)	14 (2.5)	8 (2.4)		
Aortic rupture	9 (1.0)	4 (0.7)	5 (1.5)		
Bleeding	16 (1.8)	12 (2.2)	4 (1.2)		
Sepsis	11 (1.2)	4 (0.7)	7 (2.1)		
Other	18 (2.0)	12 (2.2)	6 (1.8)		
Hospital stay - days	13.0 [8.0-23.0]	14.0 [9.0-24.0]	13.0 [8.0-23.0]	0.366	0.6
ICU stay - days	5.0 [3.0-10.0]	5.0 [3.0-11.0]	5.0 [3.0-9.0]	0.406	7.3
Ventilatory support	2.0 [2.0-5.0]	2.0 [2.0-5.0]	2.0 [2.0-5.0]	0.836	10.5
Early reoperation	257 (29.8)	174 (32.2)	83 (25.8)	0.054	3.5
Indication for reoperation				0.227	3.6
Bleeding event	170 (19.7)	116 (21.5)	54 (16.8)		
Tamponade	16 (1.9)	10 (1.9)	6 (1.9)		
Mediastinitis	8 (0.9)	6 (1.1)	2 (0.6)		
Valve dysfunction	2 (0.2)	0 (0.0)	2 (0.6)		
Other	37 (4.3)	25 (4.6)	12 (3.7)		
Gauze removal	18 (2.1)	14 (2.6)	4 (1.2)		
Infection	275 (32.4)	167 (31.4)	108 (34.0)	0.484	4.8
Bleeding	208 (24.5)	142 (26.6)	66 (20.8)	0.068	4.8
Sepsis	61 (7.2)	43 (8.1)	18 (5.7)	0.230	5.0
Myocardial infarction or ischemia	15 (1.8)	8 (1.5)	7 (2.2)	0.640	4.8
CVA after surgery	94 (11.2)	55 (10.5)	39 (12.4)	0.457	5.8
TIA after surgery	8 (0.9)	3 (0.6)	5 (1.6)	0.161[e]	5.5
Device implantation	11 (1.3)	6 (1.1)	5 (1.6)	0.811	4.6
Spinal cord lesion	15 (1.8)	12 (2.2)	3 (0.9)	0.188[e]	4.4
Lowest GFR	47.0 [28.0-60.0]	46.0 [25.0-60.0]	50.0 [32.0-60.0]	0.042*	18.5

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.
Short-term mortality= Intra– or postoperative death < 30 days or within hospital stay
Early reoperation= Reoperation < 30 days or during hospital stay
ICU= Intensive Care Unit; CVA= CerebrovascularAccident; TIA= Transient Ichemic Attack, GFR= Glomerular Filtration Rate.
* Significant at the 0.05 level
[e] Fishers exact test

Figure 4 shows mortality was comparable in males versus females in any of the Logistic Euroscore categories. The C-statistic was 0.73 in males and 0.71 in females. We found

no significant difference between males and females for all outcome measures except a lower glomerular filtration rate in males post-surgery (GFR; 46.0 IQR [25.0-60.0] vs 50.0 IQR [32.0-60.0], p=0.042). There was a trend towards more reoperations in males versus females (32.2% vs 25.8%, p=0.054).

DISCUSSION

This study investigates male-female differences in a large cohort of type A dissection patients. We found several important differences in presentation between males and females with AD-A: females presented with AD-A at older age, and more often presented with severe hypotension, nausea and tamponade. Moreover, absolute thoracic aortic diameter was not significantly different in males and females presenting with AD-A, whereas indexed aortic diameter was significantly larger in females. When comparing surgical techniques, aortic arch surgery was performed in males more often. Moreover, morbidity and mortality were comparable between males and females with AD-A.

Females more often presented with (severe) hypotension, nausea and tamponade compared to males. Similar findings were reported by Nienaber et al[6]. Females with acute coronary syndromes also present with nausea and syncope more often compared to males[18]. This similarity in symptoms suggests that females might experience and report these acute events differently than males. However, these symptoms may also partially be explained by the fact that in our study tamponade occurred more often in females. Furthermore, ASAT and ALAT values were more often elevated in laboratory results of females with AD-A, which might be due to hypotension and shock. It is important for physicians to be aware of females presenting more often with nausea, severe hypotension or tamponade, since this must trigger the physician to consider the diagnosis of AD-A. More male-female specific knowledge on presentation will optimize fast diagnosis and with that faster adequate treatment and hopefully better outcomes.

Currently, the absolute aortic diameter is used for timing of preventive aortic surgery, as is supported by clinical practice guidelines[19]. However, there has been debate about the use of absolute or corrected aortic diameters, especially in small females. The use of aortic diameter indexed for BSA, height or weight has been proposed[20]. Our findings showed no significant difference between males and females in absolute aortic diameter before and at the time of AD-A. This suggests absolute aortic diameter might be an equally good indicator of disease severity in both males and females, and the current practice of using absolute thoracic aortic diameter for timing of preventive aortic surgery might not need to be changed. However, it is important to keep in mind that aortic diameter changes when aortic dissection occurs, and that our data on aortic diameters had 80% missing's. Further

research investigating imaging of the thoracic aorta both before and at the time of AD-A presentation is important to provide better insight into the association between thoracic aortic diameter and the occurrence and outcomes of AD-A in males and females.

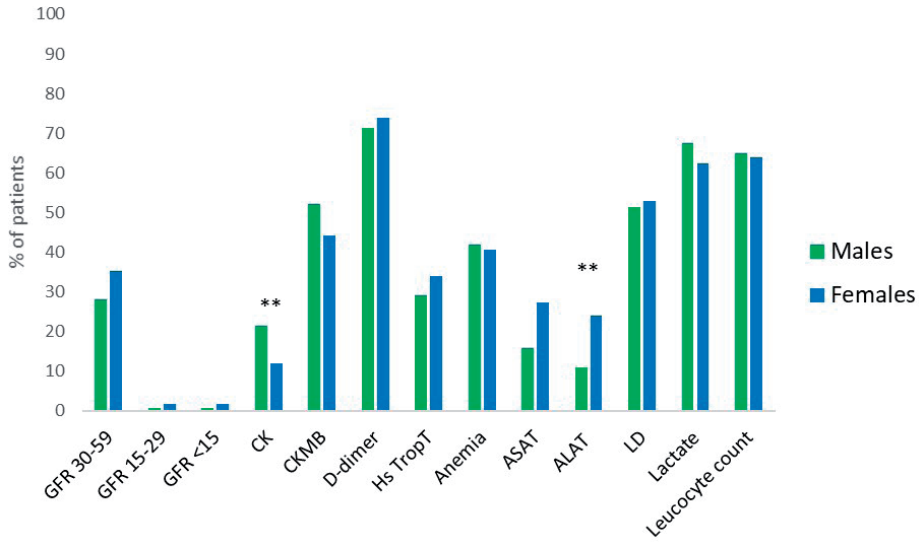

Figure 2 Comparison of abnormal laboratory results in males and females presenting with AD-A.
Data are presented as percentage of males and females with abnormal results.

AD-A: Acute Stanford type A thoracic aortic dissection; GFR= Glomerular Filtration Rate; CK= Creatinin Kinase; CKMB= Creatinin Kinase Myocardial Band; Hs TropT= High Sensitive Troponin T; ASAT= Aspartate Transaminase; ALAT= Alanine Transaminase; LD= Lactate Dehydrogenase.
** Significant at the 0.01 level

Higher short-term mortality in females compared to males with acute aortic dissection has been reported by Nienaber et al. and Smedberg et al.[6, 10]. On the contrary, several other studies reported no differences in short-term mortality after type A dissection[9, 21, 22]. In this large multicenter study, we found no significant difference and female sex was not associated with higher short-term mortality. Furthermore, mortality was not significantly different in males and females with the same Logistic Euroscore. Although the C-statistic suggests a reasonable prediction of mortality on both males and females of our population, females seem to have a lower observed mortality than the expected mortality as calculated by the Logistic Euroscore. In the Logistic Euroscore model the female factor predicts higher mortality. However, in our logistic regression analysis female sex was not associated with mortality. These findings suggest that in patients with AD-A, female sex should not lead to a higher Logistic Euroscore, which is in line with previous reports stating mortality as predicted by the Euroscore is less accurate in patients receiving aortic surgery, due to the limited amount of aortic surgery patients included in the original score development[23]. Moreover, in contrast with the Logistic Euroscore we found no significant

association between mortality and previous cardiac surgery or chronic kidney disease for patients with AD-A. Univariable analysis (supplemental file 6) showed a stronger association between chronic kidney disease (CKD) and mortality for females compared to males as earlier described by Friedrich et al[9]. This suggests a history of CKD as a risk factor should be noted with extra caution in females. In conclusion, we believe the Logistic Euroscore should be used with caution, especially in females with AD-A.

Study Limitations

This study has several limitations. First, the study has a retrospective character. For this reason, there were missing data. Because of this fair amount of missing data, sample size was reduced, and multivariable modelling was limited. Second, only patients who were diagnosed with AD-A were included in the study. Therefore, mortality might be underestimated, since only patients who reached the hospital alive and received the diagnosis of AD-A were included, which has been estimated to be about 70% of patients with any aortic dissection (Stanford type A and B)[10]. It is unknown whether male-female differences are a crucial factor which determines whether patients reach the hospital alive, and are diagnosed with AD-A.

CONCLUSIONS

In order to optimize fast diagnosis and treatment of AD-A, clinicians should be aware of the fact that females with AD-A are significantly older, and more often present with nausea, severe hypotension and tamponade compared to males. Moreover, absolute aortic diameter seems to be an equally good indicator of disease progression in males and females. Assuming males and females have equal chances to reach the hospital and receive the diagnosis of AD-A, our results suggest taking into account body size by correcting aortic diameter for BSA for timing of preventive aortic aneurysm surgery might not be indicated, especially since mortality was not different between males and females. Moreover, the Logistic Euroscore seems to overestimate short-term mortality in females with AD-A, and should be used with caution.

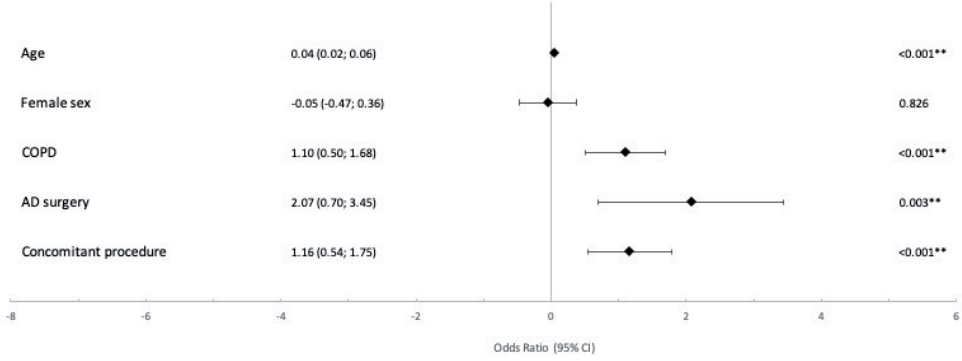

Figure 3 Final multivariable model including factors associated with 30-day mortality

Continuous data are presented as odds ratio (95% confidence interval).
COPD= Chronic Obstructive Pulmonary Disease; AD= Descending Aorta.
** Significant at the 0.01 level

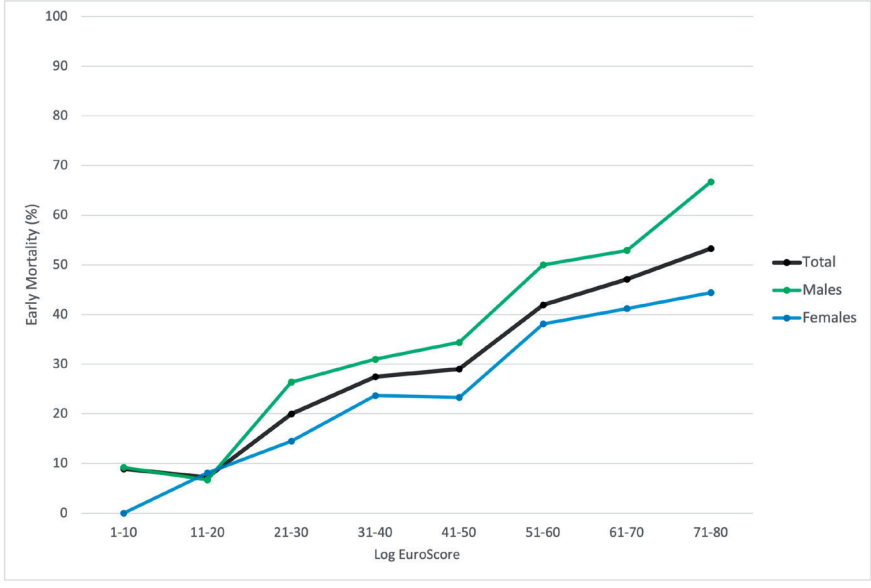

Figure 4 Observed versus expected 30-day mortality according to the Logistic Euroscore.

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SUPPLEMENTAL FILE 1

Definitions of variables as defined in case report form.

Definitions of variables regarding the patient characteristics

Variable	Unit	Definition
Age at presentation	years	Age (at time of diagnosis)
Body surface area	m^2	
Prior aortic surgery		Prior aortic surgery reported in patient history
Recent myocardial infarction		(N)STEMI < 90 days of presentation
History of myocardial infarction		(N)STEMI > 90 days before presentation
History of aortic valve stenosis		Known aortic valve stenosis categorised as: grade 1 (minimal), grade 2 (mild), grade 3 (moderate) and grade 4 (severe).
History of aortic valve regurgitation?		Known aortic valve regurgitation categorised as: grade 1 (minimal), grade 2 (mild), grade 3 (moderate) and grade 4 (severe).
Mixed aortic valve disease		Known aortic stenosis and regurgitation of at least grade 2 or higher.
History of mitral valve regurgitation		Known mitral valve regurgitation, categorised as grade 1 (minimal), grade 2 (mild), grade 3 (moderate) and grade 4 (severe).
History of hypertension		Known hypertension in patient history or medical treatment for hypertension.
History of diabetes mellitus		Known diabetes mellitus in patient history or medical treatment for diabetes mellitus.
History of COPD		Any history of Chronic Obstructive Pulmonary Disease that required medical treatment or FEV1<70%.
History of CVA/TIA		Cerebrovascular accident or transient ischemic attack in patients medical history.
History of chronic kidney disease		History of chronic kidney disease in medical history.
Smoking > 1 pack years		Currently smoking or > 1 pack year in past.
History of hyperlipidaemia		Medical treatment for hyperlipidaemia or in medical history.
Known chronic thoracic aortic dissection		Known chronic thoracic aortic dissection in medical history.
Known thoracic aortic aneurysm prior to presentation		Thoracic aortic diameter of ≥ 40 mm.
Last measured maximum aortic diameter	mm	Last measured thoracic aortic diameter.
Prior dissection or aneurysm in a major artery other than the thoracic aorta		Known dissection or aneurysm in a major artery other than the thoracic aorta.
History of pregnancy		Only for: Female patients < 50 y/o at presentation.
Bicuspid aortic valve		Presence of bicuspid aortic valve, known in patient history or seen in the operation theatre.
Presence of connective tissue disease		Known in patient history or genetic testing performed after treatment for the aortic dissection.

Definitions of variables regarding the clinical presentation

Variable	Unit	Definition
Abrupt onset of symptoms		Abrupt onset of symptoms described in patient status. If not reported the variable is registered as unknown.
Onset of symptoms during exercise		Onset of symptoms during physical activity or sports / exercise. If not reported the variable is registered as unknown.
Chest pain		As reported in patient file. If not reported the variable is registered as unknown.
Back pain		As reported in patient file. If not reported the variable is registered as unknown.
Abdominal pain		As reported in patient file. If not reported the variable is registered as unknown.
Radiating pain		As reported in patient file. If not reported the variable is registered as unknown.
Migrating pain		As reported in patient file. If not reported the variable is registered as unknown.
Type of pain		As reported in patient file. If not reported the variable is registered as unknown.
Dyspnoea		As reported in patient file. If not reported the variable is registered as unknown.
Nausea		As reported in patient file. If not reported the variable is registered as unknown.
Collapse		As reported in patient file. If not reported the variable is registered as no.
Sensibility loss		As reported in patient file. If not reported the variable is registered as unknown.
Loss of muscle strength		As reported in patient file. If not reported the variable is registered as unknown.
NYHA classification at presentation		New York Heart Association classification. If patient reported dyspnoea in rest at the emergency room, patients were classified NYHA 4. If patients did not report dyspnoea patients were classified NYHA 1. If dyspnoea was not described in patients' medical records, NYHA classification was unknown.
CCS classification at presentation		Canadian Cardiovascular Society classification. If patient reported chest pain in rest at the emergency room, patients were classified CCS. If patients did not report chest pain patients were classified CCS 1. If chest pain was not described in patients' medical records, CCS classification was unknown.
Severe hypotension at presentation		SBP <90 mmHg or medical treatment for severe hypotension at presentation or before surgery. If not reported the variable is registered as no.
Tamponade at or after presentation		As reported in patient file, if not reported the variable is registered as no.

Definitions of variables regarding the clinical presentation (continued)

Variable	Unit	Definition
CVA / TIA at presentation or before surgery		As reported in patient file, if not reported the variable is registered as no.
Resuscitation needed pre-surgery		As reported in patient file, if not reported the variable is registered as no.
Difference in right / left arm systolic blood pressure		Difference of >20 mmHg between right and left arm blood pressure.
Logistic EuroSCORE		Calculated on http://www.euroscore.org/calcold.html
Duration onset symptoms until diagnosis	hours	If reported in patients' medical record. Divided into four categories: <6 hours, 6-12 hours, 12-24 hours, and > 24 hours. If there was no information about time to diagnosis, variable was registered as unknown.
Blood pressure at presentation	mmHg	Normotensive: Systolic 90-140 mmHg, diastolic 60-90 mmHg Hypotensive: Systolic <90 mmHg or diastolic <60 mmHg Hypertensive: Systolic >140 mmHg or diastolic >90 mmHg
Hearth rhythm registered on electrocardiogram.		Sinus rhythm (60-100 bpm), sinus bradycardia (<60 bpm), sinus tachycardia (>100 bpm), supraventricular tachycardia, paced rhythm, ventricular tachycardia/ fibrillation or other. If not reported the variable is registered as unknown.
Any signs of ischemia on ECG		As reported by ECG machine or reviewed and reported by a physician.
Left ventricular ejection fraction (LVEF)		Good (> 55%), reduced (44-55%), moderate (30-45%), poor (<30%)
Transthoracic echocardiography (TTE) performed		Only if performed after admittance and before surgery. As reported in patient file. If not reported the variable is registered as no.
CT-scan performed before surgery		Only if performed after admittance and before surgery
Transoesophageal echocardiography (TEE) performed		Only if TEE was performed before cardiopulmonary bypass.
Aortic regurgitation at presentation		As reported in patient file, mild, moderate or severe. If not reported the variable is registered as unknown.
Maximum aortic diameter	mm	Maximum aortic diameter measured at presentation.
Maximum indexed aortic diameter (BSA)	mm/m^2	Maximum aortic diameter measured at presentation indexed for BSA.
Haemoglobin level	mmol Fe/L	Only if measured after admittance and before surgery.
Glomerular filtration rate	ml/min	CKD-EPI eGFR, maximum 1 year before admittance
Creatinine	micromole/L	Only if measured after admittance and before surgery
Troponin T level	microgram/ mL	Highest measured level after admittance and before surgery
CK level	U/L	Only if measured after admittance and before surgery
CKMB level	microgram/L	Highest measured level after admittance and before surgery

Definitions of variables regarding the clinical presentation (continued)

Variable	Unit	Definition
ASAT level	U/L	Only if measured after admittance and before surgery
ALAT level	U/L	Only if measured after admittance and before surgery
LDH level	U/L	Only if measured after admittance and before surgery. If measured before 04/10/2010, LDH was converted from an old LD measurement using the following formula: "LDH=0,5553 x LDH-old – 5,8296"
C-reactive protein level	mg/L	Highest measured level after admittance and before surgery
D-dimer level	microgram/ mL	Highest measured level after admittance and before surgery
Leukocyte level	*10^9/L	Only if measured after admittance and before surgery
Lactate level	mmol/L	Only if measured after admittance and before surgery
Surgery performed or attempted		If surgery was performed or attempted, then yes. If surgery was not performed or attempted, then no.

Definitions of variables regarding the postoperative hospital stay

Variable	Unit	Definition
Short-term mortality		Death within 30 days or before hospital discharge. Pre-surgery, in operating theatre or post-surgery.
Cause of in hospital death		Cardiac, neurologic, organ failure, aortic rupture, bleeding, sepsis or 'other' cause.
Number of days the patient was admitted	days	Total time in days from admission until discharge
Number of days in intensive care unit (ICU) after surgery	days	Number of days patient was on ICU after surgery.
Reoperation needed		Reoperation during admission or within 30 days.
Indication for reoperation		Bleeding event, tamponade, mediastinitis, mechanical sternum dehiscence, non-structural valve dysfunction, non -operated valve dysfunction or 'other' indication.
Diagnosis of any infection after surgery?		During admission or within 30 days after surgery.
Diagnosis of sepsis after surgery?		During admission or within 30 days after surgery.
Myocardial infarction or ischemia after surgery		During admission or within 30 days after surgery.
CVA diagnosed after surgery?		During admission or within 30 days after surgery.
TIA after Surgery?		During admission or within 30 days after surgery.
Spinal cord lesion after surgery		During admission or within 30 days after surgery.
Lowest eGFR measured during admittance after surgery?		Lowest CKD-EPI eGFR during admission or within 30 days after surgery.

SUPPLEMENTAL FILE 2

Male-female differences in clinical presentation

	All N=893	Male patients N= 558	Female patients N= 335	P value	Missing
Any symptoms	689 (97.2)	429 (97.7)	260 (96.3)	0.379	20.6
Abrupt onset	450 (98.5)	283 (98.3)	167 (98.8)	1.000[e]	48.8
During exercise	78 (27.7)	55 (31.1)	23 (21.9)	0.127	68.4
Type of pain				0.290	70.1
No pain	11 (4.1)	7 (4.1)	4 (4.1)		
Tearing	26 (9.7)	21 (12.4)	5 (5.2)		
Sharp	68 (25.5)	43 (25.3)	25 (25.8)		
Oppresive	162 (60.7)	99 (58.2)	63 (64.9)		
Radiating pain	268 (75.1)	168 (76.4)	100 (73.0)	0.555	60.0
Migrating pain	76 (47.2)	49 (49.5)	27 (43.5)	0.566	82.0
NYHA class				0.925[e]	75.3
I	135 (61.1)	87 (61.7)	48 (60.0)		
II	7 (3.2)	5 (3.5)	2 (2.5)		
III	4 (1.2)	3 (2.1)	1 (1.2)		
IV	22 (6.6)	46 (32.6)	29 (36.2)		
CCSclass				0.178[e]	62.7
I	41 (12.3)	29 (13.9)	12 (9.7)		
II	4 (1.2)	4 (1.9)	0 (0.0)		
III	22 (6.6)	11 (5.3)	11 (8.9)		
IV	266 (79.9)	46 (32.6)	29 (36.2)		
BP difference	110 (38.7)	77 (42.3)	33 (32.4)	0.127	68.2
BP					27.8
Hypotensive	196 (30.4)	97 (24.6)	99 (39.4)	<0.001	
Normotensive	327 (50.7)	215 (54.6)	112 (44.6)	0.017	
Hypertensive	122 (18.9)	83 (20.8)	40 (15.9)	0.150	
Severe hypotension	174 (24.0)	86 (19.4)	88 (31.3)	<0.001**	18.8
Tamponade	151 (21.1)	78 (18.0)	73 (26.0)	0.014*	19.9
Pericardiocentesis	7 (1.0)	5 (1.1)	2 (0.7)	0.714[e]	21.3
CVA	50 (9.3)	30 (9.2)	20 (9.5)	0.688	39.9
Resuscitation	60 (8.2)	30 (6.6)	30 (10.8)	0.060	18.1
Renal failure	26 (4.5)	15 (4.2)	11 (4.9)	0.833	34.7
Logistic EuroScore	22.4 [12.2; 37.7]	18.0 [9.3; 30.3]	30.3 [20.1; 47.4]	<0.001**	20.2
Time to diagnosis				0.249	35.6
<6h	370 (64.3)	234 (66.3)	136 (61.3)		
6-11.59h	55 (9.6)	27 (7.6)	28 (12.6)		
12-48h	73 (12.7)	44 (12.5)	29 (13.1)		
>48h	77 (13.4)	48 (13.6)	29 (13.1)		

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.

NYHA class= New York Heart Association class; CCS class= Canadian Cardiovascular Society class; BP= Blood Presure; CVA= Cerebrovascular Accident including Transient Ichemic Attack.

* Significant at the 0.05 level

** Significant at the 0.01 level

[e] Fishers exact test

SUPPLEMENTAL FILE 3

Laboratory results

	All n= 893	Male patients n=558	Female patients n=335	P value	Missing (%)
Haemoglobin – g/dL	13.4 [12.1-14.3]	13.9 [12.9-14.7]	12.3 [11.3-13.2]	<0.001**	20.5
eGFR - mL/min/1.73m^2				0.078[e]	28.4
Normal (>60)	428 (67)	280 (70.4)	148 (61.4)		
Moderate decrease (30-59)	197 (30.8)	112 (28.1)	85 (35.3)		
Severe decrease (15-29)	7 (1.1)	3 (0.8)	4 (1.7)		
Kidney failure (<15)	7 (1.1)	3 (0.8)	4 (1.7)		
Creatinine – mg/dL	1.1 [0.9-1.2]	1.1 [1.0-1.3]	0.9 [0.7-1.1]	<0.001**	25.0
Troponin T - microgram/mL	0.00	0.00	0.00	0.878	89.9
Hs Trop T – ng/L	14.0 [8.0-29.0]	13.0 [8.0-27.0]	16.0 [9.0-31.5]	0.354	78.9
CK - U/L	97/0 [65.8-159.3]	112.0 [76.0-175.8]	76.0 [55.0-115.0]	<0.001**	49.4
CKMB - microgram/L	4.2 [2.4-17.0]	5.2 [2.5-18.0]	3.9 [2.2-12.0]	0.210	72.3
ASAT - U/L	27.0 [22.0-38.0]	27.0 [22.0-36.0]	27.0 [21.5-45.5]	0.190	33.8
ALAT - U/L	23.0 [17.0-35.5]	24.0 [18.0-33.0]	22.0 [16.0-39.0]	0.653	32.5
LDH - U/L	229.0 [193.0-282.0]	229.0 [193.0-281.0]	231.0 [195.0-288.5]	0.861	38.3
CRP - mg/L	6.0 [2.4-14.0]	6.0 [2.0-11.0]	6.0 [3.0-20.0]	0.272	34.9
D-dimer - microgram/mL	18.9 [3.1-2545.0]	15.3 [3.3-2270.0]	19.9 [3.2-2800.0]	0.815	88.8
Leukocytes - x10^9/L	11.6 [9.1-14.3]	11.7 [9.0-14.6]	11.3 [9.1-14.0]	0.312	26.2
Lactate - mmol/L	2.5 [1.5-4.3	2.5 [9.0-14.6]	2.3 [1.4-4.3]	0.952	67.1

eGFR= glomerular filtration rate; Hs TropT= High sensitive cardiac troponine T; CK= creatinine kinase; CKMB= creatinine kinase muscle brain; ASAT= aspartate transaminase; ALAT= alanine transaminase; LDH= lactate dehydrogenase; CRP= C=reactive protein.
** Significant at the 0.01 level.
[e] Fisher's exact test used.

SUPPLEMENTAL FILE 4

Diagnostic imaging results

	All N= 893	Male patients N= 558	Female patients N= 335	P value	Missing
DeBakey classification				0.255	11.4
I	694 (87.7)	446 (88.8)	248 (85.8)		
II	97 (12.3)	56 (11.2)	41 (14.2)		
Location of intimal tear				0.131[e]	20.4
Ascending aorta	537 (75.5)	346 (75.4)	191 (75.8)		
Aortic arch	158 (22.2)	99 (21.6)	59 (23.4)		
Descending aorta	16 (2.3)	14 (3.1)	2 (0.8)		
Rhythm registered on ECG				0.470[e]	36.2
Sinus rhythm (60-100 bpm)	377 (66.1)	220 (64.0)	157 (69.5)		
Sinus tachycardia (>100 bpm)	22 (3.9)	16 (4.7)	6 (2.7)		
Sinus bradycardia (<60 bpm)	119 (20.9)	78 (22.7)	41 (18.1)		
Supraventricular tachycardia	34 (6.0)	21 (6.1)	13 (5.8)		
Ventricular tachycardia	1 (0.2)	0 (0.0)	1 (0.4)		
Other	15 (2.6)	8 (2.3)	7 (3.1)		
Any signs of ischemia on ECG	140 (26.9)	92 (29.1)	48 (23.4)	0.158	41.7
Measurement of LVEF - %				0.448[e]	49.8
Normal (>55%)	385 (85.9)	234 (85.4)	151 (86.8)		
Reduced (45-55%)	39 (8.7)	26 (9.5)	13 (7.5)		
Moderate (30-45%)	18 (4.0)	12 (4.4)	6 (3.4)		
Poor (<30%)	6 (1.3)	2 (0.7)	4 (2.3)		
Severity of aortic regurgitation				0.294	50.6
Mild	78 (17.7)	53 (19.3)	25 (15.1)		
Moderate	73 (16.6)	43 (15.6)	30 (18.1)		
Severe	77 (17.5)	53 (19.3)	24 (14.5)		
Maximum aortic diameter - mm	53.0 [48.0-59.3]	53.0 [49.0-60.0]	53.0 [47.0-59.0]	0.514	80.7
Maximum aortic diameter indexed for BSA - mm/m^2	26.7 [24.5-31.6]	26.1 [23.6-29.0]	28.5 [25.5-32.4]	0.001**	84.4
Aortic Rupture	40 (9.5)	24 (9.1)	16 (10.3)	0.809	53.1
Pleural effusion	42 (13.2)	24 (12.4)	18 (14.5)	0.703	64.4
Pericardial effusion	357 (53.4)	218 (53.2)	139 (53.7)	0.963	25.1

Continuous data are presented as mean ± standard deviation or as median (interquartile range) as appropriate. Categorical data are presented as absolute and percentage.

ECG= Electrocardiography; LVEF= Left Ventricular Ejection Fraction; BSA= Body Surface Area.

** Significant at the 0.01 level

[e] Fishers exact test

SUPPLEMENTAL FILE 5

Treatment of males and females with AD-A

	All n= 893	Males n= 558	Females n= 335	P-value	Missing (%)
Antihypertensive medication	124 (26.2)	80 (27.8)	44 (23.7)	0.373	46.9
Diuretics	5 (1.2)	2 (0.8)	3 (1.8)	0.632	51.6
Vasodilators	146 (31.8)	94 (33.9)	52 (28.6)	0.269	48.6
Surgery performed	880 (98.5)	551 (98.7)	329 (98.2)	0.719	0.0
Aortic valve surgery	497 (59.4)	314 (60.2)	183 (58.1)	0.607	6.3
Ascending aortic surgery	847 (97.4)	532 (97.6)	315 (96.9)	0.692	2.6
Aortic arch surgery	577 (64.6)	377 (70.8)	200 (63.0)	0.019*	4.7
(Partial) arch	136 (15.2)	91 (17.1)	45 (14.2)		
Hemi-arch	425 (47.6)	275 (51.6)	150 (47.2)		
Repair	16 (1.8)	11 (2.1)	5 (1.6)		
Descending aortic surgery	10 (1.1)	7 (1.3)	3 (0.9)	0.879	2.5
Concomitant procedures	67 (7.7)	40 (7.3)	27 (8.4)	0.407	2.5
CABG	55 (6.7)	31 (5.6)	24 (7.2)		
MV surgery	2 (0.2)	1 (0.2)	1 (0.3)		
Other	10 (1.1)	8 (1.4)	2 (0.6)		
Types of aortic valve surgery					
Bentall Procedure				0.222	3.1
Mechanical	105 (12.1)	72 (13.3)	33 (10.2)		
Biological	46 (5.3)	25 (4.6)	21 (6.5)		
VSARR Procedure				0.434	3.1
David	11 (1.3)	7 (1.3)	4 (1.2)		
(Partial) Yacoub	1 (0.1)	0 (0.0)	1 (0.3)		
Supracoronary Replacement				0.585	3.1
No AVR	328 (37.9)	201 (37.2)	127 (39.1)		
Mechanical AVR	25 (2.9)	18 (3.3)	7 (2.2)		
Biological AVR	26 (3.0)	19 (3.5)	7 (2.2)		
Valve repair	295 (34.1)	180 (33.3)	115 (35.4)		

Data are presented as absolute and percentage.

* Significant at the 0.05 level

AD-A= acute thoracic aortic dissection Stanford type A; CABG= Coronary artery bypass grafting; MV surgery= Mitral Valve surgery; VSARR= Valve Sparing aortic Root Replacement; AVR= Aortic valve replacement.

SUPPLEMENTAL FILE 6

Univariable logistic regression analysis on factors associated with mortality.

	Total n=893		Males n= 558		Females n= 335	
Variable	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Baseline						
Age	1.03 (1.02; 1.05)	<0.001**	1.03 (1.01; 1.05)	<0.001**	1.04 (1.01; 1.07)	0.004**
Sex	1.19 (0.85; 1.66)	0.318	-	-	-	-
History of hypertension	1.17 (0.82; 1.67)	0.379	0.96 (0.60; 1.50)	0.844	1.58 (0.89; 2.89)	0.128
History of hyperlipidaemia	1.05 (0.58; 1.79)	0.868	0.93 (0.39; 1.94)	0.848	1.16 (0.50; 2.48)	0.718
COPD	2.93 (1.68; 5.00)	<0.001**	3.50 (1.64; 7.22)	<0.001**	2.29 (0.98; 5.08)	0.046*
Diabetes	1.82 (0.74; 4.08)	0.156	1.54 (0.40; 4.54)	0.455	2.19 (0.57; 7.20)	0.213
Prior CVA	1.43 (0.66; 2.88)	0.333	1.81 (0.64; 4.51)	0.223	1.04 (0.29; 2.95)	0.948
Prior MI	1.30 (0.58; 2.68)	0.494	0.93 (0.27; 2.52)	0.901	1.93 (0.59; 5.54)	0.238
Chronic kidney disease	2.25 (0.90; 5.17)	0.064	1.24 (0.19; 5.06)	0.786	3.00 (0.97; 8.66)	0.045*
Prior aortic surgery	1.25 (0.45; 2.95)	0.638	1.66 (0.53; 4.40)	0.341	0.58 (0.03; 3.32)	0.609
Prior cardiac surgery	1.12 (0.89; 1.37)	0.310	1.23 (0.84; 1.43)	0.380	1.12 (0.71; 1.62)	0.549
Chronic dissection	0.78 (0.04; 4.61)	0.819	2.53 (0.12; 15.67)	0.451	0.00 (-; 1.21)	0.984
Known aortic aneurysm	1.43 (0.77; 2.52)	0.232	1.18 (0.46; 2.64)	0.703	1.68 (0.70; 3.70)	0.218
BAV	1.16 (0.33; 3.19)	0.795	0.83 (0.13; 3.10)	0.813	2.14 (0.29; 11.23)	0.388
Presentation						
DeBakey classification	1.06 (0.60; 1.79)	0.841	0.70 (0.28; 1.50)	0.391	1.57 (0.71; 3.28)	0.246
Treatment and surgery						
Aortic valve surgery	1.08 (1.01; 1.15)	0.642	1.05 (0.96; 1.14)	0.799	1.13 (1.02; 1.25)	0.652
Hemi-arch replacement	0.66 (0.46; 0.94)	0.021*	0.86 (0.54; 1.34)	0.497	0.44 (0.24; 0.78)	0.006**
(Partial) arch replacement	1.30 (0.82; 2.03)	0.251	1.25 (0.69; 2.17)	0.452	1.44 (0.66; 2.97)	0.335
Descending aortic surgery	3.24 (1.26; 9.25)	0.015*	3.64 (1.15; 13.77)	0.014*	2.61 (0.43; 18.55)	0.548
Concomitant procedures	3.54 (2.08; 5.94)	<0.001**	4.20 (2.12; 8.20)	<0.001**	2.71 (1.14; 6.16)	0.018*
Post-surgery						
Reoperation	1.39 (0.96; 2.02)	0.081	1.49 (0.92; 2.37)	0.099	1.30 (0.69; 2.38)	0.408
Device implantation	1.96 (0.43; 6.88)	0.324	2.84 (0.39; 14.78)	0.233	1.15 (0.06; 7.97)	0.900
MI	6.31 (2.23; 18.30)	<0.001**	3.48 (0.70; 14.46)	0.093	12.79 (2.68; 91.06)	0.003**
Bleeding	1.84 (1.24; 2.71)	0.002**	1.86 (1.13; 3.04)	0.014*	1.89 (0.97; 3.57)	0.055
CVA	3.23 (1.99; 5.16)	<0.001**	2.61 (1.35; 4.87)	0.003**	4.23 (2.03; 8.68)	<0.001**
Infection	0.79 (0.53; 1.18)	0.262	0.89 (0.52; 1.47)	0.653	0.66 (0.34; 1.24)	0.214

Short-term mortality= Intra– or postoperative death < 30 days or within hospital stay

HR= Hazard ratio, 95% CI= 95% Confidence Interval; COPD= Chronic Obstructive Pulmonary Disease; CVA= Cerebrovascular Accident; MI= Myocardial Infarction, BAV= Bicuspid Aortic Valve.

* Significant at the 0.05 level

** Significant at the 0.01 level

CHAPTER 6

Elective ascending aortic aneurysm surgery in the elderly

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Journal of Clinical Medicine, 2023

ABSTRACT

Background

No clear guidelines exist on performing preventive surgery for ascending aorta (AA) aneurysm in elderly patients. This study aims to provide insights by: 1) evaluating patient and procedural characteristics, and 2) comparing early outcomes and long-term mortality after surgery between elderly and nonelderly patients.

Methods

A multicenter retrospective observational cohort-study was performed. Data was collected on patients who underwent elective AA-surgery in three institutions (2006-2017). Clinical presentation, outcomes and mortality were compared between elderly (≥70 years) and nonelderly patients.

Results

In total, 724 nonelderly and 231 elderly were operated. Elderly had larger aortic diameters (57.0 mm (IQR 53-63) vs. 53.0 mm (IQR 49-58), p<0.001) and more cardiovascular risk factors at the time of surgery. Elderly females had significantly larger aortic diameters than elderly males (59.5 mm (55-65) vs. 56.0 mm (51-60), p<0.001). Short-term mortality was comparable between elderly and nonelderly patients (3.0% vs. 1.5%, p=0.16). Five year survival was 93.9% in nonelderly and 81.4% in elderly (p<0.001), which is both lower than the age-matched general Dutch population.

Conclusion

This study showed that in elderly patients a higher threshold exists to undergo surgery, especially in elderly females. Despite these differences, short-term outcomes were comparable between 'relatively healthy' elderly and nonelderly.

Graphical abstract

Elective Ascending Aortic Aneurysm Surgery in the Elderly (≥70 years) Compared to Nonelderly

INTRODUCTION

Life expectancy is increasing worldwide. The World Health Organization predicts that between 2015 and 2050 the proportion of the world's population over 60 years will nearly double from 12% to 22% [1]. Due to this demographic shift and the fact that cardiovascular disease is still the leading cause of death [2, 3], more elderly patients will become eligible for invasive cardiac and aortic interventions. The transition to an aged society raises uncertainties for cardiologists and cardiothoracic surgeons due to frailty and comorbidities that are more often seen in elderly patients [4] and the fact that increasing age is an important risk factor for postoperative morbidity and mortality [5]. In order to improve patient specific decision-making, it is important to investigate outcomes after major surgery specifically in elderly patients. Several research gaps exist when it comes to aortic root and/or ascending aortic (AA) aneurysm surgery in the elderly population.

First, most studies investigating the elderly population do not primarily focus on elective surgery of the aortic root and ascending aorta, with the exclusion of acute surgery such as aortic ruptures and dissections [6, 7]. Short-term outcomes differ significantly between acute and elective surgery. Therefore, these studies might not represent the actual outcomes of elective ascending aortic replacements in elderly. Especially in the preventive setting there is ample time to take into account all baseline characteristics available and carefully discuss with the patient the benefits and risks of intervention, but also of not performing an intervention at all in a shared decision manner.

Second, studies report contradictory results on mortality and morbidity in elderly patients after (elective) AA-surgery. Some studies conclude that outcomes after an ascending aorta and/or (hemi-)arch reconstruction are acceptable with a short-term mortality between 2.1% and 13.5% in elderly patients [8, 9]. On the contrary, other studies conclude that elderly patients showed an operative risk with higher postoperative mortality, morbidity and prolonged admission in hospital [7, 10]. Most importantly, long-term mortality in elderly patients who underwent elective AA-surgery has been investigated in very few studies [7, 9]. Therefore, due to this scarce and contradictory scientific evidence, the decision to opt for elective aortic surgery at an advanced age remains difficult.

Third, only a few studies have evaluated the patient and procedural characteristics of AA-surgery in elderly compared to nonelderly patients. Hardly any separation is made between the different surgical techniques that were performed. Studies indicate on which part of the aorta surgery is performed, but do not report specific distinctions in surgical techniques [7, 9].

Therefore, this multicenter study aims to gain more insight into elective AA-surgery in the elderly by evaluating the patient and procedural characteristics, and comparing early and long-term outcome after surgery between elderly and nonelderly patients.

METHODS

Study Design

A retrospective multicenter observational cohort study was performed of patients who underwent elective surgery for aneurysmal disease of the aortic root and/or ascending aorta in three experienced centres for aorta surgery in the Netherlands between January 2006 and December 2017. The following institutes participated in this study: Erasmus Medical Centre (Rotterdam, The Netherlands), Radboud University Medical Centre (Nijmegen, The Netherlands) and Catharina Hospital (Eindhoven, The Netherlands). The study was approved by the local ethics committees (MEC-2018-1535) of all participating centers, and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines.

Study Population

Patients were eligible for inclusion if they underwent elective surgery for aneurysmal disease of the aortic root and/or ascending aorta. Patients had to be 18 years old or older at the time of surgery. Elective surgery was defined as surgery that was planned 14 days or longer in advance. Patients who underwent surgery with concomitant cardiac surgical procedures, such as coronary artery bypass grafting (CABG) and mitral valve surgery, and aneurysms extending into the aortic (hemi-)arch including the descending aorta, were included in the analysis. Exclusion criteria were aortic dissection and/or rupture, other emergency aortic surgery, intramural hematoma, penetrating aortic ulcer, pseudo aneurysm or mycotic aneurysm, isolated reduction aortoplasty without replacement and aneurysms limited to the descending and/or abdominal aorta. Patients who underwent surgery for infected aortic prosthesis or endocarditis of the aortic valve were also excluded. A description of the surgical procedures used is presented in Supplemental File 1. Patients were stratified into two groups in the analysis: the elderly patient group aged 70 years or older, and the nonelderly patient group aged under 70 years.

Data Collection

Patients were identified using the institutional aortic surgery databases. Additionally, a profound search was performed using the hospitals' diagnosis registration systems. Files of all patients with diagnosis treatment codes (DBC's) related to any aortic disease were checked manually, to see if patients were eligible for inclusion. Data were collected from

patient files using standardized case report forms and documented in an online clinical data management system OpenClinica (OpenClinica, LLC, Version: 3.12.2). Medical history, clinical presentation including perioperative data, laboratory results and postoperative (in-hospital) outcomes were extracted from the hospitals electronic medical records. Short-term postoperative mortality and morbidity was defined as an event occurring during hospital admission or within 30 days of surgery. Long-term survival data were obtained from Dutch municipal registries. In addition to the absolute aortic diameter, the indexed aortic diameter was calculated by dividing the absolute aortic diameter by Body Surface Area (BSA), which was calculated using the Du Bois formula [11]. Valve-related postoperative complications were defined according to the 2008 Akins Guidelines for Reporting Mortality and Morbidity after Cardiac Valve Interventions [12]. All variables and definitions are shown in Supplemental File 2.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA) and computing programme *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 3.6.1). Continuous variables were presented as mean ± standard deviation (SD) when normally distributed, and as median (interquartile range, IQR) when skewed. Categorical data were presented as frequencies (percentages). A comparison was made between the elderly patient group aged 70 years or older and the nonelderly patient group aged under 70 years. Student's t-test was used to compare continuous variables with normal distribution and Mann-Whitney U test for variables without normal distribution. Furthermore, Pearson Chi-squared or Fisher's exact test was used to compare categorical variables. A subgroup analysis for 75 years and older was performed as well, which can be found in the Supplemental File 3. The Kaplan–Meier survival estimation was used to analyse the postoperative survival. The difference in survival probability between elderly and nonelderly was calculated using the Log-rank test. Data from the Dutch Central Bureau of population Statistics (CBS) was used to provide a visual comparison between survival in the elderly and nonelderly groups with respect to the general Dutch population. Missing data was handled by multiple imputation with five iterations. Only variables with less than 15% missing were eligible for imputation. Missing data patterns were studied in order to identify and exclude variables with data missing not at random. For imputation the monotone method was used if the data show a monotone pattern of missing values, otherwise, fully conditional specification was used. Cox regression analysis using the backwards selection method was performed in order to identify determinants associated with long-term mortality. Only patients who survived at least 30 days after surgery were included in this long-term analysis. Cox regression analysis was performed for the total population and stratified for elderly and nonelderly. Based on univariable analysis (p-value <0.05) and clinical relevance, variables were selected for multivariable analysis. The tests were considered statistically significant if the p-value was less than 0.05.

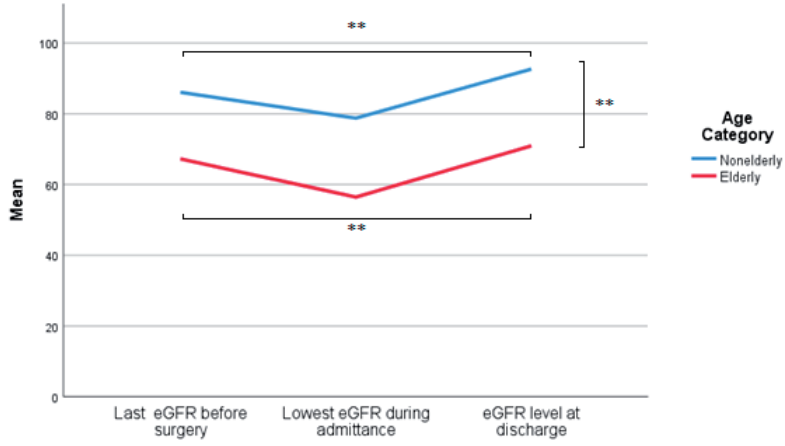

Figure 1 The Course of eGFR-Level from Admission to Discharge

* Significant at the p < 0.05 level
** Significant at p < 0.001 level

Table 1 Baseline Characteristics

	Total (n= 955)	Nonelderly (n=724)	Elderly (n= 231)	*p*-value	Missings (NE/E)[1]
Age (years)	61.0 (50.0-69.0)	55.0 (45.0-63.0)	74.0 (72.0-77.0)	<.0001**	0/955
Sex (% male)	621 (65.0)	509 (70.3)	112 (48.3)	<0.001**	0/955
BSA	2.02 ± 0.22	2.05 ± 0.23	1.95 ± 0.17	<0.001**	(1/724)/ (0/231)
History of Hypertension	570 (59.7)	384 (54.4)	186 (81.6)	<0.001**	(18/724)/ (3/231)
History of Dyslipidaemia	291 (30.5)	200 (28.5)	91 (40.3)	0.001**	(22/724)/ (5/231)
History of Diabetes Mellitus	62 (6.5)	41 (5.7)	21 (9.3)	0.067	(10/724)/ (4/231)
History of CVA/TIA	110 (11.5)	74 (10.4)	36 (15.7)	0.034*	(12/724)/ (1/231)
History of COPD	90 (9.4)	60 (8.4)	30 (13.2)	0.039*	(13/724)/ (3/231)
History of Smoking					(302/724)/
Never	182 (19.1)	134 (31.8)	48 (33.3)	0.76	(87/231)
Currently	149 (15.6)	124 (29.4)	25 (17.4)	0.004**	
In past	235 (24.6)	164 (38.9)	71 (49.3)	0.031*	
History of Chronic Kidney Disease	48 (5.0)	25 (3.5)	23 (10.1)	<0.001**	(10/724)/ (3/231)
eGFR (ml/min)				<0.001**	(0/724)/
<60	121 (12.7)	56 (7.7)	65 (28.3)		(1/231)
≥60	833 (87.2)	668 (92.3)	165 (71.7)		
History of Myocardial Infarction	50 (5.2)	37 (5.1)	13 (5.8)	0.730	(2/724)/ (6/231)
Family History of Aortic Pathology	134 (14.0)	120 (42.0)	14 (19.7)	0.001**	(438/724)/ (161/231)

	Total (n= 955)	Nonelderly (n=724)	Elderly (n= 231)	*p*-value	Missings (NE/E)[1]
Diagnosis of HTAD Prior to Surgery	129 (13.5)	123 (17.0)	6 (2.6)	<0.001**	(504/724)/ (216/231)
Marfan Syndrome	48 (5.0)	47 (6.5)	1 (0.4)	<0.001**	
Loeys-Dietz Syndrome	5 (0.5)	5 (0.7)	0 (0.0)	0.34	
SMAD3 Mutation	10 (1.0)	10 (1.4)	0 (0.0)	0.13	
Turner Syndrome	8 (0.8)	8 (1.1)	0 (0.0)	0.21	
Suspected	42 (4.4)	39 (5.4)	3 (1.3)	0.005**	
Other	16 (1.7)	14 (1.9)	2 (0.9)	0.38	
Prior Cardiac Surgery	97 (10.2)	81 (11.2)	16 (6.9)	0.062	0/955
Prior Aortic Surgery	85 (8.9)	73 (10.1)	12 (5.2)	0.024*	(1/724)/ (1/231)
Aortic Valve					(45/724)/
Stenosis	221 (23.1)	178 (26.2)	43 (20.6)	0.099	(23/231)
Insufficiency	397 (41.6)	289 (42.2)	108 (50.7)	0.033*	(39/725)/ (19/231)
NYHA Classification					(64/724)/
Class I	500 (52.4)	402 (60.9)	98 (47.1)	<.001**	(23/231)
Class II	224 (23.5)	159 (24.1)	65 (31.3)	0.040*	
Class III	135 (14.1)	91 (13.8)	44 (21.2)	0.010*	
Class IV	9 (0.9)	8 (1.2)	1 (0.5)	0.695	
CCS Classification					(87/724)-
Class I	711 (74.5)	551 (86.5)	160 (81.6)	0.092	(35/231)
Class II	79 (8.3)	53 (8.3)	26 (13.3)	0.039*	
Class III	36 (3.8)	27 (4.2)	9 (4.6)	0.84	
Class IV	7 (0.7)	6 (0.9)	1 (0.5)	1.00	
LVEF					(57/724)/
Good (>55%)	680 (71.2)	524 (78.6)	156 (71.9)	0.043*	(14/231)
Reduced (44-55%)	112 (11.7)	80 (12.0)	32 (14.7)	0.29	
Moderate (30-45%)	85 (8.9)	60 (9.0)	25 (11.5)	0.27	
Poor (<30%)	7 (0.7)	3 (0.5)	4 (1.8)	0.067	
Bicuspid Aortic Valve	375 (39.3)	332 (45.9)	43 (18.6)	<0.001**	0/955
Location of Maximal Aortic Diameter					(21/724)/ (12/231)
Sinuses of Valsalva	191 (20.0)	170 (24.1)	21 (9.6)	<0.001**	
Ascending Aorta	722 (75.6)	527 (74.8)	195 (89.0)	<0.001**	
Aortic Arch	10 (1.0)	7 (1.0)	3 (1.4)	0.71	
Descending Aorta	1 (0.1)	1 (0.1)	0 (0.0)	1.00	
Maximal Absolute Aortic Diameter (mm)	54.0 (50.0-59.0)	53.0 (49.0-58.0)	57.0 (53.0-63.0)	<0.001**	(21/724)/ (12/231)
Maximal Indexed Aortic Diameter (mm/m^2)	26.7 (24.0-30.3)	25.9 (23.4-29.2)	30.3 (26.9-34.5)	<0.001**	(21/724)/ (12/231)
Logistic EUROscore	9.0 (5.3-14.4)	7.0 (5.0-11.6)	17.4 (13.0-22.7)	<0.001**	0/955

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).

BSA: Body Surface Area, CVA/TIA: Cerebrovascular Accident/Transient Ischemic Attack, COPD: Chronic Obstructive Pulmonary Disease, GFR: Glomerular Filtration Rate, HTAD: Hereditary Thoracic Aortic Disease, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society, LCC: left coronary cusp, LVEF: Left Ventricular Ejection Fraction,Logistic EUROscore: European System for Cardiac Operative Risk Evaluation, NCC: non coronary cusp, RCC: right coronary cusp

[1]NE/E: Nonelderly/Elderly

* Significant at the 0.05 level

** Significant at the 0.01 level

Table 2. Operative Characteristics.

	Total (n= 955)	Nonelderly (n= 724)	Elderly (n= 231)	p-value	Missings (NE/E)[1]
Bentall Procedure	491 (51.4)	389 (53.7)	102 (44.0)	0.010*	0/955
Mechanical	324 (33.9)	304 (42.0)	20 (8.6)	<0.001**	
Biological	167 (17.5)	85 (11.7)	82 (35.3)	<0.001**	
David technique	117 (12.3)	110 (15.2)	7 (3.0)	<0.001**	0/955
(Partial) Yacoub technique	24 (2.5)	17 (2.3)	7 (3.0)	0.63	0/955
SCAR	390 (40.8)	264 (36.5)	126 (54.3)	<0.001**	0/955
No AVR	219 (22.9)	152 (21.0)	67 (28.9)	0.013*	
Mechanical AVR	53 (5.5)	52 (7.2)	1 (0.4)	<0.001**	
Biological AVR	89 (9.3)	44 (6.1)	45 (19.4)	<0.001**	
Valve repair	27 (2.8)	14 (1.9)	13 (5.6)	0.003**	
Concomitant Procedures	514 (53.8)	359 (49.6)	155 (66.8)	<0.001**	0/955
(Hemi-)arch	392 (41.0)	269 (37.2)	123 (53.0)	<0.001**	
CABG	106 (11.1)	67 (9.3)	39 (16.8)	0.002**	
Mitral valve surgery	32 (3.4)	20 (2.8)	12 (5.2)	0.076	
Other[b]	59 (6.2)	44 (6.1)	15 (6.5)	0.83	
Perfusion Time (min)	163.0 (125.0-198.0)	163.0 (124.0-198.5)	162.0 (129.5-197.3)	0.69	(7/724)/ (1/231)
Aortic Cross-Clamp Time (min)	107.0 (83.3-136.0)	108.0 (84.0-138.0)	103.0 (82.0-132.5)	0.12	(8/724)/ (4/231)
DHCA[c]	420 (44.0)	290 (40.1)	131 (56.5)	<0.001**	
Circulatory Arrest Time (min)	19.0 (15.0-28.0)	18.0 (14.0-27.0)	20.0 (16.0-37.0)	0.021**	(450/724)/ (108/231)
Cerebral Protection[c]	420 (44.0)	290 (40.1)	131 (56.5)	<0.001**	(3/724)/
Antegrade Unilateral	26 (2.7)	19 (2.6)	7 (3.0)	0.82	(3/231)
Antegrade Bilateral	388 (40.6)	268 (37.0)	120 (51.7)	<0.001**	
ACP time (min)[c]	33.0 (20.0-68.0)	29.0 (18.0-69.0)	35.0 (25.8-63.5)	0.26	(199/724)/ (80/231)

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).

SCAR: Supracoronary Aorta Replacement, AVR: Aortic Valve Replacement, CABG: Coronary Artery Bypass Grafting, DHCA: Deep Hypothermic Cardiac Arrest, [4]ACP: Antegrade Cerebral Perfusion [a]All patients who had reduction ascending aortoplasty, has undergone biological AVR as well, [b]Other performed concomitant procedures can be found in the appendix, [c]If the procedure was performed.

[1]NE/E: Nonelderly/Elderly

* Significant at the 0.05 level

** Significant at the 0.01 level

RESULTS

Patient Characteristics

A total of 955 patients were included: 231 patients (24.2%) were stratified in the elderly group and 724 patients (75.8%) in the nonelderly group. Baseline characteristics are presented in Table 1. The median age of the elderly was 74 years (IQR 72-77) and of the nonelderly 55 years (IQR 45-63). The elderly were more often female (51.7% vs. 29.7%, p<0.001) and had more cardiovascular risk factors compared to the nonelderly group (Table 1). Moreover, elderly patients had a significantly higher maximal absolute (57.0 mm (IQR 53-63) vs. 53.0 mm (IQR 49-58) and BSA-indexed (30.3 mm (IQR 26.9-34.5) vs. 25.9 mm (IQR 23.4-29.2) aortic diameter at the time of AA-surgery compared to nonelderly. When comparing elderly male and female patients, elderly females had larger maximal absolute aortic diameter compared to elderly males with a mean of 61.2±9.7 mm vs. 56.9±8.5 mm (median 59.5 mm (IQR 55-65) vs. 56.0 (51-60), p<0.001). In nonelderly patients, females had a mean aortic diameter of 53.2±8.2 mm vs. 54.1±7.9 in males (median 52.0 mm (IQR 48-58) vs. 53.0 (49-58), p=0.085). Cardiovascular risk factors as mentioned in Table 1 were compared as well between elderly males and females. Elderly males more often had a history of prior cardiac surgery (11.6% vs. 2.5%, p=0.007), and of prior aortic surgery (8.9% vs. 1.7%, p=0.014). Furthermore, elderly males more often had a bicuspid aortic valve (BAV) compared to elderly female (26.8% vs. 10.9%, p=0.002). No disproportionate differences were found in the elderly and non-elderly patients included from each of the different centers.

Operative Characteristics

Table 2 shows the operative characteristics of elderly versus nonelderly patients. Supracoronary aorta replacement (SCAR) was more common in the elderly group (54.3% vs. 36.5%, p<0.001). Elderly more often received biological prostheses, whereas the nonelderly received more mechanical prostheses (both Bentall and aortic valve replacement [AVR]). The David technique was performed less often in the elderly (3.0% vs. 15.2%, p<0.001). Furthermore, elderly patients received significantly more concomitant procedures during AA-surgery (66.8% vs. 49.6%, p<0.001).

Short-Term Postoperative Outcomes

Outcomes after AA-aneurysm surgery showed that in-hospital or 30-day mortality after elective aortic aneurysm surgery was 1.9% (n=18), with no significant difference between the study groups (3.0% vs. 1.5%, p=0.16; Table 3). Even when the age limit was at 75 years, there was no significant difference in mortality (3.8% vs. 1.6%, p=0.13; Supplemental File 3A). In-hospital or 30-day mortality was 3.6 % in elderly males (n=4) and 2.5% in elderly

females (n=3) which was not significantly different (p=0.642). Besides, no significant differences existed in mortality between the elderly and nonelderly in the three centers.

Table 3 shows short-term outcomes after surgery in elderly compared to nonelderly. Prolonged hospital admission (more than 20 days) was significantly more common in the elderly (11.3% vs. 6.2%, p=0.044) and more reoperations were performed on elderly patients (32.3% vs. 21.4%, p<0.001).

Short-term postoperative morbidity outcomes are shown in Table 4. Postoperatively, the elderly were significantly more often diagnosed with new supraventricular arrhythmias (39.4% vs. 21.3%, p<0.001), delirium (28.6% vs. 11.0%, p<0.001), infections which were mainly pneumonia (9.5% vs. 5.2%, p=0.02) and severe wound infections (3.0% vs. 0.4%, p=0.003). When comparing elderly female to elderly male patients there were no significant differences in duration of hospital admission, duration of ICU stay, duration of ventilator support or number of patients who needed a reoperation within 30 days.

Before AA-surgery, estimated Glomerular Filtration Rate (eGFR)-levels were significantly lower in elderly as shown in Figure 1 (eGFR 67 ml/min/1.73 m^2 vs. 86 ml/min/1.73 $m^{2,}$ p<0.001). Decreases in eGFR were observed in both groups after surgery. The average decrease was 16.2% (average eGFR 56 ml/min/1.73 m^2) in elderly patients versus 8.5% (average eGFR 79 ml/min/1.73 m^2) in the nonelderly. When comparing eGFR before surgery and at discharge, an increase was seen: 13.76% in elderly and 7.65% in the nonelderly patients, which was not significantly different. However, both increases were statistically significant from baseline eGFR with a p-value of <0.001.

Long-Term Survival

Figure 2 shows the Kaplan-Meier curve of the long-term survival in elderly and nonelderly patients compared to the age-matched general Dutch population. Mean follow-up time was 6.2±3.5 years. Long-term survival differed significantly between the elderly and nonelderly group with a p-value of <0.001. Five year survival was 81.4% in elderly and 93.9% in nonelderly (p<0.001), versus 86% and 98% in the age-matched general Dutch population. Moreover, survival in both study groups seemed lower than in the age-matched general Dutch population. Univariable analysis showed a history of hypertension (HR 2.64, 95% CI 1.21-5.78, p=0.015) and diabetes mellitus (HR 0.24, 95% CI 0.06-0.97, p=0.045) to be significantly associated with higher long-term mortality in the elderly, as well as in nonelderly. In the nonelderly, male sex was significantly associated with lower risk of long-term mortality, whereas in elderly patients this association was not found, as is shown in Supplemental File 4.

Table 3 Short-term Outcomes

	Total (n= 955)	Nonelderly (n= 724)	Elderly (n= 231)	p-value	Missings (NE/E)[1]
In-hospital or 30-day Mortality	18 (1.9)	11 (1.5)	7 (3.0)	0.16	0/955
Cause of Mortality					0/955
Cardiac (incl. Tamponade)	8 (0.8)	6 (0.8)	2 (0.9)	1.00	
Bleeding	3 (0.3)	2 (0.3)	1 (0.4)	0.57	
Aortic Rupture	2 (0.2)	2 (0.3)	0 (0.0)	1.00	
Organ Failure	1 (0.1)	0 (0.0)	1 (0.4)	0.24	
Sepsis	2 (0.2)	0 (0.0)	2 (0.9)	0.06	
Other	1 (0.1)	0 (0.0)	1 (0.4)	0.24	
Number of Days the patient was Admitted[a]					0/955
1-4	23 (2.4)	18 (2.5)	5 (2.2)	1.00	
5-9	590 (61.8)	460 (63.5)	130 (56.3)	0.048*	
10-14	205 (21.5)	154 (21.3)	51 (22.1)	0.78	
15-19	66 (6.9)	47 (6.5)	19 (8.2)	0.37	
≥20	71 (7.4)	45 (6.2)	26 (11.3)	0.014*	
Total	8.0 (7.0-11.0)	8.0 (7.0-11.0)	7.0 (9.0-13.0)	0.028*	
Number of Days in ICU after Surgery					(20/724)/
1-4	827 (86.6)	641 (91.1)	186 (81.9)	<0.001**	(4/231)
5-9	71 (7.4)	41 (5.8)	30 (13.2)	<0.001**	
10-14	18 (1.9)	11 (1.6)	7 (3.1)	0.17	
15-19	5 (0.5)	4 (0.6)	1 (0.4)	1.0	
≥20	10 (1.0)	7 (1.0)	3 (1.3)	0.71	
Total	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-4.0)	<0.001**	
Number of Days on Ventilation Support after Surgery [a]					(28/724)/ (9/231)
1	551 (57.7)	455 (65.3)	96 (43.2)	<0.001**	
2	308 (32.3)	205 (29.4)	103 (46.4)	<0.001**	
3	19 (2.0)	10 (1.4)	9 (4.1)	0.027*	
4	10 (1.0)	6 (0.9)	4 (1.8)	0.27	
≥5	31 (3.2)	21 (3.0)	10 (4.5)	0.29	
Total	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	<0.001**	
Total Reoperations	230 (24.1)	155 (21.4)	75 (32.3)	<0.001**	(127/724)/
Bleeding	157 (16.4)	112 (15.5)	45 (19.4)	0.16	(59/231)
Tamponade	31 (3.2)	21 (2.9)	10 (4.3)	0.29	
Mediastinitis	16 (1.7)	5 (0.7)	11 (4.7)	<0.001**	
Cardiac Ischemia	1 (0.1)	1 (0.1)	0 (0.0)	0.76	
Other Visceral Ischemia	2 (0.2)	0 (0.0)	2 (0.2)	0.059	
Structural Valve Deterioration	1 (0.1)	1 (0.1)	0 (0.0)	0.57	
Non-Structural Valve Deterior.	1 (0.1)	1 (0.1)	0 (0.0)	0.76	
Endocarditis	1 (0.1)	1 (0.1)	0 (0.0)	0.76	
Other	20 (2.1)	13 (1.8)	7 (3.0)	0.19	

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).
ICU: Intensive Care Unit
* Significant at the 0.05 level
** Significant at the 0.01 level

Table 4 In-hospital Postoperative Morbidity After Elective Aortic Aneurysm Surgery

	Total (n= 955)	Nonelderly (n= 724)	Elderly (n= 231)	p-value	Missings (NE/E)[1]
Tracheostoma Implantation	8 (0.8)	5 (0.7)	3 (1.3)	0.41	(1/724)/(0/231)
New Permanent Heart Rhythm Disturbances	245 (25.7)	154 (21.3)	91 (39.4)	<0.001**	(3/724)/(0/231)
Supraventricular	211 (22.1)	125 (17.3)	86 (37.2)	<0.001**	
Ventricular	6 (0.6)	6 (0.8)	0 (0.0)	0.35	
AV-block	27 (2.8)	22 (3.0)	5 (2.2)	0.65	
Pacemaker or ICD Implanted	32 (3.4)	26 (3.6)	6 (2.6)	0.54	0/955
Myocardial Infarction or Ischemia	18 (1.9)	13 (1.8)	5 (2.2)	0.78	0/955
Infective Endocarditis	4 (0.4)	3 (0.4)	1 (0.4)	1.00	(2/724)/(1/231)
Non-Structural Valve Dysfunction	2 (0.2)	2 (0.3)	0 (0.0)	1.00	0/955
CVA/TIA	43 (4.5)	33 (4.6)	10 (4.3)	0.89	(1/724)/(1/231)
New Recurrence Nerve Lesion	12 (1.3)	11 (1.5)	1 (0.4)	0.31	0/955
Diagnosis of Delirium	146 (15.3)	80 (11.0)	66 (28.6)	<0.001**	0/955
Diagnosis of Infection	130 (13.6)	82 (11.3)	48 (20.8)	0.001**	0/955
Diagnosis of Sepsis	11 (1.2)	7 (1.0)	4 (1.7)	0.31	0/955

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).
AV-block: Atrioventriculair block, CVA/TIA: Cerebrovascular Accident/Transient Ischemic Attack, ICD: Implantable Cardioverter Defibrillator
[1]NE/E: Nonelderly/Elderly
* Significant at the 0.05 level
** Significant at the 0.01 level

Figure 3 shows the multivariable analysis in the total population, and also in the elderly and nonelderly. Chronic kidney disease showed borderline significance with higher long-term mortality in the elderly (p=0.053). In nonelderly, higher age was associated with higher long-term mortality. Besides, receiving Valve Sparing Aortic Root Replacement (VSARR) was associated with lower long-term mortality (the partial Yacoub technique was included in this multivariable analysis).

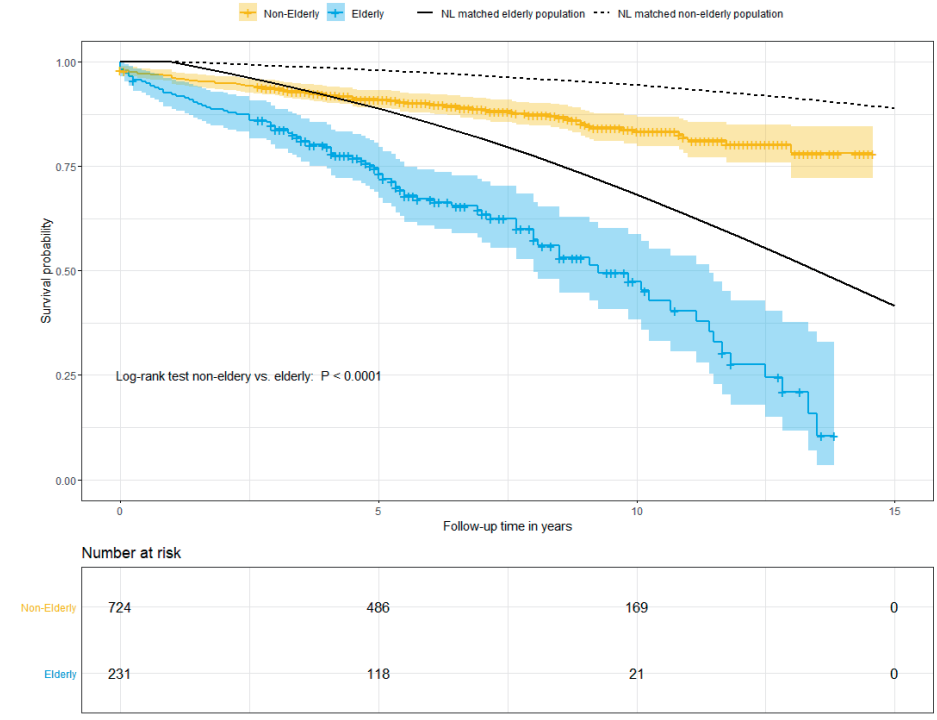

Figure 2 Kaplan-Meier Survival Analysis

Kaplan-Meier survival analysis for the elderly (blue) versus nonelderly (yellow)

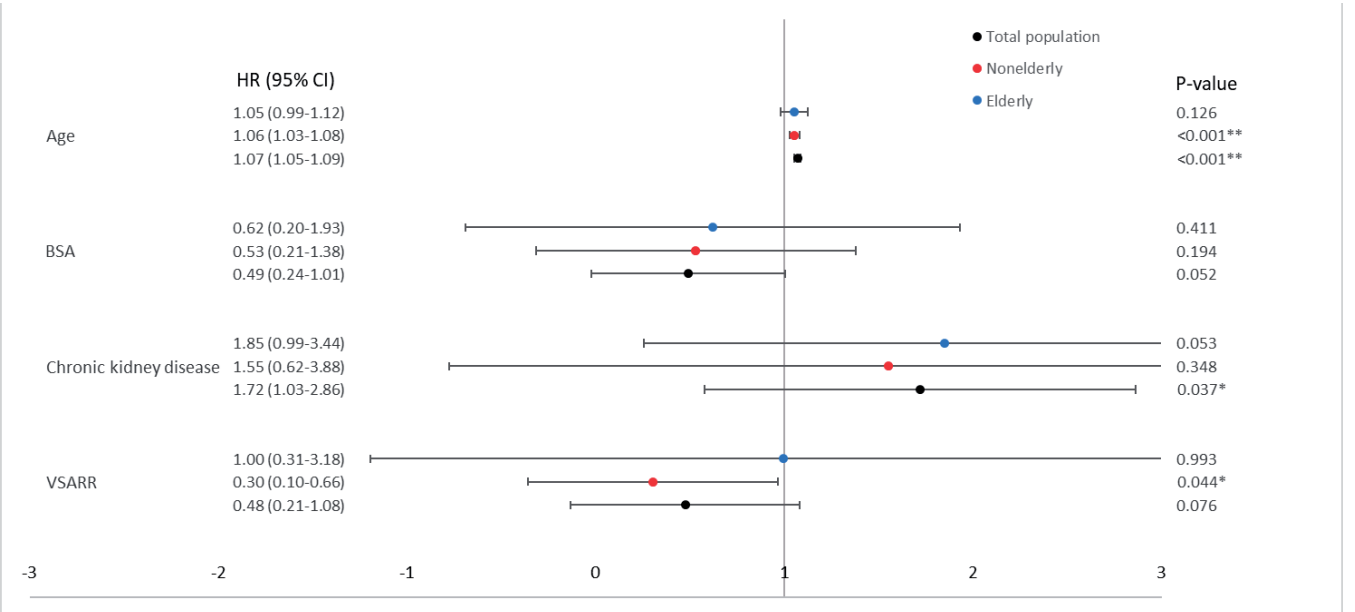

Figure 3 Forrest Plot of the Multivariable Analysis

Data are presented as Hazard Ratio's (HR) with 95% Confidence Intervals (CI)

VSARR: Valve Sparing Aortic Root Replacement (including partial Yacoub technique in this analysis); BSA: Body Surface Area.

* Significant at the 0.05 level

** Significant at the 0.01 level

DISCUSSION

In this large retrospective cohort study, elective AA-surgery was compared in elderly versus nonelderly patients. Elderly patients, and elderly females in particular, had significantly higher aneurysm diameter at the time of surgery. When it comes to surgical characteristics: SCAR, valve sparing procedures and surgery with concomitant procedures were performed more often in elderly patients, resulting in more complex procedures. Postoperative morbidity in the elderly were more prevalent, mostly due to supraventricular arrhythmias, delirium and infections. Nevertheless, short-term mortality was not significantly different and is still relatively low (3%). Long-term mortality was higher in elderly patients, but seems to have a similar effect on life expectancy compared to nonelderly. No significant differences were found between elderly male and female patients.

Patient Characteristics

Previous studies showed that normal aortic diameters increase with age [13, 14]. In our study, elderly had a significantly higher absolute and indexed maximal aortic diameter at the time of AA-surgery compared to the nonelderly, with a median absolute diameter of 57 mm which is above the current threshold for elective surgery of 55 mm [15]. This suggests that elderly patients received surgery at a later stage in the disease process. This difference between elderly and nonelderly, seems largely attributed to the fact that the elderly group contains more females (51.7% in elderly vs. 29.7% in nonelderly), since mean AA diameter before surgery was especially large in elderly females (61.2 mm). This is a very notable finding, since it was significantly larger compared to elderly males, which could suggest that surgery is performed at a later stage in elderly females. This might be because aneurysms in elderly patients are more often a coincidental finding, whereas in younger patients it is more in the context of (familial/known) aortopathy which are under regular follow-up and scheduled immediately upon reaching the operational limit. Despite the larger diameter, early outcomes in elderly males and elderly females were comparable, with a short-term mortality of 3.6% in elderly males and 2.5% in elderly females (p=0.642). Furthermore, long-term mortality was not significantly associated with female sex in the elderly group. Therefore, it seems elderly female patients did not suffer worse outcomes after surgery, despite being operated at a later stage in their disease process. When comparing risk factors, elderly males more often had prior cardiac or aortic surgery and more often had a BAV (26.8% vs. 10.9%, p=0.002). It is well-known that BAV is more common in males. The latter might partially explain the male-female difference, since in patients with BAV aortic aneurysm might be diagnosed earlier than in patients without BAV, due to family screening or heart murmurs. Furthermore, patients with BAV and additional risk factors such as persistent hypertension might receive surgery at lower diameters, according to current guidelines [13]. Nevertheless, elderly females received surgery far above the current threshold for elective aortic surgery, although our results

do not provide any reason to restrain from performing surgery in elderly females. Perhaps patient preference could have played a role in this as well. More research is needed to explore this finding, and the factors underlying this remarkable male-female difference.

Operative Characteristics

Our analysis showed that SCAR was performed significantly more often in the elderly. This seems logical since 89% of the elderly had a maximal aortic diameter located at the ascending aorta, whereas nonelderly more often had a dilated root (9.6% vs. 24.1%, p<0.001). This difference might be partially attributable to the higher number of patients

with HTAD in the nonelderly group, who more often have aneurysms located at the root [16]. If valve surgery was performed, elderly patients were operated with biological prostheses significantly more often than the nonelderly, as is recommended by international guidelines [17].

Furthermore, the analysis showed that receiving VSARR was associated with lower long-term mortality in nonelderly patients (HR 0.30, 95% CI 0.10-0.66), p=0.044). The mean age of the nonelderly patients receiving VSARR in our analysis was 46.5 years. A possible explanation for this phenomenon is that aortic valve lesions are less complex at a younger age compared to an older age, and this could result in lower long-term mortality rates. Our results are comparable with an earlier study which reported that there was an improved midterm survival among adult patients undergoing VSARR [18].

We hypothesized that the operation itself might take longer time in the elderly compared to the nonelderly, especially, since more concomitant procedures were performed. However, this was not reflected in our results. This finding is in line with previous studies which evenly reported no significant differences in perfusion time, aortic cross-clamp time and ACP time between elderly and nonelderly [7, 10]. Various studies analyzed all these intraoperative times, though their findings were not consistent [7, 8, 10, 19]. This difference can be explained by the fact that the age limit was different and that the inclusion and exclusion criteria were inconsistent in these studies (with regard to e.g. descending aorta). Since we included only patients who actually underwent aortic surgery, relatively more elderly might have been selected with better performance state and lower pre-operative burden. Another important factor that has to be taken into account is that there were missing data in intraoperative times and therefore this finding has to be interpreted with caution.

Short-Term Postoperative Outcomes

Our study showed that the elderly needed longer in-hospital and ICU admission days, which corresponds with previous reports [9, 10, 20]. Especially ≥20 days of hospitalization

occurred more often in the elderly (p=0.014). This was at least partially due to more reoperations for mediastinitis. Furthermore, elderly suffered more minor postoperative complications, especially supraventricular arrhythmias, delirium and infections which are known to be more common in the elderly [21-23].

More importantly, our in-hospital mortality after elective aortic aneurysm surgery was not significantly higher in the elderly. There is a disagreement in the literature regarding postoperative mortality after elective aortic aneurysm surgery. Some studies found higher short-term mortality in the elderly [7, 10, 20], while other studies found the postoperative mortality outcomes to be similar between the groups [7, 9]. Presumably this is explained by the fact that in the studies of Peters et al. and Guo et al. the elderly were aged 75 or 80 years and older instead of 70 years or older [10, 20]. However, our sub-analysis in elderly aged 75 years or older did not show a significant difference in short-term mortality either. This difference might be due to the fact that elderly patients in the studies op Peters et al. and Guo et al. had more cardiovascular risk factors, such as coronary artery disease, previous cardiac surgery, higher mean age and higher mean maximal aortic diameter than our patient population [10, 20].

Various factors can influence renal function during cardiopulmonary bypass (CPB), such as inflammatory responses, hypothermia, changes in hemodynamics and surgical stress [24]. Figure 1 shows that estimated glomerular filtration rate (eGFR) decreased postoperatively, but the eGFR measured at discharge was ultimately higher than the last measured eGFR before surgery. It has been reported that cardiac surgery with CPB does not necessarily have to lead to a decrease in renal function in patients with preoperative mild renal dysfunction [24]. In fact, our study showed the same phenomenon: postoperatively, there was a significant increase in eGFR compared to the eGFR before surgery (p=0.005). A possible explanation could be the small changes in hemodynamic variables [25] or the effect of the artificial kidney in the CPB. Another theory for this phenomenon is that the postoperative eGFR was increased due to medication. There have been frequent studies on medication that should be offering renal protection. Unfortunately, none of them showed a decrease in renal damage [25]. Since the increase in eGFR also occurs in other studies, it is unlikely that this finding is a coincidence and further research is clearly warranted.

Long-Term Survival

As expected, long-term survival differed significantly between the elderly and nonelderly group. Compared to the general Dutch population, survival of both elderly and nonelderly seems lower. Visually, this difference seems more pronounced in the elderly group, which suggests a greater impact of elective aortic surgery on long-term survival in elderly. However, this could not be statistically tested in this study.

In the nonelderly, higher age was associated with higher long-term mortality, whereas this was not the case in the elderly group. Perhaps the patients in the nonelderly group had more variability in age in the presence of other risk factors and comorbidities compared to the patients in the elderly group. The difference in mortality risk between younger adults and adults approaching 70 might therefore be larger than the difference within the elderly group, which lead to our finding of age being a more important risk factor within the nonelderly group. Furthermore, in nonelderly patients female sex was associated with higher long-term mortality in univariable analyses. In multivariable analysis sex was not significantly associated with long-term mortality anymore. Therefore, this finding might be attributable to confounding, warranting attention in future studies.

Study Limitations

This study has several limitations. First, this is a retrospective cohort study, for this reason there were missing data. Second, as stated before, only patients who underwent surgery were included and the study did not include patients who were not operated (for example for their comorbidity burden) which will have caused inclusion bias. Third, the impact of aortic surgery on quality of life was not determined in our study. Since this is an important factor especially in elderly, we feel this is important topic to incorporate in future research.

Thus, this study brings valuable information about the risk of elective aortic surgery in elderly patients, with a sizeable cohort operated over 10 years. Some next steps in this study exploration are the quality of life after an elective ascending aortic aneurysm surgery. Did the clinical condition of the elderly patients improve (or decline) after surgery and are they satisfied with the postoperative results? Or did they regret the choice they had made afterwards? This also brings useful information for the elderly who are considering invasive surgery. Besides, further exploration of the male-female difference in elderly is necessary, since the results of our study suggests there may be differences.

CONCLUSION

This study showed that elective ascending aorta surgery is performed at a larger aorta diameter in elderly, especially in elderly females who had very large pre-operative aortic diameters. Despite being operated at a later stage of disease, postoperative mortality and major morbidity after elective aortic aneurysm surgery were not different in elderly, nor elderly females compared to nonelderly. Therefore, reluctance towards performing elective aortic surgery in selected elderly patients is less necessary. Further exploration of the male-female difference in elderly patients is warranted.

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SUPPLEMENTAL FILE 1

Performed Surgical Techniques in this Study

During the inclusion period, there was a substantial variability in the applied surgical techniques. Below we describe the most commonly used surgical procedures are described here. The surgical interventions were performed using a median sternotomy approach. After heparinization, cardiopulmonary bypass (CPB) was initiated which was followed by aortic clamping. Due to the elective character of the surgical interventions, it was in most cases possible to cannulate in the ascending aorta. However, the aortic arch, femoral artery and subclavian artery were used as well. Venous cannulation was performed by using a two-stage cannula in the right atrium and inferior vena cava, or cannulation in the superior and inferior vena cava or in the femoral artery. Myocardial protection was performed with the use of cold cardioplegia. If deep hypothermic cardiac arrest (DHCA) was performed, patients were cooled to a nasal temperature of 20 or 25 °C nasal until pO_2 was 40 mmHg. In most cases, uni- or bilateral antegrade cerebral perfusion (ACP) was used, especially when a long DHCA time (>30 minutes) was expected. Indications for DHCA include congenital aortic arch surgery and heavy aortic calcification since distal aortic clamping would increase stroke risk. In the final years of the study, bilateral ACP was mainly used, with cooling down to below 25 degrees. When DHCA was not performed, a temperature of 32 to 35 degrees was maintained for the moderate hypothermia.

Depending on the indication, and surgeon and patient preference, Bentall(- de Bono) (1), Valve Sparing Aortic Root Replacement (VSARR) or Supracoronary Aorta Replacement (SCAR) were performed.

In the Bentall procedure, the mechanical Bentall was a ready-made tube plus valve in one. The biological Bentall was either constructed in the operating room or was a ready-made compound conduit. Firstly, the enlarged portion of the ascending aorta and the aortic valve were explanted and the coronary buttons were prepared, placing U-stitches around. The graft with valve was replaced and then an edge of aortic tissue was adhered to the prosthesis for hemostasis. Hereafter, the coronary buttons were reimplanted. Finally, an end-to-end anastomosis between prosthesis and native distal aorta was performed.

The VSARR included the David (or reimplantation) (2) and Yacoub (or remodeling) (3) techniques. In the David technique, the coronary buttons were prepared and the aortic wall was excised. The stitches were placed on felt. Then, the stitches were pulled through the base of the prosthesis and tied off. The valve was reimplanted in the prosthesis. The edges of aortic tissue were then adhered to the prosthesis, with anchoring of the commissures. Finally, end-to-end anastomosis of the graft to the distal aorta was performed.

Two Yacoub techniques were performed during the study period: the classic Yacoub and the partial Yacoub technique, which was performed in most of the patients. In the Yacoub technique, the annulus of the aorta was not involved in the procedure compared to the David technique. Furthermore, the partial Yacoub procedure consisted of the excision of the non-coronary sinus.

Finally, SCAR was also performed in the study cohort. The aorta was excised above the sinuses of Valsalva, and the graft was anastomosed to the aortic root, after which an end-to-end anastomosis of the graft to the distal aorta was performed.

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SUPPLEMENTAL FILE 2

Definitions of all included variables

Variable	Unit	Definition
Patient Characteristics		
Year of birth		Year of birth
Age at time of surgery	years	
Sex	none	Sex: male or female
Height	meters	At admittance or last measured before surgery
Weight	kilograms	At admittance or last measured before surgery
Body surface area	m^2	At admittance or last measured before surgery
Body mass index	kg/m^2	At admittance or last measured before surgery
Prior aortic surgery		Has the patient had aortic surgery before? Options: same part of aorta, other part of aorta, same and other part of aorta, other and unknown.
Description of prior aortic surgery		Short description of prior aortic surgery including date of prior surgery
Prior cardiac surgery		Has the patient had cardiac surgery before? Options: CABG, PTCA, AVR, CABG+AVR, other and unknown.
Description of prior cardiac surgery		Short description of prior cardiac surgery including date of prior surgery
Recent myocardial infarction		(N)STEMI < 90 days of presentation
History of myocardial infarction		(N)STEMI in patient history: > 90 days before presentation
History of aortic valve stenosis		Is the patient known with aortic valve stenosis? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4. Moderate aortic valve stenosis: V_{max} 3.0-3.9 m/s and AVA 1.1-1.5 cm^2, and severe stenosis: V_{max} ≥4.0 m/s and AVA ≤1.0 cm^2.
History of aortic valve insufficiency		Is the patient known with aortic valve insufficiency? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4. Moderate aortic valve insufficiency: jet width 25-64% of the left ventricular outflow tract (LVOT), and severe insufficiency: ≥65% of LVOT.
Mixed aortic valve disease		Mixed disease is defined as stenosis and regurgitation
History of mitral valve stenosis		Is the patient known with mitral valve stenosis? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4
History of mitral valve insufficiency		Is the patient known with mitral valve insufficiency? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4
History of hypertension		Medical treatment for hypertension or recorded in patient history
History of diabetes mellitus		Medical treatment for diabetes mellitus or recorded in patient history. Options: NIDDM, IDDM and unknown.
History of COPD		History of COPD that required medical treatment or when FEV1 was <70%
History of CVA		TIA and/or CVA in patient history

Definitions of all included variables (continued)

Variable	Unit	Definition
History of chronic kidney disease		Is the patient known with chronic kidney disease? Yes when this is recorded in patient history. Thus, it is not dependent on the current eGFR.
History of renal dialysis		The patient is currently receiving any type of renal dialysis for chronic kidney disease
History of smoking		From at least 1 packyear. Options: never, currently, in past and unknown.
History of hyperlipidaemia		Medical treatment for hyperlipidaemia/dyslipidaemia/ hypercholesterolemia or recorded in patient history
Prior dissection or aneurysm in a major artery other than the thoracic aorta?		Is the patient familiar with a dissection elsewhere (every vessel except the thoracic aorta)?
Known genetic disease prior to surgery?		Any genetic disorder confirmed by genetic testing, if not confirmed then: suspected. Options: Marfan syndrome, Loeys-Dietz syndrome, SMAD3 gene mutation, Ehlers-Danlos syndrome, ACTA 2 gene mutation, MYH11 mutation, Turner syndrome, et cetera.
Is there a positive family history of aortic pathology?		1st or 2nd degree family member with: thoracic aortic aneurysm or dissection; an aneurysm or dissection elsewhere < 60 y; congenital left sided heart disease or sudden death <45y.
Is there a positive family history of any connective tissue disorder?		Any connective tissue disorder in 1st or 2nd degree family members
Remarks patient characteristics		Any remarks regarding patient characteristics
Pre-operative		
How did the patient present to the clinic for the very first time?		How was the aortic aneurysm discovered? Options: coincidental finding, (family) screening, (suspected) connective tissue disorder, exercise related symptoms/complaints, non-exercise related symptoms/complaints and unknown.
At which location was the maximal diameter of the aorta measured?		Location of the maximal aortic diameter. Options: sinuses of Valsalva, ascending aorta, aortic arch, descending aorta, abdominal aorta and unknown.
Maximal aortic diameter measured before surgery	millimetres	Measured diameter of maximal aortic diameter
Dilatation of aortic valve annulus		As described in the patient files (>40 mm)
Dilatation of Sinuses of Valsalva		As described in the patient files (>40 mm)
Dilatation of ascending aorta		As described in the patient files (>40 mm)
Dilatation of aortic arch		As described in the patient files (>40 mm)
Dilatation of descending aorta		As described in the patient files (>40 mm)
Dilatation of abdominal aorta		As described in the patient files (>30 mm)
Does the aortic aneurysm extend into the brachiocephalic artery?		Does the patient has dilatation/aneurysm of the brachiocephalic artery at the same time?
Does the aortic aneurysm extend into the carotid artery?		Does the patient has dilatation/aneurysm of the carotid artery (left and/or right) at the same time?

Definitions of all included variables (continued)

Variable	Unit	Definition
Does the aortic aneurysm extend into the subclavian artery?		Does the patient has dilatation/aneurysm of the subclavian artery at the same time?
Intramural hematoma present before surgery?		Intramural hematoma of the aorta present?
Intramural ulcer present before surgery?		Intramural ulcer of the aorta present?
NYHA classification at presentation		As described in patient files. Options: NYHA class I, NYHA class II, NYHA class III, NYHA class IV and unknown.
CCS classification at presentation		As described in patient files. Options: CCS I, CCS II, CCS III, CCS IV and unknown.
Glomerular filtration rate	ml/min	Measured at admittance, or maximum 1y before surgery. For the study, only the CKD-EPI eGFR measurement was used.
Date of last eGFR measurement before surgery	dd-mm-yyyy	Date of last eGFR measurement was performed before surgery
Creatinin-level	micromol/L	Measured at admittance, or maximum 1y before surgery
Date of last creatinin measurement before surgery	dd-mm-yyyy	Date of last creatinin measurement was performed before surgery
Left ventricular ejection fraction		Last measured before surgery. Options: Good (>55%), reduced (45-55%), moderate (30-45%), poor (30%) and unknown.
Logistic EUROscore		As described in patient files
Heart rhythm registered on electrocardiogram		As described in patient file or as reported by computer on ECG itself. Options: sinus rhythm (60-100 bpm), sinus tachycardia (>100 bpm), sinus bradycardia (<60 bpm), supraventricular tachycardia (incl: atrial fibrillation/atrial flutter), paced rhythm (atrial and/or ventricular pacing), ventricular tachycardia / fibrillation, other (describe below) and unknown.
Explain 'other' rhythm seen on ECG		Other rhythm as described in patient file
Any signs of ischemia on ECG?		As described in patient file or as reported by computer on ECG itself
Remarks on pre-operative status patient		Any important details on pre-operative variables not yet specified
Imaging: transthoracic echocardiography, transoesophageal echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI)		
Date	dd-mm-yyyy	Date of the performed imaging
Annulus diameter	millimetres	As described in imaging report
Sinus of Valsalva diameter	millimetres	As described in imaging report
ST-junction diameter	millimetres	As described in imaging report
Ascending aorta diameter	millimetres	As described in imaging report
Arch diameter	millimetres	As described in imaging report
Descending aorta diameter		As described in imaging report
Aortic valve stenosis		Is the patient known with aortic valve stenosis? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4

Definitions of all included variables (continued)

Variable	Unit	Definition
Aortic valve insufficiency		Is the patient known with aortic valve insufficiency? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4
Aortic valve mixed disease		Mixed disease is defined as stenosis and regurgitation
Mitral valve stenosis		Is the patient known with mitral valve stenosis? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4
Mitral valve insufficiency		Is the patient known with mitral valve insufficiency? Trace= grade 1, slight= grade 2, moderate= grade 3, severe= grade 4
Measurement technique LVEF		Technique used to measure LVEF. Options are: M-mode, Quinones, Biplane (Modified Simpson), WMSI, or unknown.
LV(E)F	%	As described in imaging report
Other abnormalities		Other abnormalities regarding imaging of the aorta
Remarks		Any remarks regarding imaging of the aorta
Operative		
Urgency of operation		(Duration from diagnosis until surgery). Options: acute (<24 hours), urgent (within 2 weeks or during hospital stay), elective (>2 weeks) and unknown.
Operation date		The date on which the aortic surgery was performed
Incision location		Location as described in surgery report. Options: sternotomy, thoracotomy, thoracotomy and laparotomy, other and unknown.
ECC technique		Technique used for ExtraCorporeal Circulation as described in surgery report. Options: none, passive shunt, left heart bypass, full bypass and unknown.
ECC cannulation arterial		Location of arterial ExtraCorporeal Circulation placement as described in surgery report. Options: none, femoralis, subclavia, aorta ascendens, aortic arch, other and unknown.
Description of other arterial ECC cannulation		As described in surgery report
ECC cannulation venous		Location of venous ExtraCorporeal Circulation placement as described in surgery report. Options: none, vena cava superior, vena cava inferior, vena cava superior and inferior, right atrium, femoralis, other and unknown.
Description of other venous ECC cannulation		As described in surgery or anaesthesia report
Perfusion time	minutes	As described in surgery or anaesthesia report
Cardiac ischemic time	minutes	As described in surgery or anaesthesia report
Aortic ischemic time	minutes	As described in surgery or anaesthesia report
Myelum ischemic time	minutes	As described in surgery or anaesthesia report
Circulatory arrest time	minutes	As described in surgery or anaesthesia report
Cerebral perfusion type	minutes	As described in surgery or anaesthesia report. Options: none, antegrade unilateral, antegrade bilateral, retrograde and unknown.
Cerebral perfusion time	minutes	As described in surgery or anaesthesia report
Deep hypothermic cardiac arrest (DHCA) used?		As described in surgery or anaesthesia report

Definitions of all included variables (continued)

Variable	Unit	Definition
Lowest temperature	degrees Celsius	As described in anaesthesia report
Location of temperature measurement		As described in anaesthesia report
Time at start ECC	hh.mm	As described in anaesthesia report
Temperature at start of ECC	degrees Celsius	As described in anaesthesia report
Time at start DHCA	hh.mm	As described in anaesthesia report
Temperature at start of DHCA	degrees Celsius	As described in anaesthesia report
Time at end DHCA	hh.mm	As described in anaesthesia report
Temperature at end of DHCA	degrees Celsius	As described in anaesthesia report
Time at end ECC	hh.mm	As described in anaesthesia report
Temperature at end of ECC	degrees Celsius	As described in anaesthesia report
Sievers classification		Observed Sievers classification of the bicuspid aortic valve during surgery, as described in surgery report. Options: no BAV, type 0, type 1 LCC-RCC fusion, type 1 RCC-NCC fusion, type 1 NCC-LCC fusion, type 2 and unknown.
Aortic annulus surgery		Was aortic annulus surgery performed? Options: no, yes with ring and unknown.
Aortic valve surgery		Aortic valve surgery performed during aortic surgery. Options: none, repair, replacement with mechanical valve, replacement with bioprosthesis, replacement with homograft, replacement with allograft, replacement with mechanical valved conduit (mechanical Bentall), replacement with biological valved conduit (Bio-Bentall), valve sparing David (reimplantation), valve sparing Yacoub (remodeling), other or unknown.
Aortic valve graft size	millimetres	Graft size used during surgery
Aortic root graft size	millimetres	Graft size used during surgery
Ascending aorta surgery		Was ascending aorta surgery performed? Options: none, replacement, repair or other and unknown.
Ascending aorta graft size	millimetres	Graft size used during surgery
Aortic arch surgery		Was aortic arch surgery performed? Options: none, replacement, hemi-arch, repair/patch/other, elephant trunc and unknown.
Aortic arch surgery graft size	millimetres	Graft size used during surgery
Reimplantation aortic arch branches		Were reimplantation of aortic arch branches performed? Options: none, with patch, separately, en bloc and unknown.
Reimplantation brachiocephalica		Was reimplantation of the brachiocephalic artery performed?
Reimplantation left common carotid		Was reimplantation of the left common aortic performed?
Reimplantation left subclavian		Was reimplantation of the left subclavian performed?
Descending aorta surgery		Was descending aorta surgery performed? Options: none, replacement, repair/patch/other and unknown.

Definitions of all included variables (continued)

Variable	Unit	Definition
Reimplantation intercostal arteries		Was reimplantation of the intercostal arteries performed?
Reimplantation intercostal arteries number		As described in anaesthesia report
Thoracoabdominal aorta surgery		Was thoracoabdominal aorta surgery performed? Options: none, distal anastomosis suprarenal, distal anastomosis infrarenal, distal anastomosis beyond bifurcation and unknown.
Reimplantation renal arteries		Was reimplantation of the renal arteries performed?
Reimplantation visceral arteries		Was reimplantation of the visceral arteries performed?
Concomitant procedures		Other procedures than aortic aneurysm surgery, or as described before performed. Options: none, CABG, mitral valve surgery, CABG and mitral valve surgery, other and unknown.
Description of other concomitant procedures		As described in surgery report
Any remarks regarding operative variables		
Postoperative		
Numer of days the patient was admitted	days	Total time in days from admission until discharge
Date of discharge to home, other hospital or institute	dd-mm-yyyy	As described in patient files
Number of days in ICU after surgery	days	Number of days that the patient stayed in the intensive care unit after surgery
Number of days on ventilation support after surgery	days	Number of days that the patient was on ventilation support after surgery
Death within 30 days OR before hospital discharge		Mortality within 30 days or before hospital discharge. Options: no, yes pre-surgery, yes in operating theatre, yes post-surgery and unknown.
Cause of in hospital death		As described in patient files. Options: no in-hospital death, bleeding, cardiac (incl. tamponade), aortic rupture, organ failure, sepsis, neurologic, other and unknown.
Reoperation needed		Was reoperation performed? Options: no reoperation, bleeding, tamponade, mediastinitis, cardiac ischemia, other visceral ischemia, structural valve deterioration, non-structural valve dysfunction, other graft dysfunction, endocarditis, other and unknown.
Indication for reoperation		Indication of reoperation when performed
Implantation of tracheostoma postop?		Did the patient receive implantation of tracheostoma after surgery?
New permanent heart rythm disturbances after surgery?		If postoperative pacemaker or ICD implantation was performed, if medication is used to treat arrhythmia, or if it is named permanent in the patient files. Options: supraventricular, ventricular, AV-block or unknown
Pacemaker or ICD implanted after surgery?		Only when the pacemaker or ICD was implanted within 14 days after surgery. Options: no, yes pacemaker, yes ICD and unknown.
What was the indication for pacemaker implantation?		As described in patient files

Definitions of all included variables (continued)

Variable	Unit	Definition
What was the indication for ICD implantation?		As described in patient files
Myocardial infarction or ischemia after surgery		During admission or within 30 days after surgery
Other cardiac complications after surgery?		During admission or within 30 days after surgery
Explain 'other' cardiac complication after surgery		
Bleeding event after surgery		During admission or within 30 days after surgery
Explain bleeding event after surgery		During admission or within 30 days after surgery
Diagnosis of infective endocarditis after surgery?		During admission or within 30 days after surgery
Structural valve deterioration after surgery?		During admission or within 30 days after surgery. Structural valve deterioration was defined as a result of failure of the valve itself.
Describe type of structural valve deterioration:		
Non-structural valve dysfunction after surgery?		During admission or within 30 days after surgery. Non-structural valve disease was defined as not due to the fall of the valve itself resulting in stenosis, regurgitation or hemolysis. Valve thrombosis and infection are not included.
Describe type of non-structural valve dysfunction		
Valve thrombosis after surgery?		During admission or within 30 days after surgery
Left ventricular thrombus diagnosed after surgery?		During admission or within 30 days after surgery
Lowest eGFR measured during admittance after surgery?		During admission or within 30 days after surgery. For the study, only the CKD-EPI eGFR measurement was used.
Last eGFR-level measured before discharge		For the study, only the CKD-EPI eGFR measurement was used
Last creatinine-level measured before discharge	micromol/L	During admission or within 30 days after surgery
TIA after Surgery?		During admission or within 30 days after surgery
CVA diagnosed after surgery?		During admission or within 30 days after surgery
Spinal cord lesion after surgery		During admission or within 30 days after surgery
New recurrence nerve lesion after surgery		During admission or within 30 days after surgery
Other neurological complications?		During admission or within 30 days after surgery
Describe other neurological complications diagnosed.		During admission or within 30 days after surgery
Diagnosis of psychiatric disorder after surgery (e.g. delirium)?		During admission or within 30 days after surgery. Delirium also falls under this category.
Diagnosis of any infection after surgery?		During admission or within 30 days after surgery

Definitions of all included variables (continued)

Variable	Unit	Definition
Describe the type of infection(s) that occured after surgery		Superficial wound infection was defined as wound infections for which no reoperation has been performed. Deep wound infection was defined as wound infection for which reoperation has been performed.
Diagnosis of sepsis after surgery?		During admission or within 30 days after surgery
Occurence of any vascular complications (eg ischemia, thrombosis, compartment syndrome)		During admission or within 30 days after surgery
Describe the vascular complication that occured		
If any other post-surgery complications were registered (eg pulmonary embolism, pneumothorax, decubitus, urinary retention) please explain here:		During admission or within 30 days after surgery

SUPPLEMENTAL FILE 3

Extra-analyses for the ≥75 years patient population

Table 3a Short-term Mortality and Admission Days after Elective Aortic Aneurysm Surgery

	Total (n= 955)	Aged <75 yrs (n= 849)	Aged ≥75 yrs (n= 106)	p-value	Missing
In-hospital or 30-day Mortality	18 (1.9)	14 (1.6)	4 (3.8)	0.13	0/955
Cause of Mortality					0/955
Cardiac (incl. Tamponade)	8 (0.8)	7 (0.8)	1 (0.9)	1.00	
Bleeding	3 (0.3)	2 (0.2)	1 (0.9)	0.30	
Aortic Rupture	2 (0.2)	2 (0.2)	0 (0.0)	1.00	
Organ Failure	1 (0.1)	0 (0.0)	1 (0.9)	0.11	
Sepsis	2 (0.2)	2 (0.2)	0 (0.0)	1.0	
Other	1 (0.1)	0 (0.0)	1 (0.9)	0.11	
Number of Days the patient was Admitted[a]					0/955
1-4	23 (2.4)	21 (2.5)	2 (1.9)	1.00	
5-9	590 (61.7)	528 (62.2)	62 (58.5)	0.46	
10-14	206 (21.5)	183 (21.6)	22 (20.8)	0.85	
15-19	66 (6.9)	59 (6.9)	7 (6.6)	1.000	
≥20	71 (7.4)	58 (6.8)	13 (12.3)	0.044*	
Total[#]	8.0 (7.0-11.0)	8.0 (7.0-11.0)	9.0 (7.0-13.0)	0.40	
Number of Days in ICU[1] after Surgery[a]					(23/849)/ (1/106)
1-4	828 (86.6)	744 (90.0)	84 (80.0)	0.002**	
5-9	71 (7.4)	57 (6.9)	14 (13.3)	0.019**	
10-14	18 (1.9)	14 (1.7)	4 (3.8)	0.14	
15-19	5 (0.5)	4 (0.5)	1 (1.0)	0.45	
≥20	10 (1.0)	8 (1.0)	2 (1.9)	0.31	
Total[#]	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-4.0)	<0.001**	
Number of Days on Ventilation Support after Surgery[a]					(32/849)/ (5/106)
1	552 (57.7)	512 (62.6)	39 (38.6)	<0.001**	
2	308 (32.2)	257 (31.4)	51 (50.5)	<0.001**	
3	19 (2.0)	17 (2.1)	2 (2.0)	1.00	
4	10 (1.0)	9 (1.1)	1 (1.0)	1.00	
≥5	31 (3.2)	23 (2.8)	8 (7.9)	0.015**	
Total[#]	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	<0.001**	

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).

[#] Presented as median (Interquartile Range, IQR) of the total number of days in the whole, nonelderly and elderly population

ICU: Intensive Care Unit

[a] Significant differences were mainly found in the outliers in the number of days in elderly patients.

[1] NE/E: Nonelderly/Elderly

* Significant at the 0.05 level

** Significant at the 0.01 level

Table 3b Short-term Postoperative Morbidity After Elective Aortic Aneurysm Surgery

	Total (n= 955)	Aged <75 yrs (n= 849)	Aged ≥75 yrs (n= 104)	p-value	Missing
Tracheostoma Implantation	8 (0.8)	6 (0.7)	2 (1.9)	0.22	(1/849)/ (0/106)
New Permanent Heart Rhythm	245 (25.7)	201 (23.7)	44 (41.5)	<0.001**	(3/849)/
Disturbances	211 (22.1)	169 (19.9)	42 (39.6)	<0.001**	(0/106)
Supraventricular	6 (0.6)	6 (0.7)	0 (0.0)	1.00	
Ventricular	28 (2.9)	25 (2.9)	2 (1.9)	0.76	
AV-block					
Pacemaker or ICD Implanted	32 (3.3)	30 (3.5)	2 (1.9)	0.57	0/955
Myocardial Infarction or Ischemia	18 (1.9)	16 (1.9)	2 (1.9)	1.00	0/955
Other Cardiac Complications	69 (7.2)	57 (6.7)	12 (11.3)	0.086	(2/849)/ (0/106)
Infective Endocarditis	4 (0.4)	3 (0.4)	1 (0.9)	0.38	(3/849)/ (0/106)
Non-Structural Valve Dysfunction	2 (0.2)	2 (0.2)	0 (0.0)	1.00	0/955
CVA/TIA	43 (4.5)	38 (4.5)	5 (4.7)	0.81	(2/849)/ (0/106)
New Recurrence Nerve Lesion	12 (1.3)	12 (1.4)	0 (0.0)	0.38	0/955
Other Neurological Complications	33 (3.5)	28 (3.3)	5 (4.7)	0.40	(1/849)/ (0/106)
Diagnosis of Psychiatric Disorder	146 (15.3)	105 (12.4)	41 (38.7)	<0.001**	0/955
Diagnosis of Infection	130 (13.6)	108 (12.7)	22 (20.8)	0.023**	0/955
Pneumonia	60 (6.3)	49 (5.8)	11 (10.4)	0.065	
Superficial Wound Infection	15 (1.6)	12 (1.4)	3 (2.8)	0.23	
Severe Wound Infection	10 (1.0)	7 (0.8)	3 (2.8)	0.089	
Urinary Tract Infection	18 (1.9)	14 (1.6)	4 (3.8)	0.13	
Other	15 (1.6)	15 (1.8)	0 (0.0)	0.40	
Of Unknown Origin	25 (2.6)	20 (2.4)	(4.7)	0.19	
Diagnosis of Sepsis	11 (1.2)	9 (1.1)	2 (1.9)	0.35	0/955
Diagnosis of Vascular Complications	15 (1.6)	11 (1.3)	4 (3.8)	0.074	0/955

Continuous data are presented as mean ± SD when the distribution is normal, or median (Interquartile Range, IQR) for variables without normal distribution. Categorical data are presented as frequencies (percentages).

CVA/TIA: Cerebrovascular Accident/Transient Ischemic Attack

* Significant at the 0.05 level

** Significant at the 0.01 level

SUPPLEMENTAL FILE 4

Univariable analysis on factors associated with long-term survival

	Total (n=928)		Elderly (n=227)		Nonelderly (n=701)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Baseline						
Male sex	0.51 (0.38-0.69)	**<0.001****	1.07 (0.69-1.64)	0.765	0.55 (0.35-0.86)	**0.009****
Age	1.08 (1.06-1.09)	**<0.001****	1.06 (0.99-1.13)	0.081	1.06 (1.04-1.09)	**<0.001****
BSA	0.21 (0.11-0.40)	**<0.001****	0.62 (0.21-1.87)	0.398	0.45 (0.18-1.13)	0.088
History of hypertension	2.73 (1.90-3.92)	**<0.001****	2.64 (1.21-5.78)	**0.015***	1.56 (0.99-2.45)	0.055
History of hyperlipidaemia	1.64 (1.20-2.23)	**0.001****	1.12 (0.74-1.72)	0.587	1.60 (1.01-2.53)	**0.045***
Diabetes	1.42 (0.82-2.46)	0.216	0.24 (0.06-0.97)	**0.045***	3.25 (1.75-6.03)	**<0.001****
COPD	1.94 (1.26-2.98)	**0.003****	1.13 (0.62-2.05)	0.694	2.13 (1.12-4.05)	**0.021***
Prior CVA	1.02 (0.64-1.63)	0.925	1.14 (0.65-1.99)	0.645	0.60 (0.24-1.48)	0.266
Prior MI	1.34 (0.66-2.70)	0.415	0.79 (0.26-2.40)	0.678	1.82 (0.74-4.51)	0.194
Chronic kidney disease	2.75 (1.66-4.56)	**<0.001****	1.85 (1.00-3.41)	0.051	2.20 (0.88-5.46)	0.091
Prior aortic surgery	0.48 (0.25-0.92)	**0.026***	0.78 (0.29-2.14)	0.631	0.57 (0.25-1.32)	0.188
Prior dissection or aneurysm in major artery other than thoracic aorta	0.52 (0.13-2.11)	0.362	1.13 (0.26-4.86)	0.868	0.05 (0.00-36.07)	0.369
BAV	0.65 (0.47-0.90)	**0.010***	0.76 (0.42-1.37)	0.366	1.10 (0.71-1.71)	0.675
Presentation						
GFR	0.97 (0.97-0.98)	**<0.001****	0.99 (0.98-1.00)	0.112	0.98 (0.97-0.99)	**<0.001****
Log Euroscore	1.04 (1.03-1.06)	**<0.001****	1.00 (0.98-1.02)	0.944	1.03 (1.01-1.06)	**0.017***
Surgery						
Perfusion time	1.00 (1.00-1.00)	0.178	1.00 (1.00-1.01)	0.102	1.00 (1.00-1.01)	0.443
AoX time	1.00 (1.00-1.00)	0.899	1.00 (1.00-1.01)	0.272	1.00 (1.00-1.01)	0.968
DHCA	1.72 (1.26-2.33)	**<0.001****	1.26 (0.81-1.95)	0.300	1.35 (0.87-2.11)	0.180
Aortic valve surgery	1.35 (0.94-1.93)	0.107	1.01 (0.63-1.60)	0.980	1.07 (0.59-1.94)	0.828
Aortic arch surgery	0.54 (0.40-0.74)	**<0.001****	0.68 (0.44-1.06)	0.085	0.74 (0.47-1.15)	0.182
Ascending aortic surgery	8.15 (2.02-32.85)	**0.003****	1.30 (0.18-9,37)	0.794	9.46 (1.32-68.00)	**0.026***
Supracoronary replacement	1.44 (1.06-1.96)	**0.018***	1.16 (0.76-1.77)	0.483	1.07 (0.68-1.70)	0.770
VSARR	0.23 (0.10-0.52)	**<0.001****	0.89 (0.28-2.84)	0.846	0.20 (0.06-0.64)	**0.006****
Concomitant procedures	2.05 (1.47-2.85)	**<0.001****	1.35 (0.83-2.20)	0.226	1.82 (1.15-2.89)	**0.011***

Data is presented as Hazard Ratio (95% percent confidence interval)

BSA= Body Surface Area; COPD: Chronic Obstructive Pulmonary Disease, CVA: Cerebrovascular Accident, MI: Myocardial Infarction, BAV= Bicuspid Aortic Valve; AA: Aortic Aneurysm, LVEF: Left Ventricular Ejection Fraction, HTAD: Hereditary Thoracic Aortic Disease, NYHA: New York Heart Association, GFR: Glomerular Filtration Rate, DHCA: Deep Hypothermic Cardiac Arrest, BAV: Bicuspid Aortic Valve, ICU: Intensive Care Unit

PART III

Living with thoracic aortic disease

CHAPTER 7

Exercise and sports participation in patients with thoracic aortic disease: a review

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Expert Review of Cardiovascular Therapy, 2019

ABSTRACT

Introduction

Current guidelines recommend patients with thoracic aortic disease (TAD) including inherited aortopathies to avoid heavy exercise. However, evidence supporting the negative advice on exercise is scarce. We aimed to provide an up-to-date systematic review of the available evidence on risks and benefits of exercise and sports participation in TAD patients.

Areas covered

A systematic search was performed in Medline, Embase and Web of Science: thoracic aortic aneurysm or thoracic aortic dissection or inheritable aortopathies including Marfan Syndrome (MFS), Loeys-Dietz syndrome, Turner Syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve (BAV) and sports, exercise or athletes. The resulting 1,652 manuscripts were reviewed by two independent observers. Eventually, 26 studies and 12 case-reports were included, reporting on thoracic aortic dimensions in athletes, exercise related acute aortic dissections, and exercise in BAV and MFS patients.

Expert commentary

Blood pressure elevation during exercise may be associated with an increased risk of acute aortic dissection; however, no controlled trials have longitudinally evaluated the effect of exercise on survival or the risk of aortic dissection in TAD patients. Mouse-model studies suggest beneficial effects of exercise in the setting of a dilated aorta in MFS. There is a clear need for prospective research in this field.

INTRODUCTION

The incidence of thoracic aortic disease (TAD) such as thoracic aortic aneurysms and dissections is estimated to be 9.1-16.3/100,000 per year [1]. However, thoracic aortic aneurysms are mostly asymptomatic and its prevalence is probably underestimated. About 20% of patients with thoracic aortic dilatation have a positive family history of aortic disease [2], which can be an expression of an underlying disorder such as bicuspid aortic valve (BAV) or connective tissue disorders, such as Marfan Syndrome (MFS), Loeys-Dietz syndrome, Ehlers-Danlos syndrome or Turner Syndrome. BAV patients are of particular interest because this condition is not uncommon with a prevalence of about 1% in the general population [3-5]. However, BAV patients seem to be at relatively low risk for aortic dissection [6]. On the contrary, Marfan Syndrome has a lower prevalence of 6.5/100.000, but these patients are at high risk of acute aortic dissection [7].

The hemodynamic changes associated with exercise, and specifically the increase in blood pressure, is potentially associated with an enhanced risk of aortic growth and acute aortic dissection in the context of a thoracic aortic disease (TAD). Current guidelines state that patients with TAD should avoid strenuous resistance or isometric exercise and competitive sports [8-10]. Due to the lack of data, however, these European, Canadian and American guidelines are characterized by low levels of evidence [8-10]. Recommendations for specific patient groups, such as patients with BAV, are in line with these guidelines. However, MFS patients are advised to only participate in low and moderate intensity sports with regular checks including echocardiography every 6 months, even if aortic root dilatation is absent [11-13].

The importance of daily exercise became clear in the 1950's when an inverse relationship between physical activity and cardiovascular risk was discovered [14]. Ever since, it has become well understood that a sedentary lifestyle is an important modifiable risk factor for cardiovascular disease and mortality [15]. Furthermore, regular exercise is known to prevent and reduce hypertension [16]. For TAD patients it is evenly important to not have a sedentary lifestyle, but also to prevent thoracic aortic growth and the occurrence of aortic dissection, creating a difficult paradox for clinicians. In this study, we sought to provide an up-to-date systematic review of the available evidence on exercise and sports participation in TAD patients including those with inherited aortopathies, and identify gaps in knowledge. We particularly aimed to find evidence on: 1) the aortic remodelling associated with regular exercise training and upper limits of dimensions in physically active individuals, 2) the risk of acute thoracic aortic dissections during exercise, and 3) the impact of exercise on the thoracic aorta in specific patient groups, especially in BAV and MFS patients.

METHODS

Literature search

A broad systematic search was performed in Medline, Embase and Web of Science on August 2, 2018. The following search terms (including synonyms) were used: exercise, sports, athletes, training and thoracic aortic aneurysm, thoracic aortic dissection. Additionally, search terms were included for various inheritable connective tissue disorders: Marfan syndrome, Loeys-Diets syndrome (including aneurysm osteoarthritis syndrome e.g. SMAD3 mutation), Turner syndrome, Ehlers-Danlos syndrome and bicuspid aortic valve. The exact search details are shown in supplemental file 1. Additional publications were obtained by hand searching, and reference lists were crosschecked to identify possible relevant papers overlooked by the original search. Duplicates were identified and removed.

Study selection

Titles and abstracts were screened for eligibility by two independent researchers (CT and LB). Only articles in the English language were included. Solely original data was included, therefore reviews and meta-analysis were excluded. Furthermore, book chapters, double publications on the same cohort and conference abstracts were excluded. Papers that could not be accessed in full text were also excluded. Only case reports on acute thoracic aortic dissection associated with exercise were included, while case reports on thoracic aortic dilatation and case reports on aortic dissections not related to exercise were excluded. Papers on thoracic aortic dilatation in athletes were only included if aortic diameters were reported. Of all potentially eligible papers the full text was reviewed. In case of disagreement a third reviewer was asked for counsel (JR) and eligibility was assessed by reasoning.

RESULTS

Search results

Figure 1 shows the flowchart of the study selection. Our search identified a total of 1652 unique publications. After reviewing the titles and abstracts 1530 papers were excluded, and 122 potentially eligible papers were reviewed in full text. Finally, 26 studies and 12 case reports were included. We grouped the selected papers based on the abovementioned subjects of interest. Sixteen studies were found on thoracic aortic diameters in athletes. Three studies and twelve case reports were identified on the occurrence of acute aortic dissections during exercise. Three studies reported on exercise in MFS and four evaluated exercise in patients with BAV. Unfortunately, no papers were identified addressing

the association between exercise and thoracic aortic dilatation or risk of dissection in patients with Loeys-Dietz syndrome, aneurysm-osteoarthritis Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome or Turner syndrome.

Thoracic aortic dimensions in athletes

We identified 16 papers published between 1981 and 2015 which evaluate aortic dimensions in athletes practicing a variety of sports disciplines, shown in table 1. Almost all papers were cross-sectional cohort studies (15/16), and one was a longitudinal cohort study. The number of included patients differed greatly, ranging from 9 to 1929 participants. Eleven studies compared aortic diameters in athletes to a sedentary control group, shown in figure 2 [17-27]. Overall, outcomes of these studies show that athletes have significantly larger absolute aortic diameters than controls. However, the reported differences in absolute mean aortic root diameters are small: varying between 0.6 and 4 mm. Aortic diameter measurement was performed at the level of the aortic root in all studies, only two studies measured aortic diameter at multiple levels [23,28]. One study reported aortic root diameters corrected for body surface area (BSA) and found no significant difference between athletes and controls, although the absolute aortic root diameters were significantly different between the groups [26]. Three papers only included female athletes [17,19,20], and five papers only included male athletes [18,21-24]. The 99th percentile of aortic root dimensions in male athletes was found to be 40 mm and 34 mm for female athletes [29]. Five articles reported the prevalence of aortic root dilatation [27,29-32]. In these articles, different definitions of aortic dilatation were used, as shown in table 1. The reported prevalence of aortic dilatation among athletes was low (0.26-1.3%), except in one cohort of athletes from the US national volleyball team, in which 6% of female athletes had an aortic root diameter ≥34 mm, and 8% of male athletes had an aortic root diameter ≥40 mm [32]. However, these volleyball players were very tall with an average body height of 198.2 ± 8.0 cm in males and 184.1 ± 7.4 cm in females.

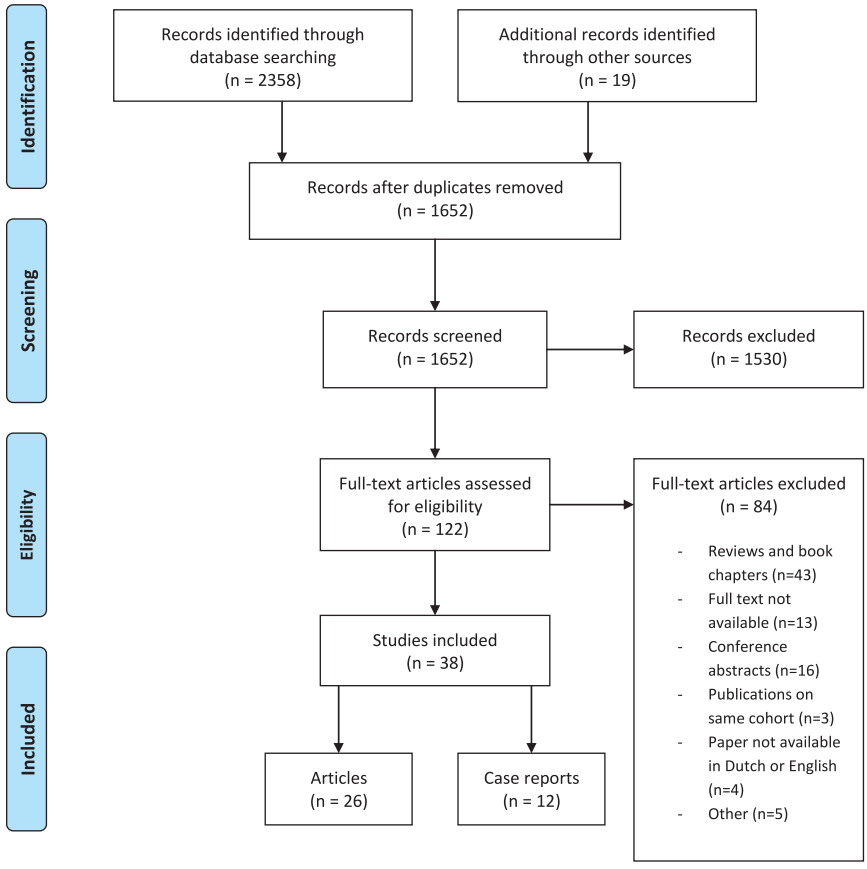

Figure 1. Flowchart of literature search and selection of studies

Four studies evaluated differences in aortic diameter between strength trained and endurance trained athletes [21,27,28,31]. Three studies report a small but significant difference in absolute aortic root diameters, with slightly larger aortic root diameters in strength trained athletes than athletes who perform dynamic exercise. The mean differences reported ranged from 2.1-5 mm. However, mean aortic root measurements were all below 40 mm [27,28,31].

Exercise-related acute thoracic aortic dissections

Table 2 presents all case reports and case series reporting the occurrence of thoracic aortic dissections during exercise. The papers were published between 1987-2016 and each describe 1 to 31 cases of acute thoracic aortic dissection occurring during sports activities. A total of 49 patients were described, of whom 42 suffered Stanford type A thoracic aortic dissections and 7 patients had Stanford type B dissections. Remarkably, only 2 out of 49

patients (4%) were female. The age ranged from 12 to 76 years. However, many reports only included young patients, with half of the papers reporting on patients up to 20 years of age [33-38]. In the majority of cases (26/49) weightlifting was the type of sport associated with the occurrence of aortic dissection [34-37,39-41]. MFS was diagnosed after presentation in four patients and one patient was known to have a connective tissue disorder other than MFS, which was not specified. Notably, family history was not obtained or reported in 7 of the 12 papers [34,35,39,41-44].

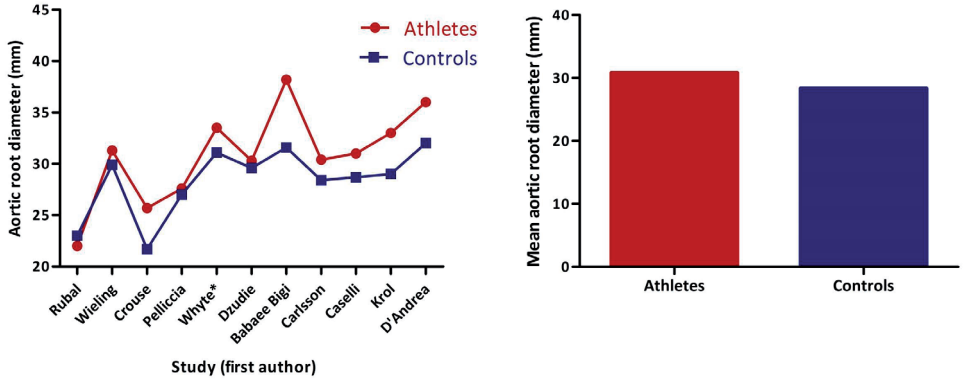

Figure 2. Studies that reported aortic root diameters in athletes and controls

*This study reported only aortic annulus diameter, not aortic root diameter

Furthermore, three retrospective cohort studies on sports related acute aortic dissections type A (AD-A) were identified, shown in table 3. Only one paper focussed on the different types of sports practised during AD-A [45]. This study described 650 patients with a mean age of 62.3 years in patients with sports-associated AD-A and 63.7 years in non-sports associated AD-A. Of all AD-A's 4.1% was found to be associated with sports activities [45]. The type of sport most often reported was golf (32%), followed by swimming and cycling (each 16%), weight lifting (12%), and dancing (8%). Figure 3 illustrates the distribution of sports-related AD-A's reported in this study over the different sports categories. These exercise related AD-A's occurred in all age groups and there was no significant difference in sex distribution between sports related AD-A's (60% males) and non-sports related AD-A's (52% males) [45]. Two retrospective cohort studies were identified specifically studying the occurrence of AD-A during a specific exercise: sexual intercourse and alpine skiing [46,47]. The first reports exercise and sexual intercourse associated AD-A's in a cohort of 365 patients and found a much higher percentage of 68% exercise associated AD-A's, with no significant difference between males and females. In this study, evidence of MFS was present in only 0.9% of patients. AD-A associated with sexual intercourse occurred only in males (17/245) [46]. The other retrospective cohort study by Schachner et al.[47] reported on AD-A's occurring during winter season and they found that 22% of all AD-A's were

associated with alpine skiing, and the majority of these cases were unrelated to trauma (82%). There was no significant difference in sex distribution between skiing associated AD-A (88% males) and AD-A not associated with skiing (77% males).

Exercise in patients with BAV

We identified four papers reporting on the association between exercise and thoracic aortic diameters or thoracic aortic dilatation rate in BAV patients, which are shown in table 4. Of these, three papers came from the same research group [48-50]. Two of which compared athletes with BAV to athletes with a normal tricuspid aortic valve (TAV) [48,49]. Both reported significantly larger aortic diameters at all measured levels in BAV athletes compared to TAV athletes. However, all reported mean diameters were below 36 mm. One cross-sectional study, which included 58 competitive athletes with BAV, showed no correlation between aortic dimensions and duration of training [48]. Two longitudinal studies presented by the same research group reported on mean aortic diameter growth rate in BAV athletes, presumably describing the same patients. The mean growth rates reported were: 0.78 mm/year at the aortic annulus (Ann), 0.61 mm/year at the Sinuses of Valsalva (SoV), 0.81 mm/ year at the sinotubular junction (STJ) and 0.98 mm/year at the proximal ascending aorta (AA) [49,50]. The mean age of these two cohorts of BAV athletes were 19 ± 8.8 years and 25 ± 11 years. No significant increase of aortic diameter was reported in TAV athletes (mean age 25 ± 5 years) after five years of follow-up. Another longitudinal study by Spataro et al. found no clear association between sports participation and valve deterioration in BAV patients, with a mean follow-up duration 13 years [51]. Unfortunately, no aortic diameter measurements were reported and no conclusions can be drawn about the effect of exercise on the aortic diameter in this cohort of BAV athletes. Only one paper compared BAV athletes to sedentary BAV subjects. This article reported no difference in aortic growth rate between the two groups at all measured levels of the thoracic aorta: Ann, SoV, STJ and AA [50].

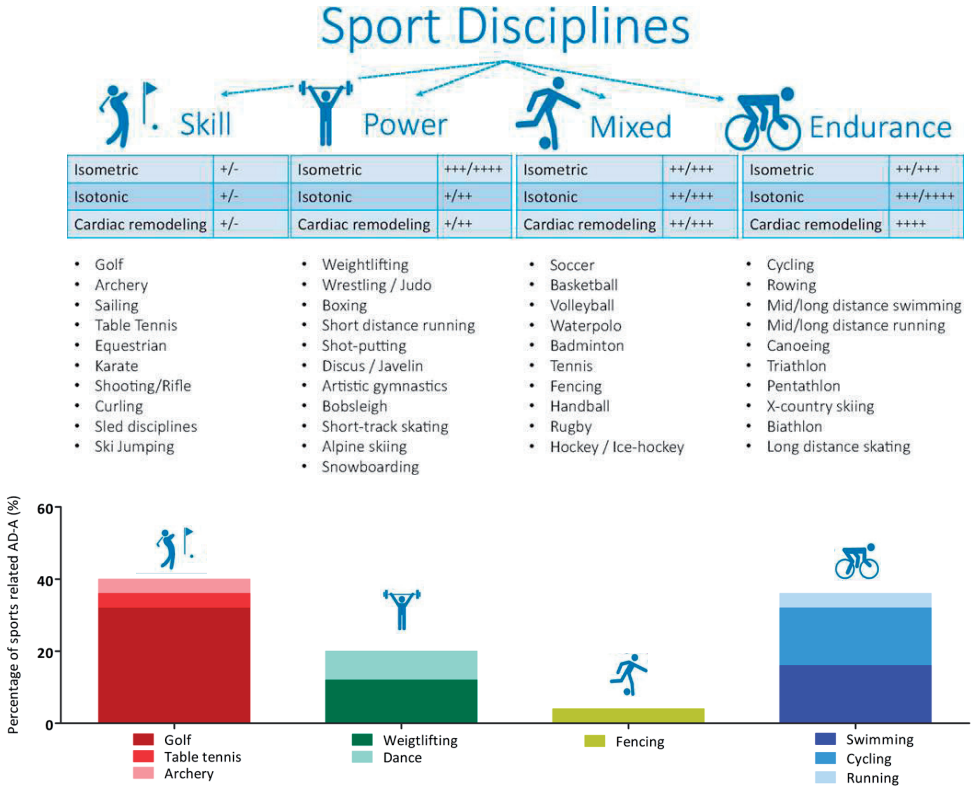

Figure 3. Classification of sports and sports related aortic dissections

Most sports require a combination static and dynamic exercise. In order to facilitate counselling about sports participation this simplified classification of the most common olympic sports disciplines was created, according to the relative isometric and isotonic components of exercise and resulting cardiovascular adaptation. Underneath the distribution of sports related aortic dissections type A (AD-A) over the four categories is displayed, based on data published by Itagaki et al. [45]. The classification of sports was reprinted from: A. Pelliccia; S. Caselli, European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete's heart, European Heart Journal, 2017, Volume 39, Issue 21, Pages 1949–1969, by permission of Oxford University Press.
AD-A= Aortic Dissection Stanford type A.

Exercise in Marfan Syndrome

Table 4 presents the three papers on exercise in MFS, all published in 2017. Two papers describe mouse model studies investigating the effects of mild-moderate dynamic exercise on the aortic wall in MFS mice [52,53]. Both were controlled trials with one or more dynamic exercise training groups and a sedentary group. The follow-up duration of both studies was five months. Both papers reported a reduction of aortic diameter growth rate in MFS mice performing mild to moderate dynamic exercise compared to sedentary MFS mice [52,53]. Also, in mice performing dynamic exercise, the aortic wall became stronger compared to sedentary MFS mice. This was testified by the larger amount of mechanical stress on the aorta required to induce rupture of the aortic wall [52]. Exercise seemed to improve aortic wall elasticity in one study [52], but no significant improvement was found in the other [53]. Dynamic exercise was not found to increase lamina ruptures, indicating no additional structural damage in the tunica media [53]. An optimum of protective effects was found at a training intensity level of 55-65% of maximum oxygen uptake (VO2max), while higher intensity of dynamic exercise training seems to blunt the positive effects [52]. The third paper is a small prospective cohort study that evaluated the feasibility and effects of a three-week rehabilitation program in 19 MFS patients with a mean age of 46.7±7.8 years [54]. During the one-year follow-up, no adverse medical events were reported, physical fitness improved, and psychological distress decreased. These effects were already present after three weeks of rehabilitation, and mostly remained persistent throughout the one-year follow-up [54]. Unfortunately, no information on aortic diameters was provided.

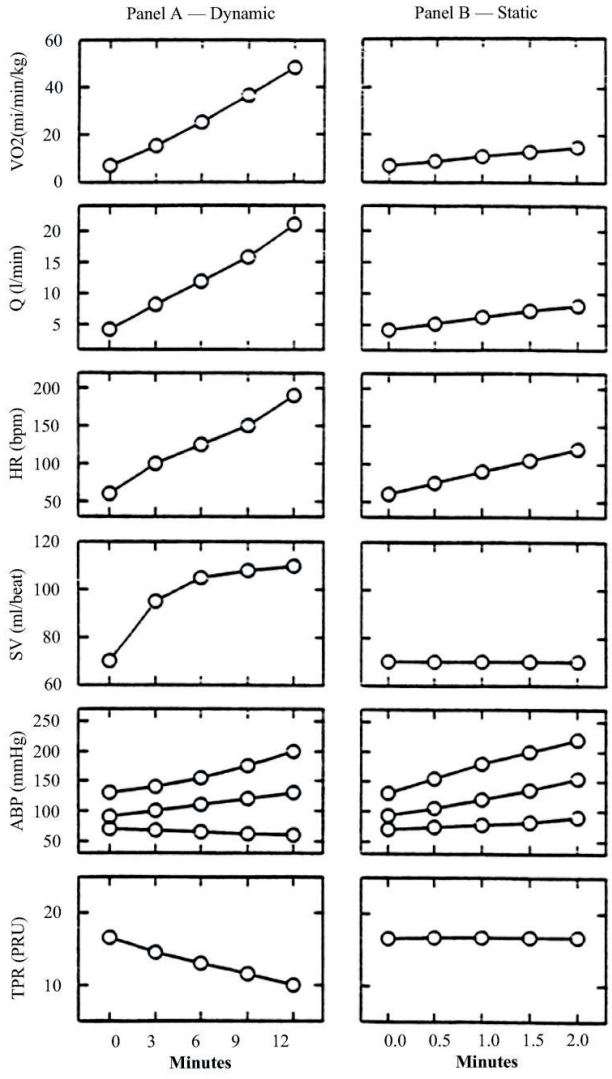

Figure 4. Hemodynamic response to exercise.
(A) Response to dynamic exercise of progressively increasing workload. This causes a volume overload as a result of increased cardiac output (Q) and arterial blood pressure (ABP), with a decrease in total peripheral resistance (TPR). **(B)** Response to a static handgrip contraction. This causes a pressure overload as a result of increased blood pressure, but no decrease in total peripheral resistance.

ABP (mm Hg): systolic, mean and diastolic arterial blood pressures; HR: heart rate (beats/min); Q: cardiac output (liters/min); SV: stroke volume (ml/beat); TPR: total peripheral resistance (PRU); VO2: oxygen uptake (ml/min/kg).

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DISCUSSION

To our knowledge, this is the first systematic review describing the effect of exercise and sports participation in TAD patients. We were not able to identify any controlled or randomized trials evaluating the longitudinal effect of exercise on survival or risk of aortic dissection in TAD patients. When focusing on the association between exercise and thoracic aortic growth rate very limited data can be found. In total, we identified 38 papers of interest, of which 9 were case reports, 3 case series, 8 longitudinal cohort studies and 16 cross-sectional cohort studies. Two were mouse-model studies: one non-randomized controlled trial and one randomized controlled trial. Assessment of methodological quality of the included papers was planned, but ultimately not performed quantitatively, since the large variety of study designs made consistent and comparable quality assessment impossible and meaningless. Eventually it can be concluded that most papers would reach low scores.

Are aortic dimensions different in athletes?

Screening before participating in competitive sports provides a lot of easily accessible data resulting in a large number of studies performed in athletes. The absolute thoracic aortic diameters reported are larger in athletes compared to non-athletic controls, although the differences are very small. This is consistent with the findings of a fairly recent meta-analysis reporting a small but significantly larger aortic root diameter in elite athletes than in non-athletic controls [55]. One study showed that after indexing aortic root diameter for BSA, the significant difference in aortic root diameter between athletes and controls was blunted [26]. Indicating the differences in aortic diameter might be attributed to a difference in body size between athletes and controls, which is known to be associated with thoracic aortic diameter [56]. The larger aortic diameters reported in athletes are therefore not necessarily caused by a pathological process, but presumably result from higher cardiac output and difference in body size. Whether this is associated with an increased risk of aortic dissection is yet to be determined. The findings mentioned above seem to be comparable in male and female athletes. However, they might not be applicable to less intensively trained and older individuals, and patients who already have TAD.

Is there an association between exercise and acute thoracic aortic dissections?

The incidence of sudden cardiac death among the younger population (< 40 years) is approximately 1.3 to 8.5 per 100,000 person-years [57]. Approximately 1-5% of sudden death in young athletes is caused by acute aortic dissections [58-60]. Over the past decades, there have been many reports, especially case-reports, that link exercise (mainly high intensity static exercise) to acute aortic dissection. Aortic dissection is an emergency situation with a reported in-hospital mortality of up to 33% [61]. This has made clinicians

cautious when counselling TAD patients about exercise. We found a striking difference in the reported amount of acute thoracic aortic dissections related to exercise: Itagaki et al. [45] reported a relation to exercise in 4.1% of all AD-A's and Gansera et al. [46] in 68% of all AD-A's . This difference might partially be explained by a different definition of 'sports related aortic dissections'. Whereas one study classified non-sports exertion and Valsalva manoeuvres such as lifting or moving a heavy load, defecation, or sexual activity, into the non-sports group (Itagaki et al.), the other classified these into the sports group (Gansera et al.). The true amount of sports-related type A aortic dissections might be somewhere in between, such as the 22% of all winter season AD-A's related to alpine skiing, as reported by Schachner et al [47]. Apart from the theoretical physiological impact, we found no evidence supporting the theory of static exercise being more prone to inducing acute thoracic aortic dissections than dynamic exercise. The majority of the identified case reports described acute thoracic aortic dissection during weightlifting. However, this might be due to selection bias, since a larger series showed the type of sport associated with AD-A most frequently was golf (32%), which is classified as a low isometric and low isotonic sport (skill category, figure 3) [45]. It seems that aortic dissection can also occur during relatively mild intensity sports such as golf, but for interpreting the results of figure 3 keep in mind that this is based on only one study and more research is clearly warranted. Of course, the size and composition of the study population is crucial here. When a study includes all patients with dissection, the mean age will be relatively high, and golf will be a sport which is prevalently practised. In younger cohorts, a totally different sports involvement pattern is likely to be found. Furthermore, this study was conducted in Japan where golf is known to be a very popular form of exercise. Therefore, in the absence of reliable information on rates of sports participation, no conclusion can be drawn on the association between dissection and a specific sports activity. Concerning the impact of sex, it was striking that almost all case reports describe males with acute aortic dissections related to exercise. However, this does not seem representative since the larger series both from Itagaki and Gansera reported no significant differences in sex distribution [45,46]. Population based studies might provide additional information, but data on the prevalence of participation in different types of sports, aortic diameters and long-term follow-up are scarce.

How does exercise influence the thoracic aorta in BAV and Marfan patients?

Although bicuspid aortic valve is the most prevalent congenital heart disease and an important underlying etiology of thoracic aortic dilatation, the association between exercise and aortic diameter and growth rate has been investigated to a limited extent in this patient group. In BAV patients, Galanti et al. and Stefani et al. state that the aortic growth rate they reported in BAV athletes does not differ from aortic growth rate reported in the general BAV population [49,50]. Indeed, the reported dilatation rate of 0.98 mm/year

found in the athletes with BAV seems comparable to the reported aortic dilatation rate in various studies reporting aortic growth rate in the general BAV population [62,63].Even though the BAV populations studied by Stefani et al and Galanti et al were relatively young (19 ± 8.8 years and 25 ± 11 years), and younger age is known to be associated with higher aortic growth rates [64]. These findings suggest that aortic growth rate is not significantly influenced by exercise in BAV patients.

Two recently published papers have investigated the effect of dynamic exercise on the thoracic aorta in mice with MFS. Both studies reported mild to moderate dynamic exercise had a positive effect on aortic growth rate and seemed to improve aortic wall structure. This suggests that exercise does not only have potential negative effects on the thoracic aorta in TAD patients, but might be actually be beneficial [52,53]. Further research is needed to evaluate these potential positive effects of exercise on the thoracic aorta in MFS patients and patients with other thoracic aortic diseases. Especially, since mouse model studies on the aorta might not always be reliable [65]. One randomized trial has been performed in patients with an abdominal aortic aneurysm (AAA) in 2014 [66]. In this trial 140 patients with AAA were randomized to either standard care or exercise training including dynamic as well as isometric exercise (rowing). No difference in abdominal aortic growth rate was reported between the groups. Although AAA has a different aetiology than thoracic aortic aneurysms and should therefore be seen as a different disease entity, the findings of this study are promising. A randomized study, such as the one illustrated above for AAA patients, would provide important additional information about the effect of exercise in TAD patients.

CONCLUSION

Although several case reports have described aortic dissection occurring during exercise, no high quality studies have been performed to illuminate the association between exercise and acute aortic dissection. In athletes, aortic diameters are only slightly larger than in controls. Evenly, aortic diameter growth rate does not seem to be enhanced by exercise in BAV patients. In mice with MFS a positive effect of mild to moderate dynamic exercise on the thoracic aorta diameter was found. There clearly is a gap in knowledge about the effects of exercise and sports participation in TAD patients. Currently there is no unequivocal evidence to support discouragement of exercise and sports participation in TAD patients. Hence, mild to moderate regular exercise should be encouraged, for its known positive effects on overall health. However, based on theoretical knowledge, participation in heavy static exercise should likely be avoided in TAD patients.

EXPERT COMMENTARY

When a patient is diagnosed with TAD , discussing lifestyle modification is mandatory. Next to cessation of smoking, controlling hypertension and prevention of obesity, discussing exercise and sports participation is important. However, there is not enough evidence to strongly discourage exercise or recommend any particular type of exercise or sport. Theoretically, high blood pressure is unfavourable. Therefore, it is important to distinguish between dynamic (also isotonic) and static (also isometric) exercise [61], since both initiate a different hemodynamic response (illustrated in figure 4). On the other hand exercise and sports participation are also known to have many positive effects on cardiovascular and overall health. For the general population the Dutch and American health councils, as well as the World Health Organization recommend a target rate of 150 to 300 minutes per week of moderate to heavy intensity exercise [67-69], as participation in regular physical activity has shown to have many benefits[67,68].

Therefore, we believe it is mandatory to explain both the negative and positive effects of exercise to TAD patients. In order to create full understanding and ideally reach a shared decision, rather than imposing restrictions on sports participation. In order to prevent TAD patients becoming scared of physical activities and to minimize concerns, stress and anxiety further affecting TAD patient's quality of life, which was shown to be reduced compared to healthy controls [70].

Ideally future research would be (randomized) controlled trials longitudinally evaluating the effect of exercise on thoracic aortic aneurysm dilatation rate, the risk of thoracic aortic dissections, quality of life and survival of TAD patients. Secondly, the effect of different types and intensities of exercise on thoracic aortic growth rate acceleration needs to be evaluated. More research is especially needed in patients with Loeys-Dietz syndrome, aneurysm-osteoarthritis Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome and Turner syndrome, on which we found no evidence at all.

FIVE-YEAR VIEW

In the upcoming five years we envision that more research will be carried out on the association between exercise and thoracic aortic growth and acute aortic dissection. Further exploring the potential beneficial effect of dynamic exercise on the aortic wall in humans is warranted. This knowledge will enable us to better understand and predict the risks of exercise and sports participation in TAD patients. This will hopefully enforce better counselling, with more detailed and well-founded advice to TAD patients.

Table 1. Aortic dimensions in trained individuals

				Study population				Outcome				
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Control group**	**Outcome measures**	**Prevalence aortic dilatation**	**Results**	**Conclusion**
17	Rubal	1981	Medicine and Science in Sports and Exercise	Cross-sectional cohort study	9	Female softball athletes	100	10 age-and body size-matched sedentary controls	Left ventricular parameters, aortic root diameter	Not reported	Mean aortic root diameter in athletes was 22 mm ±1 and 23 mm ±1 in controls.	There was no statistically significant difference in aortic root diameter between athletes and controls.
18	Wieling	1981	British Heart Journal	Longitudinal cohort study	23	Male oarsmen: seniors (n=14) and freshmen (n=9)	0	17 healthy age-matched controls	Left ventricular parameters, right ventricular diameter, aortic root diameter at end-diastole	Not reported	At the beginning of the season aortic root diameter was 31,3mm ±1,5 in senior oarsmen, 28,8mm ±2,0 in freshmen, and 29,9mm ±2,8 in control subjects.	At the beginning of the season aortic root diameter was greater in senior oarsmen than in freshmen, but did not differ from control subjects. No consistent increase was observed in aortic root diameter at the end of the season.
19	Crouse	1992	Research Quarterly for Exercise and Sport	Cross-sectional cohort study	15	Female basketball athletes	100	22 age-matched non-athletic controls	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 25.7 mm ±3.3 in athletes and 21.7 mm ±2.4 in controls.	Aortic root diameter was significantly higher in athletes than in controls.
20	Pelliccia	1996	JAMA	Cross-sectional cohort study	600	Female athletes from Italian national teams	100	65 age-matched untrained females and 738 age-, ethnicity, sports discipline and training intensity matched elite male athletes	Left ventricular parameters, aortic root diameter	Not reported	The aortic root was 27.6 mm ±2.5 in athletes, 27.0 mm ±1.8 in controls, and 30.3 mm ±2.0 in male athletes.	The aortic root was significantly larger (2% larger) in athletes than in controls, and significantly larger in male athletes.

Table 1. Continued

				Study population			Outcome					
21	Whyte	1999	International Journal of Sports Medicine	Cross-sectional cohort study	29	Elite modern pentathletes (n=11) and triathletes (n=18)	0	13 sedentary controls	Left ventricular parameters, aortic annulus diameter	Not reported	Aortic annulus diameter was 28,8 mm ±5,1 in triathletes, 33,5 mm ±2,1 in pentathletes and 31,1 mm ±1,9 in controls.	There was no statistically significant difference in aortic annulus diameter between triathletes, pentathletes and controls. Whilst the large training volume elicits significant morphological adaptation in triathletes and modern pentathletes, all measures were within normal limits.
30	Kinoshita	2000	American heart Journal	Cross-sectional cohort study	1929	Athletes active in competitive sports	19	No control group	Aortic root diameter	Aortic root >40mm: 0,26-0,36% and 0,96% in basketbal and volleybal players	0,26-0,36% of athletes had aortic root dilatation >40 mm, 0,96% of basketbal en volleybal players had aortic root dilatation >40 mm.	A higher prevalence of aortic dilatation is to be anticipated among basketball and volleyball players, many of whom are very tall.
22	Dzudie	2006	European Journal of Echocardiography	Cross-sectional cohort study	21	Male handball players	0	21 age-, sex-, height- and weight-matched sedentary men	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 29.6 mm ±3.6 in control subjects and 30.3 mm ±2.8 in handball players.	Aortic root diameter was slightly larger in control subjects than in handball players, but this difference was not significant.

Table 1. Continued

				Study population			Outcome					
23	Babaee Bigi	2007	American Journal of Cardiology	Cross-sectional cohort study	100	Male elite athletes	0	128 age- and height-matched healthy men	Aortic diameter, aortic regurgitation	Not reported	Aortic diameters were measured at Ann 25.1±2.9 in athletes and 21.8±2.4 in controls, SoV 38.2 ±4.1 in athetes and 31.6 ±3.2 in controls, STJ 34.1 ±2.8 and 29.5 ±3.1 in controls, AA 36.1 ±4.5 in athetes and 31.0 ±2.9 in controls.	Aortic root diameters in all segments of the aortic root were significantly greater in elite strength-trained athletes compared with an age- and height-matched population.
29	Pelliccia	2010	Circulation	Cross-sectional cohort study	2317	Highly trained athletes	44	No control group	Aortic diameter	Aortic root >40 mm: 1,3% of male athletes. Aortic root >34 mm: 0,9% of female athletes	Mean aortic root diameter was 32.2mm ±2.7 in male athletes with 99th percentile 40 mm, and 27.6 mm ±2.6 in female athletes with 99th percentile 34 mm.	Aortic root enlargement (40 mm in males and 34 mm in females) is particularly uncommon in highly trained athletes.
31	D'Andrea	2010	American Journal of Cardiology	Cross-sectional cohort study	615	Elite athletes: endurance-trained athletes (n=370) and strength-trained athletes (n=245)	33	No control group	Aortic diameter	Ascending aortic dilatation >95% CI of overall distribution: 1% of athletes	The mean aortic root diameter at the SoV was 31 mm (2.8–3.6) in endurance trained athletes and 36 mm (3.2–4.2) in strength trained athletes.	The aortic root diameters at all levels were significantly greater in strength trained athletes. Significant ascending aortic dilatation and aortic regurgitation proved to be uncommon in strength trained athletes.

Table 1. Continued

				Study population			Outcome					
24	Carlsson	2010	European Journal of applied physiology	Cross-sectional cohort study	10	Male endurance athletes	0	10 untrained men	Cardiac functional parameters, cardiac structural parameters (among which aortic root diameter)	Not reported	Aortic root diameter was 30.4 mm ± 3.2 in athletes and 28.4 mm ± 4.4 in controls.	Aortic root diameter was not significantly larger in athletes than in controls.
25	Caselli	2011	European Journal of Echocardiography	Cross-sectional cohort study	429	Athletes from Italian national teams	22	98 healthy controls	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 31.0 mm±3.8 in athletes and 28.7 mm±3.3 in controls.	Aortic root diameter was significantly larger in athletes than in controls.
26	Krol	2011	Echocardiography	Cross-sectional cohort study	38	Members of the Polish Olympic team (rowing, cycling, speed-skating)	16	41 sex and age matched, healthy sedentary individuals	Left ventricular parameters, right ventricular parameters, aortic diameter (level of measurement not specified)	Not reported	Aortic diameters were 33 mm ±4 in het athletes and 29 mm ±2 in controls. After indexing for BSA the mean aortic size index for athletes was 1.6 cm/m2 ± 0.1 and 1.5 cm/m2 ± 0.2 for controls.	Aortic diameters were significantly larger in het athletes group than in controls. However after indexing for BSA there was no significant difference between the groups.

Table 1. Continued

				Study population			Outcome					
27	D'Andrea	2012	Journal of the American Society of Echocardiography	Cross-sectional cohort study	410	Elite athletes: endurance-trained athletes (n=220) and strength-trained athletes (n=190)	38	240 healthy controls	Aortic root diameter, aortic root distensibility and elasticity	Aortic root dilatation >95% CI of overall distribution: 1% of male power athletes	Aortic root diameter was 36 mm±5 in strength trained, 31 mm±6 in endurance trained athletes and 32 mm ±3 in controls.	Aortic root diameters and stiffness were significantly greater in strength trained athletes than in endurance trained athletes and controls. While aortic distensibility was higher in endurance trained athletes compared to controls.
28	Aparci	2013	Expirimental & Clinical Cardiology	Cross-sectional cohort study	60	Personnel Etimesgut Military Hospital: strenuous activity trainers (n=30) and ordinary activity trainers (n=30)	Unknown	No control group	Aortic diameters, left ventricular parameters, left atrial diameters	Subjects with abnormally enlarged aortic diameters (≥40 mm) were excluded	In the strenuous activity training group mean aortic diameters were: 35.6 mm (SoV) and 36.8 mm (AA), in the ordinary activity training group the mean aortic diameter was 33.5 mm (SoV) and 34.4 mm (AA).	Aortic root and ascending aortic diameter were significantly higher in the strenuous activity training group.
32	Davis	2015	Clinical Journal of Sport Medicine	Cross-sectional cohort study	70	Athletes from the US national volleyball team	47	No control group	Aortic diameter and Ghent criteria (signs of Marfan syndrome)	Aortic root diameter ≥40 mm: 8% of male athletes. Aortic root diameter ≥34mm: 6% of female athletes	34% of the athletes had at least 1 characteristic of MFS (Ghent criteria) but none had more than 2 characteristics.	Elite US volleyball players have a higher than expected prevalence of dilation of the aortic sinuses and ascending aorta. In the absence of MFS.

Ann; Aortic Annulus, SoV; Sinus of Valsalva, STJ; Sinotubular Junction, AA; Ascending Aorta

Table 2. Case reports and case series on acute aortic dissections during exercise

				Study population				Outcome					
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Age (years)**	**Sex**	**Stanford Classification**	**Max. aortic diameter**	**Type of sport**	**Aortopathy**	**Family history**	**Conclusion**
33	Bain	1987	The American Journal of Forensic Medicine and Pathology	Case-report	1	20	M	Type A	60 mm	Fitness	Marfan Syndrome	Positive for sudden death	This case demonstrates Marfan Syndrome presenting as sudden, unexpected death.
39	De Virgilio	1990	The Annals of Thoracic Surgery	Case series	4	22-57	M	Type A	Unknown	Weightlifting	Not suspected	Unknown	Individuals who have evidence of cystic medial disease or family histories of this disease should avoid weight lifting.
34	Schor	1993	Journal of Vascular Surgery	Case-report	1	18	M	Type B (periaortic hematoma)	Unknown	Weightlifting	Not suspected	Unknown	Weight lifting, with its profound cardiovascular effects, may be the major, if not sole cause of aortic dissection.
35	Baumgartner	1997	The Annals of Thoracic Surgery	Case-report	1	19	M	Type A	Unknown	Weightlifting	Marfan Syndrome	Unknown	Individuals with Marfan Syndrome, cystic medial disease or family histories of the disorder should be strongly urged to refrain from weight-lifting activities.
36	Elefteriades	2003	Journal of the American Mediucal Association	Case series	5	19-53	Unknown	Type A	40-52 mm	Weightlifting, push ups, heavy lifting	Not suspected	Positive for aortic disease in 1 patient	The risk of weight lifting as a cause of aortic dissection has generally been underappreciated.
40	Hogan	2005	Emergency Medicine Journal	Case-report	1	27	M	Type A	Unknown	Weightlifting	Non-Marfan's fibrillinopathy	Positive for aortic dissection	Aortic dissection should be considered in symptomatic patients with a family history of early cardiac deaths, suspect of a connective tissue disorder, or who practice weightlifting.

Table 2. Continued

					Study population					Outcome			
37	Hatzaras	2007	Cardiology	Case series	31	19-76	30 M, 1 F	Type A: 87% (n=27), Type: B 13% (n=4)	30-78 mm	Weightlifting or push-ups (n=16), heavy lifting (n=9), dynamic exercise like swimming or tennis or racquetball (n=5)	Unknown	Positive for aortic disease in 3 patients	Increased blood pressure due to heavy weight lifting raises aortic wall stress to a level that produces aortic dissection in individuals with pre-existing mild to moderate aortic enlargement.
38	Uchida	2009	Interactive CardioVascular and Thoracic Surgery	Case-report	1	12	M	Type B	Unknown	Swimming	Not suspected	Negative	Swimming coaches and pediatricians should recognize that swimming exercises like the butterfly stroke are a risk factor for aortic dissection in children.
42	Westaby	2011	Circulation	Case-report	1	28	M	Type B	Unknown	Soccer	Bicuspid aortic valve, aortic coarctation	Unknown	Aortopathy associated with a bicuspid aortic valve and coarctation may contribute to aneurysmal transformation and rupture.
43	Chattranukulchai	2013	British Medical Journal Case Reports	Case-report	1	38	M	Type A	52 mm	Bowling	Marfan Syndrome	Unknown	Early diagnosis of Marfan Syndrome is crucial as it has a positive influence on the outcome.
41	Ozyildirim	2015	The American Journal of Cardiology	Case-report	1	28	M	Type A	Unknown	Weightlifting	Unknown	Unknown	Weight lifting creates significant stress along the aortic wall and this produces predisposition to acute aortic dissection.
44	Cereda	2016	European Heart Journal	Case-report	1	25	F	Type A	100 mm	Volleybal	Marfan Syndrome	Unknown	Echocardiography has a potential role in preventing tragic sudden death in sport.

Table 3. Papers on sports related aortic dissections

				Study population				Outcome			
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Definition**	**Missing (%)**	**Exercise related dissections (%)**	**Additional results**
47	Schachner	2013	BioMed Research International	Retrospective cohort study	140, of which 77 (55%) during winter season	Patients with aortic dissection involving the ascending aorta during the winter season (from the beginning of November until the end of April).	21 (16/77)	Onset of symptoms during alpine skiing.	Not reported	22	In 14/17 (82%) patients symptoms occurred during recreational skiing without additional trauma. Only 1 patient (6%) had a skiing accident with consequent ascending aortic dissection.
46	Gansera	2015	The Thoracic and Cardiovascular Surgeon	Retrospective cohort study	365	Patients who underwent surgery for aortic dissection involving the ascending aorta.	32	Onset of symptoms occurred during physical exercises, such as sports or lifting of heavy weights.	24	68	Peri- or postcoital aortic dissection occurred in none of the females, but in 17 of 245 males. Mortality in females < 65 years was higher (20.2%), compared with their male counterparts (14.9%).
45	Itagaki	2017	Surgery Today	Retrospective cohort study	650	Patients who underwent surgery for aortic dissection involving the ascending aorta.	47 (323/615)	Onset of symptoms during a sports activity. Non-sports exertion, such as lifting or moving a heavy load, defecation, or sexual activity, were classified into the non-sports group.	5	4.1 (5% of all daytime type A dissections)	The sport most frequently associated with type A aortic dissections in this series was golf (n = 8; 32%), followed by swimming and cycling (each n = 4; 16%), then weight lifting (n = 3; 12%), dance (n = 2; 8%), and finally, long-distance running, fencing, table tennis, and archery, (each n = 1; 4%).

Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
51	BAV	Spataro	2008	International Journal of Sports Medicine	Longitudinal cohort study	81	Competitive athletes with BAV from Italian national teams divided into 2 groups: the low-risk group (n=51) and the high-risk group (n=30)	NA	10	No control group	Aortic regurgitation, aortic stenosis and left ventricular parameters, aortic root diameters.	13 ± 4.9 years (range 5–19 years)	Over the follow-up period, six of the initially low-risk athletes (7%) and all of the high-risk patients showed significant worsening of morphologic features of bicuspid aortic valve and/or incidence of symptoms. In high risk subjects the progression of valvular disease occurred independently from the former athletic activity.	Continued sport participation is not responsible itself of BAV worsening. However, long-term athletic training may be associated with progressive worsening of the valvular lesion and the appearance of clinical symptoms.
48	BAV	Stefani	2008	British Journal of Sports Medicine	Cross-sectional cohort study	58	Non-elite but competitive athletes with BAV	NA	0	75 non-elite but competitive athletes with TAV	Aortic regurgitation, aortic stenosis and aortic root diameters.	NA	Aortic root dimensions at all levels were significantly greater in athletes with BAV than in athletes with a normal TAV. No relation was found with age, body surface area, aortic regurgitation or years of training.	A short echocardiographic examination should be performed at least once during an athlete's sporting life.

Table 4. Continued

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
49	BAV	Galanti	2010	British Journal of Sports Medicine	Longitudinal cohort study	88	Athletes with BAV and mild aortic regurgitation	NA	Unknown	56 athletes with TAV	Left ventricle parameters and aortic diameters	5 years (30/88 subjects)	There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.61 mm/year; STJ: 0.81 mm/year; AA: 0.98 mm/year). This increase became significant from the last 2 years of the 5-year follow up. In TAV athletes, there was no significant increase of aortic diameters (Ann 0.17 mm/year; SoV 0.12 mm/year; STJ 0.21 mm/year; AA: 0.32 mm/year)	In athletes with BAV, aortic dimensions increase significantly more than in TAV athletes, but do not differ from those in the general BAV population.

Table 4. Continued

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
50	BAV	Stefani	2014	Cardiology Research and Practice	Longitudinal cohort study	292	Subjects with BAV who were evaluated at the Sports Medicine and Exercise Centre, divided into three different groups: athletes (n=210), sedentary (n=59), and ex-athletes (n=23)	NA	Unknown	No control group	BAV morphology classification, left ventricular parameters and aortic diameters	5 years	Typical BAV morphology was most frequent in all three groups (68% athletes, 67% sedentaries, and 63% ex-athletes). The aortic dimensions showed a progressive enlargement during follow-up, with no difference between athletes and sedentary subjects. There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.61 mm/year; STJ: 0.81 mm/year; AA: 0.98 mm/year).	In BAV patients the ascending aorta is involved in normal progressive, not necessarily pathological, enlargement.
54	MFS	Benninghoven	2017	Orphanet Journal of Rare Diseases	Longitudinal cohort study	19	Patients with MFS or similar syndrome in stable condition	Not specified	71	No control group	Adverse events, physical fitness and psychological assessment	1 year	No adverse medical events were reported. Physical fitness improved from admission to discharge. Psychological distress decreased. Admission to discharge effects mostly persisted through the one year follow-up but declined to smaller sizes.	The three week rehabilitation program improved physical fitness and psychological wellbeing. Medical assessments ruled out medical problems or adverse events caused by participation in the program.

Table 4. Continued

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
52	MFS	Gibson*	2017	Journal of Applied Physiology	Non-randomised controlled trial (mouse-model study)	16	Male mice with MFS divided in a sedentary group (n=10), voluntary exercise group (n=3) and forced exercise group (n=3)	Fbn1C1039G/+	0	19 mice without MFS, divided in a sedentary group (n=4), voluntary exercise group (n=7) and forced exercise group (n=8)	Histological characteristics, isometric force, aortic wall elasticity and stiffness and combined benefit score for: elastin fiber length, elastin fragmentation, and elasticity	5 months	Both voluntary and forced exercise routines reduced aortic diameter, prevented aortic wall weakening, increased the breaking stress and improved aortic wall elasticity in MFS aorta. There is an optimum of protective effects at training intensity levels between 55% and 65% (of VO2max) which significantly reduces elastin fragmentation and disorganization within the aortic wall.	The present study provides helpful insights into the potential protective effects of a mild exercise routine in MFS patients in the absence of pharmacological interventions.

Table 4. Continued

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
53	MFS	Mas-Stachurska*	2017	Journal of the American Heart Association	Randomized controlled trial (mouse-model study)	19	Mice with MFS, randomized to a sedentary group n=9 and exercise group n=10	Fbn1C1039G/+	47	21 mice without MFS, randomized to a sedentary group n=11 and exercise group n=10	Left ventricular parameters, aortic root diameter, aortic pulsatility, aortic stiffness and histological characteristics of aortic wall tissue	5 months	In MFS mice subjected to exercise aortic root diameter was smaller than in their sedentary littermates and aortic dilatation rate was blunted, becoming comparable to the controls. Exercise training improved aortic stiffness in controls but not in MFS mice, but did not increase lamina ruptures in MFS mice, indicating no additional structural damage in the tunica media.	Moderate dynamic exercise prevented aortic root dilation and mitigates cardiac hypertrophy.

* Mouse-model study

MFS; Marfan Syndrome, BAV; Bicuspid Aortic Valve, TAV; Tricuspid Aortic Valve, Ann; Aortic Annulus, SoV; Sinus of Valsalva, STJ; Sinotubular Junction, AA; Ascending Aorta

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SUPPLEMENTAL FILE 1

Search terms used to identify publications of interest

Search date: August 2, 2018

Embase

'thoracic aorta aneurysm'/de **OR** 'Loeys Dietz syndrome'/de **OR** 'Ehlers Danlos syndrome'/de **OR** 'Turner syndrome'/de **OR** 'Marfan syndrome'/de ***OR*** 'bicuspid aortic valve'/de **OR** 'aneurysm osteoarthritis syndrome'/de **OR** 'Smad3 protein'/de **OR** 'smad3 gene'/de **OR** 'thoracic aortic dissection'/de **OR** 'thoracic aortic aneurysm and dissection'/de **OR** (((thoracic OR thorax) NEAR/3 (aortic OR aorta) NEAR/3 (aneurysm* OR dilatation* OR dissect*)) OR 'Loeys Dietz' OR 'Ehlers Danlos' OR Turner OR Marfan OR ((bicuspid) NEAR/3 (aort*) NEAR/3 (valve)) OR 'aneurysm osteoarthritis syndrome' OR 'Smad3'):ab,ti

AND

'sport'/exp **OR** 'exercise'/exp **OR** 'training'/de **OR** 'athlete'/exp **OR** (sport* OR exerci* OR athlet* OR training):ab,ti

Medline

Aortic Aneurysm, Thoracic/ **OR** Loeys-Dietz Syndrome/ **OR** Ehlers-Danlos Syndrome/ **OR** Turner Syndrome/ **OR** Marfan Syndrome/ **OR** (bicuspid aortic valve).nm. **OR** Smad3 Protein/ **OR** (((thoracic OR thorax) ADJ3 (aortic OR aorta) ADJ3 (aneurysm* OR dilatation* OR dissect*)) OR Loeys Dietz OR Ehlers Danlos OR Turner OR Marfan OR ((bicuspid) ADJ3 (aort*) ADJ3 (valve)) OR aneurysm osteoarthritis syndrome OR Smad3).ab,ti.**)**

AND

exp Sports/ **OR** exp Exercise/ **OR** Athletes/ **OR** (sport* OR exerci* OR athlet* OR training).ab,ti.

Web of Science

((((thoracic OR thorax) NEAR/2 (aortic OR aorta) NEAR/2 (aneurysm* OR dilatation* OR dissect*)) **OR** "Loeys Dietz" **OR** "Ehlers Danlos" **OR** Turner **OR** Marfan **OR** ((bicuspid) NEAR/2 (aort*) NEAR/2 (valve)) **OR** "aneurysm osteoarthritis syndrome" **OR** "Smad3")**)**

AND

sport* **OR** exerci* **OR** athlet* **OR** training

Google Scholar (200 top relevant)

"thoracic aortic aneurysm|dilatation|dissection"|"Loeys Dietz"|"Ehlers Danlos"|"Turner syndrome"|Marfan|"bicuspid aortic valve"|"aneurysm osteoarthritis syndrome"|Smad3 sport|sports|exercise|athletics|athletes|training

CHAPTER 8

Male-female differences in quality of life and coping style in patients with Marfan syndrome and hereditary thoracic aortic diseases

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Journal of Genetic Counseling, 2020

ABSTRACT

Hereditary thoracic aortic diseases (HTAD) such as Marfan Syndrome (MFS) affect multiple organ systems, and provide a risk of acute aortic dissection, which causes lifelong uncertainties. Although health-related quality of life (HRQOL) was found to be reduced in HTAD patients, no studies have evaluated male-female specific aspects of HRQOL and coping in this population. This study aims to: evaluate HRQOL in HTAD patients compared to the general population; assess male-female differences in HRQOL and factors associated with HRQOL; evaluate coping styles in male and female HTAD patients and identify factors associated with acceptance. All consecutive adult patients who visited the specialized HTAD outpatient clinic between 2013-2018, were asked to complete three HRQOL questionnaires: the Short-Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS) and the Nijmegen Clinical Screening Instrument (NCSI). In total 142 patients were included (mean age 42.1 years, 65 females, 123 MFS). Compared to the general population, HTAD patients scored significantly lower on multiple SF-36 sub-domains (males: General Health 54.5±18.8 vs 71.6±20.6, p<0.001; Vitality 58.3±20.4 vs 71.9±18.3, p<0.001; females: Physical Functioning 67.5±23.8 vs 80.4±24.2, p=0.003; Role Physical 58.3±45.1 vs 73.8±38.5, p=0.047; General Health 49.4±24.3 vs 69.9±20.6, p<0.001; Social Functioning 73.5±22.0 vs 82.0±23.5, p= 0.027). Females scores significantly lower than males on the SF-36 physical component score (41.6 (IQR 35.5-53.1) vs 49.3 (IQR 42.3-54.6), p=0.035). Males scored significantly higher on the coping style denial than females (2.75 (IQR 2.00-3.25) vs 2.25 (IQR 1.75-3.25), p=0.018). High scores on acceptance were found in 38 (26.8%) of HTAD patients, these patients showed significantly better scores on the NCSI, SF-36 and HADS, except on NCSI Satisfaction Relationships and SF-36 Physical Functioning and Mental Health. Acceptance was associated with more medication use (beta blocker use, p=0.008; angiotensin receptor blocker use, p=0.003) and less hypertension (p=0.001). In patients with MFS, employment was strongly associated with better scores on the NCSI. In conclusion HTAD patients showed subnormal HRQOL, especially females. Interestingly, in both males and females factors such as employment, coping style, and disease acceptance seem more important for HRQOL than disease related factors. This highlights the importance of genetic counselling and guidance for HTAD patients, and offers valuable leads for HRQOL improvement.

INTRODUCTION

The incidence of thoracic aortic diseases including thoracic aortic aneurysms and dissections has been increasing, and is currently estimated to be about 9 per 100,000 per year in women, and 16 per 100,000 per year in men[1]. In over 20 percent of cases there is an inherited pattern for thoracic aortic aneurysms[2], and often multiple family members are affected. Patients with these hereditary thoracic aortic diseases (HTAD), such as Marfan Syndrome (MFS), often experience multiple serious complaints during their lifetime, which are mostly due to skeletal, ocular or cardiovascular manifestations. On top of that, these patients are at risk of acute aortic dissection[3]. Therefore, HTAD patients with or without aortic involvement face many uncertainties and require lifetime medical surveillance, lifestyle alterations, pharmaceutical treatment and often surgical procedures.

Evidence of the effects of living with this potentially life-threatening inheritable disease on health related quality of life (HRQOL) is scarce. So far, it has been shown that HTAD patients have a lower HRQOL compared to the general population, and comparable to other chronic diseases[4,5]. Physical aspects seem affected rather than mental well-being[5,6]. Moon et al. showed that apart from disease related factors, there are other important factors which influence HRQOL in MFS patients, such as: social support (e.g. family / friends support) and bio-behavioral factors (e.g. anxiety, depression, fatigue, pain)[7]. Even though evidence on HRQOL in HTAD patients, and MFS patients in particular, is gradually increasing, guidelines on current clinical practice do not yet include any HRQOL assessment, psychosocial assessment, or psychological counselling[8,9].

Better insight into HRQOL in HTAD patients could help guide genetic counseling, help to explain the relevance of HRQOL to our patients, and aid the creation of intervention strategies for improving HRQOL in this population. In particular it is important to know in which specific subgroups of HTAD patients HRQOL is most impaired, in order to increase clinician awareness of HRQOL impairment and coping problems in these patients. However, patient specific evidence is lacking. Even though HRQOL is known to be different in men and women both in the general population and in specific patient groups[10,11], no studies have evaluated male-female specific aspects of HRQOL in this population. Furthermore, very little is known about coping strategies and disease acceptance in HTAD patients, whilst the latter is known to be an important patient-related factor contributing to patients' adherence to long-term treatments[12,13]. Therefore this study aims to 1) Evaluate male-female specific HRQOL in HTAD patients compared to the general population, 2) Assess male-female differences in HRQOL and identify male-female specific factors associated with HRQOL, and 3) Evaluate coping styles in male and female HTAD patients and identify factors associated with the coping style acceptance.

METHODS

Participants

All consecutive adult patients (≥18 years old) who visited the specialized HTAD outpatient clinic at the Radboud University Medical Center in Nijmegen between 2013 and 2018, were asked to fill-out three quality of life questionnaires: the Short-Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS) and the Nijmegen Clinical Screening Instrument (NCSI). The HTAD outpatient clinic is a multidisciplinary clinic in which patients are seen by cardiologists, nurse practitioners, or clinical geneticists over the course of annual visits. Questionnaires were distributed directly after an outpatient clinic visit, which was a cardiovascular follow-up visit with their cardiologist or nurse specialist. If patients completed the questionnaires multiple times, only the first measurements were used, in order to avoid bias created by counselling sessions at the HTAD outpatient clinic. Exclusion criteria were related to inability to complete the online surveys, such as: a language barrier, intellectual disability, no access to a computer or email address, or unwillingness to complete the questionnaires. The questionnaires were primarily used in clinical practice for patients visiting the HTAD outpatient clinic of our tertiary care center, in order to assess overall mental and physical health status and to develop patient specific treatment goals for counselling if necessary. Additional data was collected from the patient files using a standardized case report form shown in supplemental file 1. Only information collected within three months from the date of completion of the questionnaires was used. Diagnosis of MFS was defined as fulfilment of the criteria of the revised Ghent nosology[14]. This study was approved by the local ethics committee (ethics committee of the Radboud University Nijmegen Medical Centre, file number: 2019-5451) and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines[15-17].

Questionnaires

The SF-36 questionnaire is a widely used HRQOL questionnaire with 36 items, which comprises eight domains: Physical Functioning (PF), Role limitations due to Physical health problems (RP), Bodily Pain (BP), General Health perceptions (GH), Vitality (VT), Social Functioning (SF), Role limitations due to Emotional problems (RE), and general Mental Health (psychological distress) (MH)[18,19]. The first four domains (PF, RP, BP & GH) comprise the Physical Component Summary (PCS) and the last four domains (VT, SF, RE & MH) comprise the Mental Component Summary (MCS). All SF-36 sub-domains have a score range of 0-100, with higher scores reflecting a better quality of life. The SF-36 has been translated, and validated in the Dutch language, and norm scores of the general Dutch population are available[18]. Male and female scores of HTAD patients on the eight sub-domains of the SF-36 were compared to male-female specific norm

values[18]. Unfortunately, no age-specific norm values are available for males and females separately; additional age-matching was therefore not possible [18]. Male-female specific PCS and MCS scores were calculated using the mean and standard deviations from the general Dutch population. SF-36 scores of patients who previously underwent aortic surgery were compared to patients who had not undergone aortic surgery, and patients who experienced previous aortic dissection were compared to those who did not.

The HADS is a commonly used questionnaire to assess signs of anxiety and depression. This 14-item scale is divided in two dimensions: anxiety (seven items) and depression (seven items). The responses result in a score for each dimension with a score range of 0-21 and a total overall score range of 0-42. Higher scores represent higher levels of anxiety and depression. The HADS was validated in the Dutch language[20]. A score of 8+ on the HADS anxiety and depression subscales was defined as elevated, since this cut-off point was found to be the most optimal[21].

The NCSI contains 49 questions and was designed to assess the overall health status of patients, identifying patient specific treatment goals in order to facilitate behavioral changes[22]. The NCSI has eight sub-domains: General Quality Of Life; Health Related Quality of Life; Satisfaction with Relationships; Subjective Impairments; Behavioral Impairments; Subjective Symptoms; Emotions about Symptoms; and Fatigue. Each of the eight sub-domains has its own specific score range as shown in table 3, with higher scores reflecting more problems on the sub-domain. Therefore, lower scores on the NCSI sub-domains reflect a better quality of life. Additionally, the NCSI includes the ADIQ questionnaire as a measure of coping style, which is based on the stages of grief by Kübler-Ross[23], which shows resemblances with the stages of disease acceptance: denial, resistance, sorrow and acceptance. For assessment of each stage there are three to four questions[24]. Scores on every stage are transformed to a score range of 1-4, with higher scores reflecting better agreement of this stage with the coping style used by the patient. High scores on the ADIQ stages were defined as a score of 3+. Scores on the ADIQ were compared between males and females for each coping style. Both the NCSI and ADIQ were originally designed and validated in patients with chronic obstructive pulmonary disease[22,24], and were used thereafter in patients with Q-fever and asthma[25,26]. Unfortunately, norm scores for the general Dutch population are not available; therefore the NCSI could not be used to compare HTAD patients to the general population.

Data Analysis

Data were analyzed using SPSS statistics (IBM SPSS Statistics version 25). Continuous data were presented as mean and standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when skewed. Categorical data were presented as frequencies with percentages. Students t-test or non-parametric Wilcoxon test were

used to compare continuous variables, chi-squared test was used to compare categorical variables. The one-sample student's t-test was used to compare SF-36 norm-values to the study population means. For the patients with MFS, baseline variables that showed a significant association with scores on one of the NCSI sub-domains ($p<0.05$) in univariate analysis were included in a multifactor analysis of variance to identify those strongly associated with scores on this sub-domain. A p-value of <0.05 was considered significant.

RESULTS

In total, 142 HTAD patients (65 females) completed one or more questionnaires. All 142 patients completed the NCSI questionnaire, 76 patients (36 females) subsequently completed the SF-36 questionnaire, and 113 patients (49 females) completed the HADS. Baseline characteristics (shown in table 1) were compared between males and females; patients who completed the SF-36 and those who did not; and patients who completed the HADS and those who did not. Males had a significantly larger aortic root diameter compared to females (p=0.001), although the aortic root Z-scores were not significantly different (p=0.635). Patients who completed the SF-36 had a significantly larger aortic root diameter (41.5±5.3 mm vs 38.6±5.3 mm, p=0.006), and aortic root Z-score (3.2 (IQR 1.9-4.8) vs 2.2 (IQR 1.2-3.5), p=0.004) than those who did not. Patients who completed the HADS questionnaire had significantly larger aortic diameters than those who did not (40.7± 5.4 mm vs 38.2± 5.6 mm, p=0.042). However, the aortic root Z-score was not significantly different (p=0.135). There was no significant difference between the percentage of males and females who completed the SF-36 (52.6% vs 47.4%, p=0.682) and the HADS (56.6% vs 43.4%, p=0.255). A large proportion of our cohort (123/142 patients) was diagnosed with MFS. Therefore, we additionally compared patients with diagnosis of MFS to patients without MFS, as is shown in supplemental file 2. Patients with MFS were significantly younger (41.0±14.3 vs 49.2±16.3, p=0.023). The remaining patients were diagnosed with Loeys-Dietz Syndrome (n=8), *ACTA2* mutation (n=1), other genetic mutations (n=5), or had no established genetic mutation but did have a thoracic aortic aneurysm and positive family history of aortic disease.

Table 1 Baseline characteristics

	Total (n= 142)	Males (n= 77)	Females (n= 65)	p-value
Age - y	42.1±14.8	42.1 ± 14.9	42.1 ± 14.8	0.977
BMI - kg/m2	23.5±4.5	24.2 ± 4.7	22.7 ± 4.2	0.059
Hypertension	17 (12.0)	9 (11.7)	8 (12.3)	0.910
Hyperlipidaemia	16 (11.3)	11 (14.3)	5 (7.7)	0.216
Current smoker	17 (12.9)	8 (11.0)	9 (15.3)	0.464
Renal dysfunction	2 (1.8)	0 (0)	2 (4.2)	0.097
Beta blocker use	92 (64.8)	55 (71.4)	37 (56.9)	0.071
ARB use	59 (41.5)	34 (44.2)	25 (38.5)	0.493
Aortic root diameter - mm	40.1±5.5	41.8 ± 5.0	38.4 ± 5.5	0.001
Z-score	2.7±2.0	2.6 ± 2.0	2.8 ± 2.1	0.635
Abdominal aortic aneurysm	18 (12.9)	12 (16.0)	6 (9.4)	0.246
Normal LVEF	135 (96.4)	72 (94.7)	63 (98.4)	0.240
Previous Surgery	46 (32.4)	28 (36.4)	18 (27.7)	0.271
Previous dissection	21 (14.8)	13 (16.9)	8 (12.3)	0.444
Diagnosis				0.317
Marfan Syndrome	123 (86.6)	66 (85.7)	57 (87.7)	0.730
Loeys-Dietz Syndrome	8 (5.6)	4 (5.2)	4 (6.2)	
ACTA2 mutation	1 (0.7)	0 (0.0)	1 (1.5)	
Other	5 (3.5)	2 (2.6)	3 (4.6)	
None	5 (3.5)	5 (6.5)	0 (0.0)	
Positive systemic score >7	41 (28.9)	25 (32.5)	16 (24.6)	0.304
Positive family history MFS	80 (62.5)	44 (65.7)	36 (59.0)	0.437
Current partner	85 (68.5)	48 (71.6)	37 (64.9)	0.421
Current work [1]	88 (66.2)	42 (72.4)	27 (62.8)	0.304

Data are expressed as mean ± SD or as absolute and percentage.
HTAD=Hereditary Thoracic Aortic Disease; BMI= Body Mass Index; ARB= Angiotensin II receptor blocker; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome.
[1] Only working age (25-65 years) n=107

HRQOL in HTAD patients

Table 2 shows the SF-36 scores of male and female HTAD patients compared to male and female norm scores of the general Dutch population [18]. Overall, male and female HTAD patients both showed lower scores than the general population on most SF-36 sub-domains. In females however, scores were significantly lower in HTAD patients compared to the general population for: Physical Functioning (67.5±23.8 vs 80.4 ± 24.2, p=0.003), General Health (49.4±24.3 vs 69.9±20.6, p<0.001, Social Functioning (73.5±22.0 vs 82.0±23.5, p=0.027) and Role Physical (58.3±45.1 vs 73.8±38.5, p=0.047). Males showed significantly lower scores compared to the general population for: General Health (54.5±18.8 vs 71.6±20.6, p<0.001) and Vitality (58.3±20.4 vs 71.9± 18.3, p<0.001).

HRQOL in males versus females

Table 3 shows male-female specific scores on all sub-domains of the three HRQOL questionnaires. On the SF-36 questionnaire, females scored lower on most sub-domains, with a significantly lower score on Physical Functioning (90.0 (IQR 70.0-95.0) vs 75.0 (IQR 55.0-83.8), p=0.005) and on the Physical Component Summary (47.8 ±9.1 vs 43.0 ±10.6, p=0.034) but not on the Mental Component Summary (50.5 (IQR 44.4-55.5) vs 52.4 (IQR 44.5-56.2), p=0.411). On the HADS questionnaire no significant differences were seen between sub-scores of males and females. Of females, 18/49 (36.7%) demonstrated elevated scores on the HADS anxiety sub-domain versus 18/64 (28.1%) of males (p= 0.330). On depression 9/49 (18.4%) of females showed elevated scores versus 14/64 (21.9%) of males (p= 0.646). On the NCSI females scored significantly higher than males on the sub-domain Behavioral Impairments (8.8 (IQR 0.0-19.3) vs 0.0 (IQR 0.0-11.0), p=0.013), reflecting a lower quality of life on this sub-domain.

Additionally, HTAD patients rated their overall quality of life on a 0-10 scale; the mean rate in both males and females was 7.3.

Table 2 SF-36 scores: Comparison of HTAD males and females to the general population

SF-36 subdomain	Males HTAD (n=40)	Males general population	p-value	Females HTAD (n=36)	Females general population	p-value
Physical Functioning	81.4 (18.7)	85.4 (21.0)	0.181	67.5 (23.8)	80.4 (24.2)	0.003
Role Physical	68.1 (39.2)	78.7 (34.1)	0.096	58.3 (45.1)	73.8 (38.5)	0.047
Bodily Pain	79.1 (22.4)	77.3 (22.7)	0.609	73.5 (22.0)	71.9 (23.8)	0.658
General Health	54.5 (18.8)	71.6 (20.6)	<0.001	49.4 (24.3)	69.9 (20.6)	<0.001
Vitality	58.3 (20.4)	71.9 (18.3)	<0.001	57.8 (21.3)	64.3 (19.7)	0.075
Social Functioning	79.1 (22.4)	86.0 (21.1)	0.059	73.5 (22.0)	82.0 (23.5)	0.027
Role Emotional	80.8 (36.1)	85.5 (29.9)	0.419	81.5 (33.3)	78.5 (35.7)	0.594
Mental health	74.0 (18.2)	79.3 (16.4)	0.074	73.6 (18.3)	73.7 (18.2)	0.963

HTAD= Hereditary Thoracic Aortic Disease; SF-36= Short Form 36 questionnaire.

Previous aortic complications

SF-36 scores of patients who previously underwent aortic surgery (22/76) or had an aortic dissection (10/76), were compared to patients who did not. Patients who did have surgery showed significantly less favorable scores on the sub-domain Physical Functioning on the SF-36 (64.1 ±25.4 vs 79.2 ±19.4, p=0.014) compared to patients with no prior surgery. Additionally, they showed less favorable (=higher) scores on the sub-domain Behavioral Impairments on the NCSI (13.4 ±16.0 vs 8.7 ±13.9, p=0.039). Patients with previous aortic dissection showed less favorable scores on the SF-36 sub-domains Physical Functioning (57.5 ±21.4 vs 77.4 ±21.3, p=0.006), Social Functioning (62.8 ±18.8 vs 78.6 ±22.1, p=0.019) and Bodily Pain (62.8 ±18.8 vs 78.6 ±22.1, p=0.019).

Coping styles

Male and female scores on the ADIQ were compared for the use of different coping styles. Males scored significantly higher on the coping style denial than females (2.75 (IQR 2.00-3.25) vs 2.25 (IQR 1.75-3.25), p=0.018). High scores on the subscale disease acceptance were present in 38 (49.4%) of males and 23 (35.4%) of females (p=0.094). However, a false view of acceptance might be presented if patients who have high denial as well as high acceptance are included in this analysis. Therefore, we additionally performed analyses for patients with 'true acceptance', who showed a high score on the coping style acceptance without a high score on denial. This led to a true acceptance rate of 22 (28.6%) in males and 16 (24.6%) in females (p=0.596). Table 4 shows differences in scores on all sub-domains of the three HRQOL questionnaires between patients with high acceptance or true acceptance, and patients without. Differences in baseline characteristics between patients with and without true acceptance were assessed. Patients with true acceptance were significantly younger (38.1±15.1 vs 43.5±14.5, p=0.044), used beta blockers significantly more often (78.9% vs 59.6%, p=0.033), and significantly more often had a genetically confirmed *FBN1* mutation (97.3% vs 83.2%, p=0.029). Multivariate analysis showed significant associations between acceptance and the following baseline characteristics and NCSI sub-domains after correction for sex and age: hypertension (p=0.001), current beta blocker use (p=0.008), and angiotensin receptor blocker (ARB) use (p=0.003).

Baseline characteristics associated with HRQOL in MFS patients

HTAD patients who were employed showed significantly lower scores (indicating a better quality of life) on seven out of eight NCSI sub-domains, compared to HTAD patients who were not employed. One sub-domain (General Quality of Life) was borderline significant (p=0.053). This analysis was done for the whole cohort (all ages), but the difference was even more pronounced when only HTAD of working age (18-65 years old, n=129) were included in the analysis. No differences could be found for any of the baseline variables between HTAD patients of working age (18-65 years old) with and without employment. Except patients with employment had significantly less hyperlipidemia than those without (21.6% vs 4.8%, p= 0.005).

Multivariate analysis showed significant associations with the following baseline characteristics and NCSI sub-domains after correction for sex and age. Employment was associated with more favorable scores on 5/8 NCSI sub-domains: Health Related Quality of Life; Subjective Impairments; Behavioral Impairments; Subjective Symptoms and Fatigue Symptoms. Hypertension was significantly associated with less favorable scores on: General Quality of Life; Health Related Quality of Life; Subjective Impairments and Emotions about Symptoms. Larger aortic root diameter was significantly associated with less favorable scores on Subjective Symptoms. Having a partner was significantly

associated with better scores on Satisfaction Relationships. Smoking was associated with less favorable General Quality of Life score. Sex was not significantly associated with scores on any sub-domain of the NCSI.

Table 3 HTAD male-female differences in scores on NCSI, SF-36, and HADS subdomains

	Males (n= 77)	Females (n= 65)	p-value
NCSI (total score range)	n= 77	n= 65	
General Quality of Life (1-101.6)	15.0 (7.5-25.6)	15.4 (5.0-24.9)	0.336
Health Related Quality of Life (2-10)	4.0 (3.0-6.0)	4.0 (2.0-6.0)	0.821
Satisfaction Relationships (2-10)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	0.350
Subjective Impairments (4-28)	10.1 ± 6.0	11.3 ± 6.1	0.246
Behavioral Impairments (0-135.5)	0.0 (0.0-11.1)	8.8 (0.0-19.3)	0.013
Subjective Symptoms (2-20)	8.6 ± 5.2	9.3 ± 4.7	0.246
Emotions about Symptoms (6-24)	9.0 (7.0-12.0)	9.0 (8.0-12.0)	0.566
Fatigue symptoms (8-56)	33.9 ± 13.0	35.7 ± 13.6	0.438
SF-36	n= 40	n= 36	
Physical Functioning	90.0 (70.0-95.0)	75.0 (55.0-83.8)	0.005
Role Physical	87.5 (25.0-100.0)	75.0 (0.0-100.0)	0.331
Bodily Pain	90.0 (67.5-100.0)	68.8 (60.0-97.5)	0.268
General Health	54.5 ±18.8	49.4 ± 24.3	0.312
Vitality	58.3 ± 20.4	57.8 ± 21.3	0.922
Social Functioning	90 (67.5-100.0)	68.8 (60.0-97.5)	0.268
Role Emotional	100.0 (75.0-100.0)	100.0 (66.7-100.0)	0.898
Mental health	74.0 ± 18.2	73.6 ± 18.3	0.916
PCS	49.3 [42.3-54.6]	41.6 [35.5-53.1]	0.035
MCS	50.5 (44.4-55.5)	52.4 [44.5-56.2]	0.411
HADS	n= 64	n= 49	
Anxiety score	5.0 (2.3-8.0)	6.0 (2.0-9.0)	0.623
Depression score	4.0 (2.0-7.0)	3.0 (1.0-6.0)	0.251
Total score	9.5 (5.0-15.0)	9.0 (4.5-15.0)	0.814

Data are expressed as mean with SD when parametrically distributed or as medians (IQR) when non-parametrically distributed. Every NCSI subdomain has its own specific score range, displayed as: subdomain (total score range).
NCSI=Nijmegen Clinical Screening Instrument; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale; PCS= Physical Component Summary; MCS= Mental Component Summary.

DISCUSSION

To our knowledge, this is the first study to evaluate male-female specific aspects, and male-female differences in HRQOL in HTAD patients. Very few studies have previously evaluated coping styles in these patients. We found both male and female HTAD patients had lower HRQOL compared to the general population. In female HTAD patients physical well-being and behavioral functioning seemed most affected. Disease acceptance was comparable in male and female HTAD patients, while males scored significantly higher on the coping style 'denial'. Disease acceptance was found to be independently associated

with medication use and absence of hypertension. Although HRQOL was lower in females, we could not identify any factors associated with HRQOL specifically for either for males or females that could explain this difference. However employment and disease acceptance were strongly associated with better HRQOL in both males and females.

Compared to the general Dutch population, both male and female HTAD patients scored lower on almost all SF-36 sub-domains. These findings are in accordance with the findings of studies in HTAD patients and patients with MFS, including children and young adults, which equally showed a reduced HRQOL compared to the general population[4-6,27,28]. This in contrast to adults with congenital heart disease, who were found to report a better HRQOL than the general population[29,30]. Females predominantly reported problems on physical rather than mental aspect shown by significantly lower scores on 3/4 sub-domains of the PCS (table 2). Remarkably, both male and female HTAD patients did not show lower scores on Bodily Pain when compared to the general population. This indicates that, it might not be pain or discomfort causing lower scores on physical well-being, but caused instead by physical disabilities.

In our study, females showed more unfavorable scores on all three HRQOL questionnaires than males, which was also observed in the general Dutch population and other specific patient groups[18]. This male-female difference was significant for: Behavioral Impairments (NCSI) and Physical Functioning (SF-36). These two sub-domains on the NCSI and SF-36 questionnaires have been compared previously, and were found to correlate well (R=0.71)[25]. Moreover, females scored significantly lower on the PCS of the SF-36. On the other hand, there was no significant difference between males and females for any of the baseline characteristics, including: systemic score of MFS (according to the revised Ghent criteria) and previous aortic surgery or dissection[14]. It seems therefore that females were not more physically affected by the disease than males. Potentially this drop in self-reported physical well-being can be explained by the physical disabilities and limitations that HTAD patients experience in daily life, rather than the presence of pain or symptoms themselves.

We found a non-significant slightly higher prevalence of anxiety in females compared to males. A higher prevalence of anxiety in females compared to males was also found in the general population[10,31]. In female HTAD patients however, prevalence of anxiety seems to be markedly higher than in the general Dutch population (36.7% vs 19.3%)[31]. Surprisingly, the HADS outcomes showed a non-significant higher prevalence of depression in male HTAD patients compared to females. This is inconsistent with epidemiological studies which demonstrate a higher prevalence of depression in females compared to males. Although the prevalence is comparable to the general Dutch population where the prevalence of mood disorders was reported to be about 19%[31]. On the other hand, this is

much lower than the rate of 44% depression previously reported in MFS[32], although this was measured using a different questionnaire for assessment of depressive symptoms.

HTAD patients with high scores on disease acceptance showed significantly better scores on almost all sub-domains, including lower scores on the HADS anxiety and depression subscales, which overall represents a better HRQOL. Males showed significantly higher scores on denial than females. Denial has been associated with lower distress[33]. Theoretically, this might contribute to males showing better scores on HRQOL and less anxiety. Even though males show higher denial, the true acceptance rate corrected for denial was not significantly different between males and females. Disease acceptance in our HTAD population was markedly lower than the 54-65% previously reported[13,34]. This could be caused by the lack of a gold standard for measuring coping styles, which leads to the use of different measurement methods. In this study we have used the ADIQ questionnaire, whereas previous studies have used the 'Utrechtse Coping Lijst' and 'The Coping Orientation to Problems Experienced inventory (COPE)'[13,34]. Furthermore, one study used the old Ghent Criteria for the diagnosis of MFS for inclusion of patients, and additionally included much younger patients (mean age 22.6 ± 4.8 years)[34]. Moreover, these studies all have very small sample sizes, which might contribute to the variation in findings. More importantly, disease acceptance is known to be an important factor in relation to patients' adherence to treatment[12,13]. HTAD patients are always under long-term surveillance, receive counselling on lifestyle modifications (e.g. exercise, smoking) and are often prescribed medication. Beta blocker and ARB use were found to be positively associated with acceptance, and hypertension was negatively associated with acceptance. Furthermore, hypertension was associated with less favorable scores on the NCSI, indicating more problems and lower HRQOL. This strengthens the assumption that disease acceptance improves patients' adherence to medical treatment, with adherent patients having less hypertension. Our results emphasize that coping style, and especially disease acceptance is underexposed, but truly important in the management of HTAD patients. These findings correspond with a previous study showing that bio-behavioral factors play a big role in quality of life of MFS patients[7].

Employment seems to be a very important factor in HRQOL of patients with MFS. It is striking that the association with such daily life aspects seems so strong, whereas medical and disease related factors such as aortic root diameter, previous surgery, family history and previous aortic dissection showed almost no association with HRQOL. These finding are very similar to the findings of the largest HRQOL in HTAD patients performed so far by Goldfinger et al.[4] and Moon et al.[7]. Similar findings were also reported in a very recent study in children and adolescents with MFS[28]. No explanation could be found from the differences in baseline variables between HTAD patients of working age with and without employment. Nonetheless employment is influenced by many factors: disease related

factors, daily life aspects (also bio-behavioral factors) and demographic factors. In turn, employment has consequences on many factors as well, mainly social support and daily life aspects (independence, self-worth, family life and social life). The connection between employment and all these different factors might explain its strong association with HRQOL, and makes it an important factor to consider when counselling HTAD patients.

Table 4 Comparison of NCSI, SF-36, and HADS subdomain scores in HTAD participants with and without disease acceptance/true disease acceptance

	Acceptance (n=61)	**No acceptance (n=81)**	**p-value**
NCSI	n=61	n=81	
General Quality of Life (1-101.6)	9.4 (4.0-15.2)	20.7 (11.5-37.1)	<0.001
Health Related Quality of Life (2-10)	3.0 (2.0-4.0)	5.0 (4.0-7.0)	<0.001
Satisfaction Relationships (2-10)	3.0 (2.0-3.5)	4.0 (2.0-5.0)	0.147
Subjective Impairments (4-28)	7.0 (4.0-10.0)	12.0 (8.0-17.0)	<0.001
Behavioural Impairments (0-135.5)	0.0 (0.0-7.0)	9.8 (0.0-19.9)	<0.001
Subjective Symptoms (2-20)	6.5 (3.0-12.0)	10.00 (6.00-14.00)	0.001
Emotions about Symptoms (6-24)	8.00 (7.0-10.3)	10.00 (8.00-13.00)	0.005
Fatigue symptoms (8-56)	29.0 (12.4)	39.1 (12.3)	<0.001
SF-36	n=35	n=41	
Physical Functioning	85.0 (75.0-95.0)	75.0 (57.5-90.0)	0.068
Role Physical	100.0 (75.0-100.0)	50.0 (0.0-100.0)	0.002
Bodily Pain	89.8 (67.4-100.0)	67.4 (44.9-89.8)	0.010
General Health	54.3 (12.7)	52.7 (12.7)	<0.001
Vitality	70.7 (15.5)	52.2 (19.2)	<0.001
Social Functioning	100.0 (87.5-100.0)	75.0 (62.5-87.5)	<0.001
Role Emotional	100.0 (100.0-100.0)	100.0 (33.3-100.0)	0.016
Mental health	60.0 (56.0-64.0)	56.0 (52.0-60.0)	0.153
HADS	n=46	n=67	
Anxiety score	4.0 (3.3)	7.1 (4.4)	<0.001
Depression score	2.8 (2.5)	6.1 (4.8)	<0.001
Total score	6.8 (5.1)	13.3 (8.3)	<0.001
	True acceptance (n=38)	**No true acceptance (n=104)**	**p-value**
NCSI	n=38	n=104	
General Quality of Life (1-101.6)	6.0 (3.0-14.6)	17.7 (8.1-31.0)	<0.001
Health Related Quality of Life (2-10)	3.0 (2.00-4.3)	5.0 (3.0-7.0)	<0.001
Satisfaction Relationships (2-10)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	0.322
Subjective Impairments (4-28)	7.0 (5.5-10.0)	10.5 (6.0-16.0)	0.003
Behavioural Impairments (0-135.5)	0.0 (0.0-8.5)	5.4 (0.0-18.2)	0.010
Subjective Symptoms (2-20)	5.0 (3.0-12.3)	10.0 (6.0-14.0)	0.006
Emotions about Symptoms (6-24)	8.0 (6.8-9.3)	10.0 (8.0-13.0)	0.008
Fatigue symptoms (8-56)	29.6 (12.3)	36.6 (13.2)	0.005
SF-36	n=24	n=52	
Physical Functioning	80.0 (71.3-93.8)	80.0 (60.0-93.8)	0.500
Role Physical	87.5 (56.3-100.0)	75.0 (0.0-100.0)	0.247
Bodily Pain	89.8 (67.4-97.5)	77.6 (57.1-100.0)	0.409
General Health	55.0 (12.9)	52.7 (12.5)	0.462
Vitality	70.4 (15.0)	56.3 (20.3)	0.003

Table 4 Continued

	True acceptance (n=38)	No true acceptance (n=104)	p-value
Social Functioning	100.0 (87.5-100.0)	75.0 (62.5-100.0)	0.00
Role Emotional	100.0 (100.0-100.0)	100.0 (33.3-100.0)	0.131
Mental health	60.0 (56.0-64.0)	60.0 (52.0-60.0)	0.154
HADS	n=28	n=85	
Anxiety score	4.32 (3.44)	6.39 (4.37)	0.025
Depression score	2.64 (2.11)	5.45 (4.61)	<0.001
Total score	6.96 (4.69)	11.84 (8.31)	<0.001

Data are expressed as mean with SD when parametrically distributed or as medians (IQR) when non-parametrically distributed. HTAD= hereditary thoracic aortic diseases; NCSI=Nijmegen Clinical Screening Instrument; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale

Even though no association between previous aortic dissection and HRQOL scores on the NCSI could be found, patients with previous aortic dissection scored lower on most SF-36 sub-domains. This was especially prominent in the PCS. Patients who previously underwent aortic surgery showed significantly lower scores on the sub-domain Physical Functioning, but overall seemed to show less prominent reduction in HRQOL. When interpreting these findings, it is important to keep in mind that the SF-36 was only completed by a subset of our cohort (n=76), which could explain why no statistically significant difference was detected.

Clinical implications

The findings of this study should lead to more awareness among patients, families, and health care providers such as clinical geneticists, genetic counselors, cardiologists, and psychologists about the impact aortic disease has on the patient's HRQOL. In genetic counselling as well as cardiovascular treatment of HTAD patients HRQOL assessment should be incorporated, since this is crucial in order to provide the counselling and guidance needed for HTAD patients and their families. Additionally, we identified several factors which influence HRQOL in HTAD patients, which are valuable leads for counselling. We found that disease related factors appear less important for HRQOL in HTAD patients than daily life aspects and coping style, which seems to positively influence HRQOL, and patients' adherence to medical treatment. It has been mentioned before that subjective perception of the diagnosis may be an important factor influencing HRQOL [35]. Therefore, interventions aimed at modifying coping strategy and other daily life aspects should be considered. The first step towards this can be made by incorporating patient reported quality of life into clinical practice, in order to select the patients who need extra counselling and guidance.

Limitations

This study has some limitations. Most importantly, the SF-36 and HADS questionnaires were not completed by all participants. This was due to logistic issues, because of which the SF-36 and HADS questionnaires could not be distributed during a certain period of time. Therefore, we do expect the distribution of the completed SF-36 and HADS questionnaires over our study population to be random. No significant difference was found between the percentage of males and females who completed the SF-36 and HADS questionnaires. Patients who completed the SF-36 had significantly larger aortic root diameters than those who did not. However, no associations were found between aortic root diameter and HRQOL. Furthermore, no significant difference in scores on any of the NCSI questionnaire sub-domains was found between patients who did, and those who did not complete the SF-36 questionnaire. There was no difference in HRQOL measurements between those two groups, since the NCSI sub-domains were found to correlate well with the SF-36 sub-domains [25]. It seems therefore that the subset of HTAD patients who completed the SF-36 and HADS questionnaires were representative of our total study population. Unfortunately, with the NCSI no comparison with the general population could be made. Therefore our comparison between HTAD patients and the general Dutch population is limited. Furthermore, the response rate to the questionnaires was 47.1%, which is comparable to other online surveys[36]. Finally, our study population contained many patients diagnosed with MFS (n=123). However, baseline characteristics for patients with and without MFS seemed comparable (supplemental file 2). Therefore, all participants were included in analysis comparing HTAD patients to the general population and comparing males and females. For studying associations between HRQOL and baseline characteristics only the patients with MFS were included.

CONCLUSIONS

HTAD patients showed subnormal HRQOL. Females reported markedly lower HRQOL compared to males and females in the general population, predominantly on physical well-being. Disease acceptance was associated with better HRQOL and patients' adherence to treatment. Interestingly, factors such as employment, coping style, and disease acceptance seem more important for HRQOL than disease related factors. These findings offers valuable leads for counselling and guidance of both male and female HTAD patients.

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SUPPLEMENTAL FILE 1

Case report form

- Date of birth (dd-mm-yyyy)
- Sex (male / female)
- Age (years)
- Weight (kg)
- Length (m)
- Hypertension (yes / no)
  Yes if: in medical history or use of antihypertensive medication.
- Hyperlipidemia (yes / no)
  Yes if: in medical history or use of lipid lowering medication.
- Renal dysfunction (yes / no)
  Yes if: in medical history
- Smoking (yes currently, former, never)
- Beta-blocker use (yes / no)
- Angiotensin receptor blocker use (yes / no)
- Confirmed genetic mutation (*FBN1, TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, COL3A1, ACTA2*, Other – specify, None)
- Systemic score for Marfan Syndrome (Is any of the following present yes / no: wrist sign; thumb sign; pectus carinatum or excavatum or asymmetry; hindfoot deformity or flat foot; pneumothorax in medical history; Dural ectasia; protrusio acetabuli; arm-height ratio; scoliosis or kyphosis; reduced elbow extension; facial characteristics; striae; severe myopia; mitral valve prolapse)
- Positive family history of aortic disease (yes / no)
  Yes if: First or second degree family member with thoracic aortic aneurysm or dissection, or aneurysm or dissection elsewhere <60 years old, or congenital left sided heart defect or sudden death <45 years old.
- Positive family history of Marfan Syndrome (yes / no)
  Yes if: First or second degree family member with diagnosis of Marfan Syndrome
- Previous aortic surgery (yes / no)
- Thoracic aortic aneurysm (yes / no)
- Abdominal aortic aneurysm (yes / no)
- Aortic dissection (yes / no)
- Employment (yes / no)
- Partner (yes / no)
- Questionnaires
  - Date of completion questionnaire
  - Date of visit outpatient clinic

- Echocardiogram (if available from outpatient clinic visit)
  - Overall left ventricular function (good, reasonable, moderate, poor)
- MRI / CT-scan (if available from outpatient clinic visit)
  - Aortic root diameter (mm)
  - Aortic root Z-score (calculated if not reported)

SUPPLEMENTAL FILE 2

Baseline characteristic of patients with and without MFS

	Total (n= 142)	MFS (n= 123)	No MFS (n= 19)	p-value
Age - y	42.1±14.8	41.0±14.3	49.2±16.3	0.023
Sex - % females	65 (45.8)	57 (46.3)	8 (42.1)	0.730
BMI - kg/m2	23.5±4.5	23.7±4.6	22.3±3.6	0.205
Hypertension	17 (12.0)	14 (11.4)	3 (15.8)	0.582
Hyperlipidaemia	16 (11.3)	12 (9.8)	4 (21.1)	0.147
Current smoker	17 (12.9)	15 (13.2)	2 (11.1)	0.810
Renal dysfunction	2 (1.8)	2 (2.1)	0 (0.0)	0.562
Beta blocker use	92 (64.8)	82 (66.7)	10 (52.6)	0.233
ARB use	59 (41.5)	54 (43.9)	5 (26.3)	0.148
Aortic root diameter - mm	40.1±5.5	40.0±5.5	40.7±5.7	0.669
Z-score	2.7±2.0	2.7±2.0	2.7±2.1	0.678
Abdominal aortic aneurysm	18 (12.9)	17 (13.9)	1 (5.9)	0.354
Normal LVEF	135 (96.4)	117 (96.7)	18 (94.7)	0.669
Previous Surgery	46 (32.4)	42 (34.1)	4 (21.1)	0.256
Previous dissection	21 (14.8)	18 (14.6)	3 (15.8)	0.895
Positive systemic score >7 [1]	41 (28.9)	37 (30.1)	4 (21.1)	0.419
Positive family history MFS	80 (62.5)	80 (72.7)	0 (0.0)	<0.001
Current partner	85 (68.5)	73 (67.6)	12 (75.0)	0.551
Current work	88 (66.2)	78 (68.4)	10 (52.6)	0.178

Data are expressed as mean ± SD or as absolute and percentage. BMI= Body Mass Index; ARB= Angiotensin II receptor blocker; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome.

[1] n=101 due to missing data on this variable

CHAPTER 9

9

Health-related quality of life and lived experiences in males and females with thoracic aortic disease and their partners

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Open Heart, 2020

ABSTRACT

Objective

Thoracic aortic disease (TAD) may have substantial impact on health related quality of life (HRQOL). We described HRQOL in TAD-patients, cardiovascular screening-participants and their partners; identified factors associated with HRQOL; and explored lived experiences and feelings of anxiety or depression using a mixed methods design.

Methods

For this cross-sectional study all consecutive patients visiting the TAD outpatient clinic (2017-2019) at our center were asked to complete three questionnaires: the Short Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS), and the Rotterdam Disease Specific Questionnaire (RDSQ). A subsample was invited for in-depth interviews.

Results

In total, 261 participants were included: 147 TAD-patients (thoracic aortic diameter ≥40mm; 54 females, 36.7%), 114 screening-participants (cardiovascular family screening; 71 females, 62.3%) and 66 partners. Compared to the general population, TAD-patients showed markedly lower HRQOL, whereas screening-participants' HRQOL was less impaired. Female and younger participants scored significantly lower on the SF-36 and HADS compared to male and older participants. Smaller aortic diameter was associated with better RDSQ score, and previous aortic surgery was associated with higher HADS depression scores. Furthermore, partners scored significantly lower on 2/8 SF-36 sub-domains when compared to the general population. From 11 interviewees, determinants of psychological distress included coping strategies, impact on social and professional life, disease-related knowledge, state of aortic diameters and physical symptoms.

Conclusions

Healthcare professionals must be aware of HRQOL impairments in TAD-patients, particularly in younger females. Moreover, attention for partners is needed. Coping strategies and communication within the family were found to be important factors influencing psychological distress, and might be valuable leads for counselling and HRQOL improvement in this population.

INTRODUCTION

Thoracic aortic disease (TAD), including thoracic aortic aneurysms and dissections, has an estimated prevalence of 9/100,000 per year in females, and 16/100,000 per year in males[1]. These patients are at risk of sudden cardiac death[2]. An inherited pattern of TAD is found in about 20% of cases[3]. Therefore, patients and family members are often included in genetic and cardiovascular screening programs, and may face lifelong uncertainties[4].

The scarce evidence on health-related quality of life (HRQOL) in TAD-patients showed suboptimal results[5,6]. Most research has been performed in patients with hereditary thoracic aortic diseases (HTAD) such as Marfan Syndrome and Loeys-Dietz syndrome. In HTAD-patients, HRQOL was reduced as compared to the general population, and comparable to other chronic diseases[7-10].

To achieve HRQOL improvement, it is important to obtain more patient and disease-specific information on HRQOL and lived experiences. However, no studies to date have evaluated male-female specific HRQOL in TAD-patients. Furthermore, the impact of the disease on HRQOL of TAD-patients' partners has not yet been investigated. It has been suggested that studies using disease-specific questionnaires and a combined quantitative and qualitative approach would provide better insight[6]. Therefore, in addition to existing well-validated questionnaires, we developed a disease-specific questionnaire, and aimed to: 1) evaluate HRQOL, anxiety and depression in TAD-patients, screening-participants and partners and compare this to the general population, 2) compare HRQOL between males and females, 3) identify factors associated with HRQOL, and 4) explore TAD-patients lived experiences and feelings of anxiety or depression.

METHODS

Study populations

All consecutive patients who visited the specialized TAD outpatient clinic of our tertiary care center between October 2017 and July 2019, were eligible for inclusion. The TAD outpatient clinic is a specialized outpatient clinic in which patients are seen by cardiologists or physician assistants for cardiovascular family screening or aortic surveillance, including referral from primary care and secondary care. Inclusion criteria were: adult age (≥ 18 years), outpatient clinic visit for cardiovascular (family) screening or follow-up of TAD. Exclusion criteria were intellectual disability or language barrier. All eligible patients were invited to participate in the study, reasons for exclusion or failure to complete the questionnaires are shown in Figure 1. Included participants were divided into two

groups: participants with a (genetic) predisposition and/or positive family history of TAD, hereafter referred to as 'screening-participants'; and 'TAD-patients' under surveillance for confirmed thoracic aortic aneurysm defined as a thoracic aortic diameter of ≥40 mm.

Data collection

All included patients completed three questionnaires: the Short Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS), and the Rotterdam Disease Specific Questionnaire for TAD (RDSQ) which was developed for this study. The questionnaires were distributed 1-2 weeks before the scheduled outpatient visit. Partners were asked to complete the same set of questionnaires either during the outpatient clinic visit or via email. All questionnaires were documented using a secured web-based application for distribution of questionnaires during clinical research (GEneric Medical Survey Tracker, Erasmus MC and Equipe Zorgbedrijven, latest release 2019, version 1.8.6, open source). This application did not allow any missing answers. Patients who did not complete all three questionnaires were excluded. Additional data was collected from the patient files using a standardized case report form. Body Surface Area (BSA) was calculated using the DuBois and DuBois formula[11]. This study was approved by the local ethics committee (METC Erasmus MC, MEC-2017-057), and was designed, performed and controlled in accordance with current local and international good clinical practice guidelines. Written and signed informed consent was obtained from all participants. This study was designed and performed without patient involvement.

Questionnaires

The SF-36 questionnaire is a widely used HRQOL questionnaire with 36 items, which has eight domains: Physical Functioning (PF), Role limitations due to Physical health problems (RP), Bodily Pain (BP), General Health perceptions (GH), Vitality (VT), Social Functioning (SF), Role limitations due to Emotional problems (RE), and general Mental Health (psychological distress) (MH) [12,13]. The first four domains (PF, RP, BP & GH) together form the Physical Component Summary (PCS) and the last four domains (VT, SF, RE & MH) form the Mental Component Summary (MCS). All SF-36 subdomains have a score range of 0-100, with higher scores reflecting a better quality of life. The SF-36 has been translated and validated in the Dutch language[12]. Male and female SF-36 scores of participants were compared to male-female specific norm values[12]. Unfortunately, no age-specific norm values were available for males and females separately. Therefore, an additional analysis was performed to compare participants to an age-matched general Dutch population[12]. Likewise, SF-36 scores of partners were compared to the general population. Male-female specific physical and mental component scores (PCS and MCS) were calculated using the mean and standard deviations of the general Dutch population.

The HADS questionnaire assesses signs of anxiety and depression, and has been validated in the Dutch language[14]. This 14-item scale is divided in two dimensions: anxiety (seven items) and depression (seven items). The responses result in a score for each dimension with a score range of 0-21 and a total overall score with a score range of 0-42. Higher scores represent higher levels of anxiety and depression. A score of ≥8 on the HADS anxiety and depression subscales is internationally used as the cut-off score to define elevated levels of anxiety/depression[15]. HADS scores of participants were compared to age-matched norm values[14].

The RDSQ for TAD was developed by a multidisciplinary team in our center, including a cardiologist, psychologist, PhD-candidate and physician assistant (supplemental file 1)[10,16]. The purpose of this disease-specific questionnaire was to assess the impact of having TAD on daily life factors, such as: employment; family life; sexual functioning and sports participation. The questionnaire contains 18 statements which participants were asked to rate on a 10-point Likert scale. A higher score reflects better agreement with the statements, and more impaired TAD-related quality of life.

In-depth interviews

Eleven participants were purposively selected by an independent researcher based on differences in age, sex, genetic disorder, previous surgery, symptoms of depression and anxiety (HADS score) and RDSQ score (Figure 1), in order to create a heterogeneous group. They were invited for a semi-structured qualitative interview using a topic list, which evolved over the course of the study as an iterative process. Interviews were audio-taped using a voice recorder and non-verbal signs were noted. A verbatim transcript of the interviews was made on the same day.

The verbatim transcripts were analyzed using content analysis, applying a multi-step consecutive approach starting with an initial open coding phase, followed by axial coding and finishing with a selective coding process[17]. In addition to the interviewer (SD), two other researchers (CGET and EG) read the interview transcripts, and the individual narrative of each participant was constructed (i.e., open coding). In the second phase, these researchers independently coded the individual narratives to identify significant and common aspects (i.e., axial coding). When necessary, decisions were made in consensus. In a third phase, SD and EG analyzed the codes together to construct the narrative syntheses (i.e., selective coding) and the final coding tree, including an overview of the most important factors. The coding process was carried out using the NVIVO 12 plus software (QSR International, March 2018).

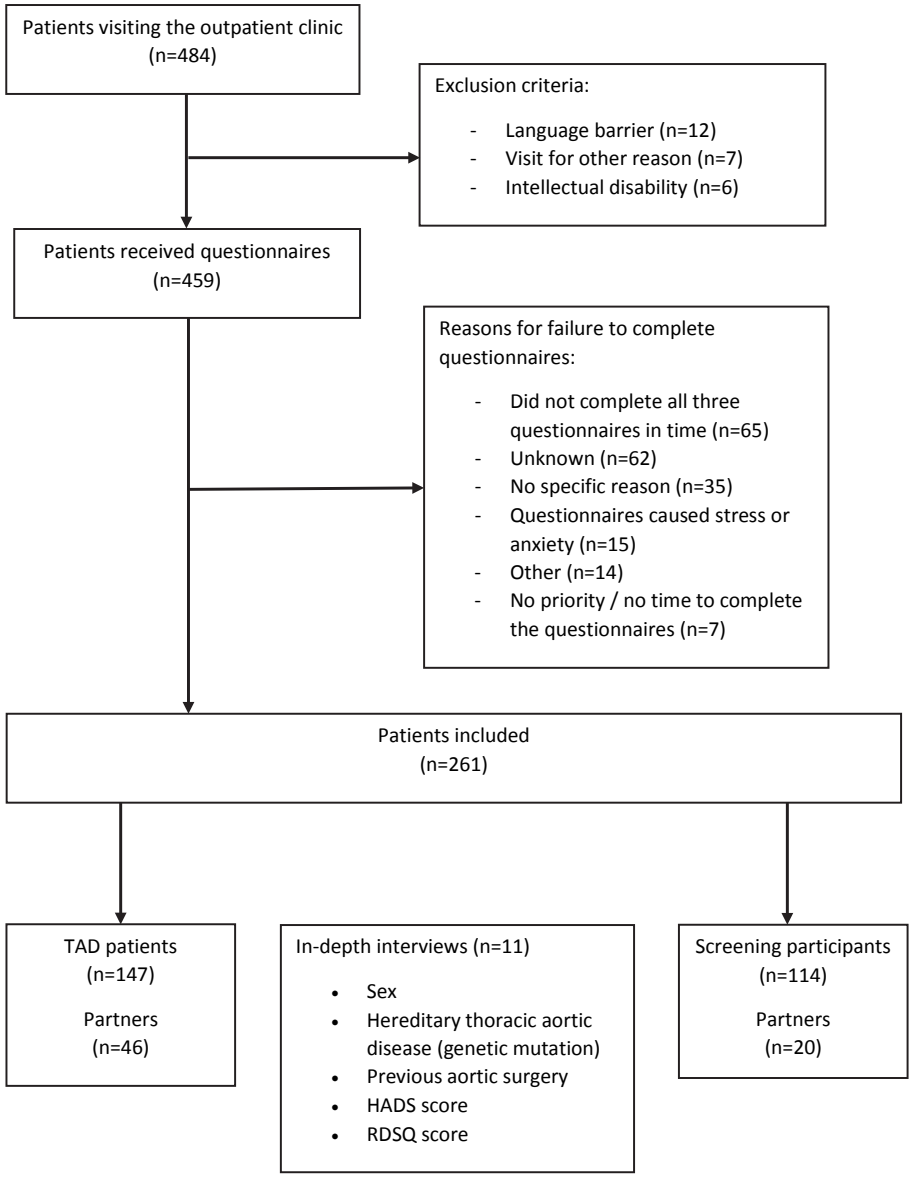

Figure 1 Flowchart of patient inclusion

TAD patients= Patients with confirmed thoracic aortic aneurysm ≥ 40 mm; HADS = Hospital Anxiety and Depression Scale; RDSQ= Rotterdam Disease Specific Questionnaire.

Statistical analysis

Data were analyzed using SPSS statistics (IBM SPSS Statistics version 25). Continuous data were presented as mean and standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when skewed. Categorical data were presented as frequencies with percentages. Comparison between patient and normative data was analyzed using means and SD. Unpaired students t-test or non-parametric Wilcoxon test were used to compare continuous variables, chi-squared or Fisher's exact test were used to compare categorical variables. The one-sample students t-test was used to compare norm-values to the study population means. Associations between baseline characteristics and RDSQ and HADS scores were evaluated using univariable linear regression models. Factors with a p-value of <0.2 and factors that were considered clinically relevant were considered for multivariable linear regression models. All models were adjusted for age and sex. Linear regression analyses were performed for screening-participants and TAD-patients combined, and for partners separately. An α-value of <0.05 was considered significant. Bonferroni correction for multiple testing was applied.

RESULTS

Patient population

Figure 1 shows a flow chart of the inclusion process. In total, 261 participants were included comprising 147 TAD-patients (54 females, 36.7%) and 114 screening-participants (71 females, 62.3%). Furthermore, 66 partners completed the questionnaires. The partners' sex was registered in 53 participants (80%), of which 63% was female.

Table 1 shows baseline characteristics of included males and females. Males showed significantly higher height, weight, body surface area (BSA) and absolute diameters of the thoracic aorta. Females showed higher adjusted ascending aortic diameters (indexed for BSA). A significantly higher percentage of males used ACE-inhibitors (p=0.006) and angiotensin receptor blockers (ARB's) (p=0.021). Males were more often employed, and performed regular exercise more often, whereas females more often had a history of depression. Additionally, baseline characteristics between TAD-patients and screening participants were compared (shown in supplemental file 2).

Table 1 Patient characteristics

	Total (n=261)	Interviews (n=11)	p-value	Males (n=136)	Females (n=125)	p-value
Age - y	52.9±15.8	55.5±14.2	0.588	53.7±15.9	52.1±15.7	0.407
Length - cm	177.2±14.7	178.0±8.5	0.853	184.0±13.9	169.7±11.7	<0.001**
Weight - kg	83.9±19.4	84.5±16.5	0.923	92.2±17.9	75.3±17.1	<0.001**
BSA - m^2	2.0±0.2	2.0±0.2	0.794	2.1±0.2	1.9±0.2	<0.001**
Hypertension	117 (44.8)	8 (72.7)	0.061	66 (48.5)	51 (40.8)	0.267
Hyperlipidemia	66 (25.3)	4 (36.4)	0.427	42 (30.9)	24 (19.2)	0.082
Smoking	25 (9.6)	0 (0.0)	0.347	10 (7.4)	15 (12.0)	0.250
Diabetes	9 (3.4)	0 (0.0)	0.523	5 (3.7)	4 (3.2)	0.833
Renal dysfunction	5 (1.9)	0 (0.0)	0.636	2 (1.5)	3 (2.4)	0.584
History of depression	16 (6.1)	1 (9.1)	0.673	2 (1.5)	14 (11.2)	0.001**
History of anxiety disorder	4 (1.5)	1 (9.1)	0.037*	2 (1.5)	2 (1.6)	0.932
Beta blocker use	60 (23.0)	5 (45.5)	0.075	35 (25.7)	25 (20.0)	0.271
ARB use	34 (13.0)	3 (27.3)	0.149	24 (17.6)	10 (8.0)	0.021*
ACEi use	42 (16.1)	3 (27.3)	0.320	30 (22.1)	12 (9.6)	0.006**
Diagnosis						
Marfan Syndrome	10 (3.8)	1 (9.1)	0.314	7 (5.1)	3 (2.4)	0.267
Loeys-Dietz Syndrome	10 (3.8)	3 (27.3)		4 (2.9)	6 (4.8)	0.407
Ehlers-Danlos Syndrome	2 (0.8)	0 (0.0)		0 (0.0)	2 (1.6)	0.133
Other	12 (4.6)	0 (0.0)		6 (4.4)	6 (4.8)	0.841
Confirmed genetic mutation	61 (23.4)	4 (36.4)	0.551	28 (20.6)	33 (26.4)	0.537
Positive family history aortic disease	132 (50.6)	6 (54.5)	0.818	64 (47.1)	68 (54.4)	0.489
Abdominal aortic aneurysm	9 (3.4)	2 (18.9)	0.006	8 (5.9)	1 (0.8)	0.025*
Maximal diameter aortic root[1]	37.6±5.7	38.9±4.5	0.577	40.1±5.5	34.7±4.3	<0.001**
Indexed diameter aortic root[1] - mm/BSA	19.0±2.9	23.5±13.9	0.303	18.7±2.4	19.0±2.7	0.395
Maximal diameter ascending aorta[1]	37.0±6.8	41.8±6.4	0.015*	38.4±6.6	35.7±7.0	0.004**
Indexed diameter ascending aorta[1] - mm/BSA	18.7±3.9	20.8±3.5	0.060	17.9±3.3	19.5±4.2	0.003**
Maximal diameter descending aorta[1]	27.1±6.3	27.6±3.2	0.819	28.0±6.2	25.2±6.2	0.004**
Indexed diameter descending aorta[1] - mm/BSA	13.7±3.3	14.1±2.3	0.709	13.1±2.8	13.7±3.7	0.276
Previous aortic surgery	33 (12.6)	3 (27.3)	0.149	21 (15.4)	12 (9.6)	0.156
Previous dissection	23 (8.8)	1 (9.1)	0.970	9 (6.6)	14 (11.2)	0.192
Current partner	126 (48.3)			73 (53.7)	53 (42.4)	0.115

Table 1 Continued

	Total (n=261)	Interviews (n=11)	p-value	Males (n=136)	Females (n=125)	p-value
Current employment[2]	103 (39.5)	6 (54.5)	0.573	64 (47.1)	39 (31.2)	0.008**
Paid job	96 (36.8)	6 (54.5)		62 (45.6)	34 (27.2)	
Volunteer work	7 (2.7)	0 (0.0)		2 (1.5)	5 (4.0)	
Retired	57 (21.8)	3 (27.3)		28 (20.6)	29 (23.2)	
Student	16 (6.1)	0 (0.0)		7 (5.1)	9 (7.2)	
Unable to work / disabled	16 (6.1)	2 (18.2)		8 (5.9)	8 (6.4)	
Unemployed	12 (4.6)			1 (0.7)	11 (8.8)	
Exercise			0.799			
Sports participation[3]	105 (40.2)	4 (36.4)		63 (46.3)	42 (33.6)	0.035*
Walking or cycling	104 (39.8)	5 (45.5)		47 (34.6)	57 (45.6)	
None	36 (13.8)	2 (18.2)		18 (13.2)	18 (14.4)	

Data are expressed as mean ± SD or as absolute and percentage. BSA=Body Surface Area; ARB= Angiotensin II receptor blocker; ACEi= Angiotensin Converting Enzyme inhibitor; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome; LDS 3= Loeys-Dietz Syndrome type 3 (SMAD3 mutation).

[1] Only patients without previous aortic surgery.

[2] Current employment= Paid job or volunteer work.

[3] Defined as: Participating in any sport other than daily walking or cycling at any level at least once a week.

* Significant at the 0.05 level

** Significant at the 0.01 level

Scores of TAD-patients and screening-participants compared to the general population

Figure 2 shows comparison of SF-36 sub-scores of TAD-patients and screening-participants to a sex-matched general population. Male screening-participants showed a significantly higher score on the sub-domain Bodily Pain (77.3±22.7 vs 86.3±19.5, p=0.004), whereas male TAD-patients showed significantly lower scores on Physical Functioning (77.9±25.0 vs 85.4±21.0, p=0.005), General Health (54.0±23.1 vs 71.6±20.6, p<0.001) and Vitality (61.7±24.1 vs 71.9±18.3, p<0.001). Female screening-participants showed a significantly lower score on General Health (54.0±25.8 vs 69.9±20.6, p <0.001) and Vitality (54.8±26.4 vs 64.3±19.7, p=0.003). Female TAD-patients showed significantly lower scores on all SF-36 sub-domains except Bodily Pain and Mental Health when compared to the general population: Physical Functioning 64.7±26.3 vs 80.4±24.2, p=<0.001; Role Physical 46.3±42.5 vs 73.8±38.5, p=<0.001; General Health 49.0±21.9 vs 69.9±20.6, p=<0.001; Vitality 49.0±23.6 vs 64.3±19.7, p=<0.001; Social Functioning 69.9±28.8 vs 82.0±23.5, p=0.003; Role Emotional 60.5±42.0 vs 78.5±35.7, p=0.003.

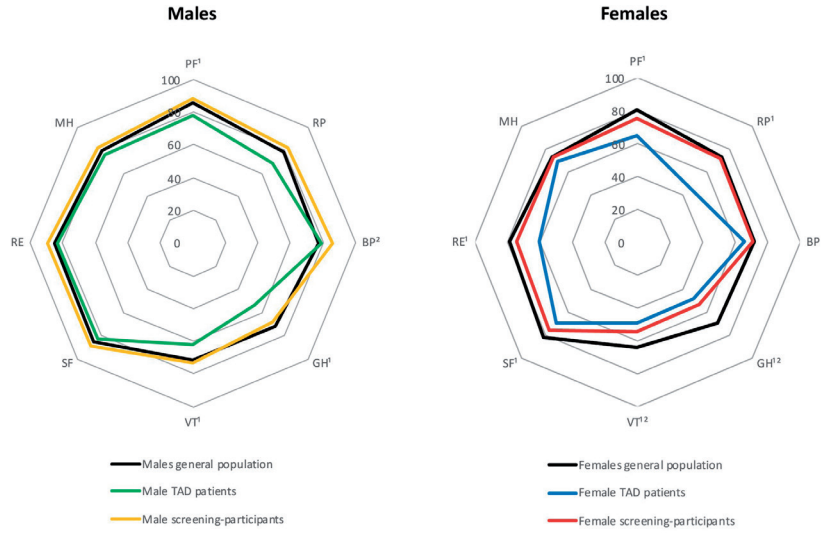

Figure 2 Comparison of SF-36 scores of male and female participants to the general population.

SF36= Short Form 36 questionnaire; TAD= Thoracic aortic disease; PF= Physical Functioning; RP= Role Physical; RE= Role emotional; VT= Vitality; MH= Mental Health; SF= Social Functioning; GH= General Health; BP= Bodily Pain.
[1]= Significant difference between TAD patients and the general population after Bonferroni correction; [2]= Significant difference between screening-participants and the general population after Bonferroni correction.

Figure 3 shows SF-36 scores of screening-participants and TAD-patients compared to the age-matched general population. Younger TAD-patients and screening-participants showed lower scores on all SF-36 sub-domains, with increasing age this difference became smaller. HADS scores of TAD-patients and screening-participants aged 18-65 years were not significantly different compared to the age-matched general population. TAD-patients and screening-participants older than 65 years showed lower scores when compared to the age-matched general population, especially on the HADS depression sub-domain (2.9±3.7 vs 4.6±3.6, p=0.001).

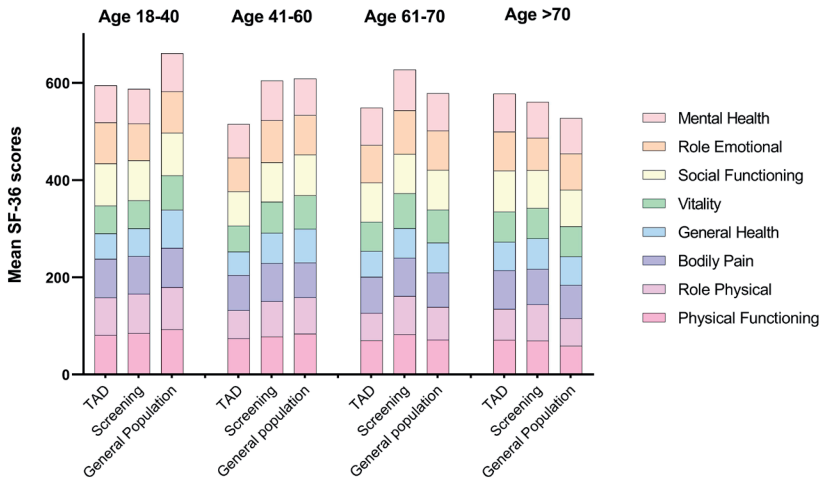

Figure 3. Comparison of SF-36 scores of participants with age-matched general population.

SF-36= Short Form 36 questionnaire; TAD= Thoracic aortic disease, defined as confirmed thoracic aortic aneurysm of ≥ 40 mm.

Differences between HRQOL scores of males and females

Table 2 shows scores of male and female participants on sub-domains of all questionnaires. Elevated scores (≥8) on the HADS anxiety sub-domain occurred significantly more in females (12.5% vs 29.6%, p=0.001).

Supplemental file 3 shows stratified analysis of male-female HRQOL for screening-participants and TAD-patients. Results were comparable to the un-stratified analysis.

Supplemental file 4 shows median scores of males and females on the RDSQ questionnaire. A significant difference was found between males and females on question 13, which indicates whether the participant experiences more anxiety than before the (potential) diagnosis of TAD (1.0 (IQR 1.0-3.0) vs 2.0 (IQR 1.0-5.0), p= 0.011) and question 17 which indicates worries about the heredity of TAD (5.0 (IQR 2.0-8.0) vs 7.0 (IQR 5.0-9.0), p<0.001).

Table 2 Male-female scores of participants on all questionnaires

	Total (n=261)	Males (n=136)	Females (n=125)	p-value
RDSQ				
Total score	51 .0 (32.0-80.0)	48.0 (29.3-78.5)	53.0 (34.5-85.5)	0.160
SF-36				
Physical Functioning	85.0 (60.0-95.0)	95.0 (71.3-100.0)	80.0 (50.0-95.0)	<0.001*
Role Physical	100.0 (25.0-100.0)	100.0 (50.0-100.0)	75.0 (12.5-100.0)	0.024
Bodily Pain	80.0 (57.5-100.0)	90.0 (67.5-100.0)	67.5 (45.0-100.0)	<0.001*
General Health	55.0 (40.0-100.0)	60.0 (40.0-80.0)	55.0 (35.0-70.0)	0.030
Vitality	60.0 (40.0-80.0)	70.0 (50.0-83.8)	50.0 (35.0-75.0)	<0.001*
Social Functioning	87.5 (62.5-100.0)	100.0 (75.0-100.0)	75.0 (62.5-100.0)	<0.001*
Role Emotional	100.0 (66.7-100.0)	100.0 (100.0-100.0)	100.0 (33.3-100.0)	<0.001*
Mental health	80.0 (64.0-88.0)	84.0 (69.0-92.0)	76.0 (56.0-88.0)	0.007
PCS	49.2 (38.2-55.8)	51.6 (41.8-56.3)	46.2 (35.4-54.5)	0.017
MCS	51.9 (42.8-56.9)	54.4 (48.0-57.4)	48.5 (37.9-55.0)	<0.001*
HADS				
Anxiety score	4.0 (2.0-7.0)	4.0 (2.0-6.0)	4.0 (2.0-8.0)	0.023
Depression score	2.0 (1.0-5.0)	1.5 (0.0-4.8)	2.0 (1.0-5.0)	0.043
Anxiety score ≥8	54 (20.7)	17 (12.5)	37 (29.6)	0.001*
Depression score ≥8	39 (14.9)	16 (11.8)	23 (18.4)	0.133
Total score	6.0 (3.0-12.0)	5.0 (2.3-10.0)	6.0 (4.0-15.5)	0.037

Data was non-parametrically distributed and therefore expressed as medians (IQR), or as absolute and percentage.
Participants= screening-participants and TAD-patients; RDSQ= Rotterdam Disease Specific Questionnaire; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale; PCS= Physical Component Summary; MCS= Mental Component Summary.
* Significant after Bonferroni correction.

Health-related quality of life of partners

Table 3 shows the partners' scores on all three questionnaires. Scores in partners were not significantly different compared to TAD-patients and screening-participants. When compared to the general population, partners showed significantly lower scores on 2/8 SF-36 sub-domains after Bonferroni correction: General Health and Vitality. There were no significant differences in scores on the three questionnaires between partners of TAD-patients (n=46) and partners of screening-participants (n=20).

Factors associated with HRQOL in TAD-patients, screening-participants and their partners

Multivariate analysis showed only history of anxiety disorder was associated with higher HADS anxiety score. Additionally, history of anxiety disorder, previous aortic surgery, diabetes and indexed descending aortic diameter were found to be associated with higher HADS depression score. Higher RDSQ score was significantly associated with employment.

ARB use and history of aortic dissection in participants were associated with higher HADS anxiety scores in partners. Higher HADS depression scores of partners was associated

with previous aortic surgery in the participants. Higher RDSQ score of partners was found to be associated with history of aortic dissection in the participants. The results of the univariable and multivariable analyses are displayed in supplemental file 5.

Table 3 Scores of partners compared to participants and to the general population.

	Partners (n=66)	Participants (n=261)	p-value	General population	p-value
RDSQ					
Total score	49.5 (32.5-77.0)	51 .0 (32.0-80.0)	0.784		
SF-36					
Physical Functioning	76.1±25.2	76.1±26.5	0.991	83.0±22.8	0.035
Role Physical	65.6±41.1	67.4±4.6	0.748	76.4±36.3	0.044
Bodily Pain	74.1±25.4	75.5±25.7	0.707	74.9±23.4	0.806
General Health	55.8±21.8	55.4±24.4	0.902	70.7±20.7	<0.001*
Vitality	60.1±23.4	59.0±25.1	0.768	68.6±19.3	0.006*
Social Functioning	80.1±24.2	79.2±25.8	0.802	84.0±22.4	0.216
Role Emotional	84.7±31.4	77.2±37.5	0.108	82.3±32.9	0.553
Mental health	76.9±17.1	75.2±19.4	0.529	76.8±17.4	0.957
PCS	45.5±11.5	46.4±11.5	0.568		
MCS	50.1±9.7	48.2±11.5	0.255		
HADS					
Anxiety score	4.0 (2.0-6.0)	4.0 (2.0-7.0)	0.554		
Depression score	1.0 (0.0-4.0)	2.0 (1.0-5.0)	0.158		
Total score	5.5 (3.3-10.0)	6.0 (3.0-12.0)	0.112		

Participants= screening-participants and TAD-patients; RDSQ= Rotterdam Disease Specific Questionnaire; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale; PCS= Physical Component Summary; MCS= Mental Component Summary.
* Significant after Bonferroni correction.

In-depth interviews

11 Participants (6 females, mean age 57 years) were interviewed: four had a low scores; four had intermediate and three had high scores on the HADS and the RDSQ; four had known genetic mutations (Loeys Dietz Syndrome (n=3), Marfan Syndrome (n=1)); five had familial TAD but no genetic diagnosis; three had already undergone aortic surgery, one had been accepted for surgery. Anxiety was not found to be a major topic in the interviews. Participants described a form of psychological distress related to having TAD and the risk of sudden events. Roughly, three groups could be distinguished, representing (almost) no psychological distress (n=5); moderate psychological distress (n=3); or prominent psychological distress (n=3). Among these groups there was great variability in the degree their daily life, personality and professional career were affected. Several factors seemed to positively influence the level of psychological distress: disease-related communication with family-members; level of the disease-related knowledge of the participant; evolution

of the aortic disease (stable aortic diameter) and coping strategies such as expressing emotions and seeking emotional support. Factors that negatively influenced the level of distress were: physical complaints; sense of loss of identity due to the disease, including sports participation and choice of profession. Figure 4 was made to create an overview and shows which of these factors resulting from the coding tree were found to influence psychological distress the most. All participants had physical complaints such as thoracic pain, dyspnoea or tachycardia causing psychological distress. Sense of loss of identity was found to be a trigger in a smaller number of participants. Regular controls and stable aortic diameters had a great positive influence on psychological distress for the majority of participants. Knowledge about the disease seemed to decrease distress, although some participants expressed becoming more distressed after knowing what could happen. The unpredictable and uncertain course of the disease triggered a certain loss of control and increased psychological distress in almost all participants. Lifestyle restrictions on physical activity and professional career were accepted by most of the participants. The majority (n=9) stated that their level of distress increased shortly prior to regular check-ups of the aortic diameter, and decreased again when the results showed a stable aortic diameter. Coping strategies seemed to influence all factors mentioned above. A more detailed description of the in-depth interviews results can be found in supplemental file 6.

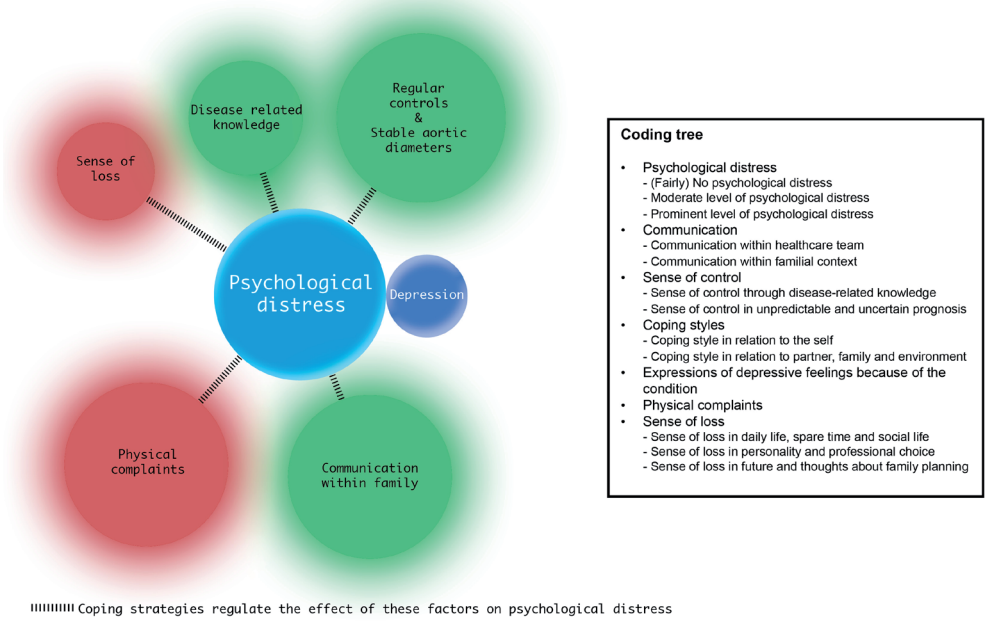

Figure 4 The influence on psychological distress of factors described in the coding tree
Red circle= negative influence on psychological distress, Green circle= positive influence on psychological distress

The size of the circles corresponds with the amount of participants in whom psychological distress was triggered by this factor. Depression can result from a large amount of psychological distress. Patients' coping strategies regulate the effect of these factors.

DISCUSSION

To our knowledge, this is the first study describing male-female specific aspects of HRQOL in both screening-participants and TAD-patients using a mixed methods approach. Male and female TAD-patients reported clearly impaired HRQOL compared to the general population, while screening-participants were affected to a lesser extent. Moreover, female and younger participants showed the lowest HRQOL scores. HRQOL in partners was also found to be suboptimal, although less impaired than in TAD-patients. Additionally, TAD-patients' levels of anxiety was not found to be a major topic in the in-depth interviews, participants rather described a form of psychological distress.

In this study TAD-patients were found to have decreased HRQOL, coping problems and psychological distress, similar to the findings of Olsson et al. and Connors et al.[5,18]. Additionally, we found HRQOL in screening-participants was impaired, although to a lesser extent. We hypothesized that the risk of having TAD would equally impact screening-participants compared to TAD-patients. However, having an aortic diameter ≥40 mm clearly had a more profound impact on HRQOL. This does not seem to result in clinically relevant levels of anxiety or depression, since HADS scores of TAD-patients were comparable to the general population. As has been reported before most of our participants accepted restrictions on physical activity and employment as 'part of life'[18].

In the general population HRQOL is known to decline with increasing age[12]. We found a much less pronounced decline in TAD patients. Presumably, the impact of having a serious disease with reduced life-expectancy is more distinct at young age. In addition, we found less favorable scores, and more anxiety in females compared to males. This is also described in the general population[12,19] and in patients with heart disease as well as chronic kidney disease [20,21], but has not previously been reported in TAD-patients[6]. Multiple studies reported these male-female differences were largely attributable to sociodemographic factors such as income, physical activity and marital status [22,23]. This might also apply to our population, since employment status and physical activity were significantly different between males and females. However, this does not completely seem to explain male-female difference in HRQOL[23]. Another potential explanation might be that females experience their functional capacity and quality of life different from males, and this certainly needs more attention in future studies.

Partners' HRQOL was also found to be affected, although to a lesser extent, and seemed to be negatively influenced by factors related to aortic events and disease progression in the participants. HADS anxiety scores in partners were associated with ARB use of the participants. This may be due to the increased risk of aortic expansion and eventually dissection when hypertension persists. The need of antihypertensive medication might

therefore cause more worries and anxiety in partners. The impact of TAD on partners has been underexposed, but might be very important, especially since interviewed participants reported that communication with their partners and family about the disease was an important factor influencing their level of psychological distress. Therefore, we believe the impact of the disease on the quality of life in partners should be assessed on a regular basis as it might impact the HRQOL of the patients. More research is needed to evaluate which factors are important and can be easily addressed. It is essential to involve partners in counselling and interventions for HRQOL improvement, and provide practical advice on coping with the disease for patients as well as their partners.

Goldfinger et al. and Moon et al. showed that daily life aspects such as employment or health insurance impacted HRQOL rather than disease-related factors[8,24]. In contrast, we found mainly disease-related factors, such as a history of aortic dissection or surgery and the diameter of the aorta, to be associated with HRQOL. These factors emerged from results of both the quantitative and qualitative analyses. Potentially this is due to the presence of a reliable social-security system in the Netherlands. Interviewed participants experienced the disease as a continuous threat, as was previously described in patients with abdominal aortic aneurysm[25]. When looking into the RDSQ results in more detail, we noticed the highest scores were found on questions about heredity and surgery (supplemental file 4), which indicates these factors warrant attention. Our findings emphasize the importance of expectation management and counseling regarding the disease course and treatment plan to the patient and their partner or family members, as well as providing clear and patient specific information about the disease and treatment options for shared decision making. Clinicians should be aware of HRQOL impairments, anxiety and depression in TAD-patients and their partners, and systematic screening is mandatory. Several factors were identified which might improve HRQOL: employment of constructive coping strategies such as expressing one's emotions, seeking emotional support, grieving loss of one's identity; and good communication within the family . When indicated, psychological support should be offered. More research is needed to evaluate the potential positive effect of psychological support and counselling in these patients.

Limitations

In this study, we used three (digital) questionnaires to measure self-reported quality of life. Two are well-known validated questionnaires, the RDSQ questionnaire, however, was newly developed and used in one previous study so far[10]. Its psychometric properties have to be further evaluated. Therefore, results of this questionnaire are to be interpreted with caution. The SF-36 is more suited to assess overall HRQOL and the HADS was used for detecting clinically relevant anxiety and depression. With the addition of the RDSQ, especially when combined with the results from the in-depth interviews, we were able to identify specific disease-related factors influencing HRQOL in this population. The overall

response rate of patients participating in this study was 57%, which is comparable to other (online) surveys[26]. In order to provide insight into potential selection bias, the selection process is represented in Figure 1. Although some bias cannot be ruled out, we expect to have included a representative sample. The number of partners included was limited (25%). Not all patients had a partner, but still this number is relatively low and better coverage of the partners is important for future research.

Conclusions

HRQOL of TAD-patients was found to be impaired, most significantly in younger females. Previous aortic surgery, aortic dissection and larger diameter of the aorta were found to be associated with impaired HRQOL. Partners' HRQOL was also reduced, warranting further attention. TAD-patients and partners should be systematically screened for symptoms of depression and anxiety, and when indicated psychological support should be offered. Counselling patients to employ constructive coping strategies and good communication within the family might reduce psychological distress and improve HRQOL in this population.

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SUPPLEMENTAL FILE 1

Rotterdam Disease Specific Questionnaire

thoracic aortic aneurysm

This questionnaire addresses possible limitations, consequences, concerns or anxiety that you may experience because of (the risk of) a dilatation of the aorta in the chest. Please read each question carefully and circle the number that best reflects how you felt during **the last month**.

Do not think too long about each question, as your initial response often best reflects your feelings about the subject.

The possibility, or presence, of a vascular dilatation of the aorta in my chest:

1. Causes limitations in my work environment

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

2. Causes limitations in hobby's/ leisure activities:

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

3. Has a negative influence on my family life

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

4. Has a negative influence on the relationship with my partner

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

The possibility, or presence, of a vascular dilatation of the aorta in my chest:

5. Causes limitations in my sexual functioning

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

6. Causes avoidance of physical activities

Totally disagree					**Neutral**				**Totally agree**
1	2	3	4	5	6	7	8	9	10

7. Causes anxiety to be alone

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

8. Causes chest pain

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

9. Causes worries/anxiety

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

10. Causes insomnia (related to stress/worrying/anxiety)

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

The possibility, or presence, of a vascular dilatation of the aorta in my chest:

11. Causes nightmares

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

12. Causes avoidance of travelling alone

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

13. Causes more anxiety than prior

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

Because of the possibility, or presence, of a vascular dilatation:

14. I worry about my health in the future

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

15. I worry about my work situation in de future

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

16. I worry that I die prematurely

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

17. I worry about the heritability of an aortic dilatation (whether my children may develop aortic dilatation)

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

18. I am concerned about surgery because of an aortic dilatation

Totally disagree					Neutral				Totally agree
1	2	3	4	5	6	7	8	9	10

19. Are there any other factors that negatively affect the quality of life due to the possibility, or presence, of an aortic dilatation that have not been addressed in the questions above?

.....
.....
.....

20. Has living with the possibility, or presence, of an aortic dilatation brought you something good? (eg. the realization of what is important in life)

.....
.....
.....

Thank you for your time!

SUPPLEMENTAL FILE 2

Patient characteristics of TAD-patients and screening-participants

	Total (n=261)	TAD patients (n= 147)	Screening-participants (n= 114)	p-value
Age - y	52.9±15.8	59.2±12.6	44.9±15.9	<0.001**
Sex - % female	125 (47.9)	54 (36.7)	71 (62.3)	<0.001**
Length - cm	177.2±14.7	178.4±14.2	175.6±15.3	0.137
Weight - kg	83.9±19.4	87.9±19.1	78.7±18.6	<0.001**
BSA - m^2	2.0±0.2	2.0±0.2	1.9±0.2	<0.001**
Hypertension	117 (44.8)	84 (57.1)	33 (28.9)	<0.001**
Hyperlipidemia	66 (25.3)	51 (34.7)	15 (13.2)	<0.001**
Smoking	25 (9.6)	13 (8.8)	12 (10.5)	0.647
Diabetes	9 (3.4)	7 (4.8)	2 (1.8)	0.187
Renal dysfunction	5 (1.9)	4 (2.7)	1 (0.9)	0.281
History of depression	16 (6.1)	8 (5.4)	8 (7.0)	0.599
History of anxiety disorder	4 (1.5)	2 (1.4)	2 (1.8)	0.797
Beta blocker use	60 (23.0)	50 (34.0)	10 (8.8)	<0.001**
ARB use	34 (13.0)	30 (20.4)	4 (3.5)	<0.001**
ACEi use	42 (16.1)	32 (21.8)	10 (8.8)	0.005**
Diagnosis				<0.001**
Marfan Syndrome	10 (3.8)	6 (4.1)	4 (3.5)	
Loeys-Dietz Syndrome	10 (3.8)	4 (2.7)	6 (5.3)	
Ehlers-Danlos Syndrome	2 (0.8)	0 (0.0)	2 (1.8)	
Other	12 (4.6)	2 (1.4)	10 (8.8)	
Confirmed genetic mutation	61 (23.4)	31 (21.1)	30 (26.3)	0.001
Positive family history aortic disease	132 (50.6)	60 (40.8)	72 (63.2)	0.001
Abdominal aortic aneurysm	9 (3.4)	8 (5.9)	1 (0.8)	0.025*
Maximal diameter aortic root[1]	37.6±5.7	40.4±5.5	34.3±4.0	<0.001**
Indexed diameter aortic root[1] - mm/BSA	19.0±2.9	19.7±3.0	18.0±2.5	<0.001**
Maximal diameter ascending aorta[1]	37.0±6.8	40.8±5.5	32.2±5.1	<0.001**
Indexed diameter ascending aorta[1] - mm/BSA	18.7±3.9	20.1±3.7	16.8±3.2	<0.001**
Maximal diameter descending aorta[1]	27.1±6.3	30.0±5.9	23.9±5.2	<0.001**
Indexed diameter descending aorta[1] - mm/BSA	13.7±3.3	14.7±3.3	12.5±2.9	<0.001**
Previous aortic surgery	33 (12.6)	32 (21.8)	1 (0.9)	<0.001**
Previous dissection	23 (8.8)	20 (13.6)	3 (2.6)	0.002**
Current partner	126 (75.9)	50 (66.7)	76 (83.5)	0.012

Table 1 Continued

	Total (n=261)	TAD patients (n= 147)	Screening-participants (n= 114)	p-value
Current employment[2]	103 (39.5)	61 (51.7)	42 (48.8)	0.687
Paid job	96 (36.8)	57 (48.3)	39 (45.3)	
Volunteer work	7 (2.7)	4 (3.4)	3 (3.5)	
Retired	57 (21.8)	43 (36.4)	14 (16.3)	
Student	16 (6.1)	1 (0.8)	15 (17.4)	
Unable to work / disabled	16 (6.1)	10 (8.5)	6 (7.0)	
Unemployed	12 (4.6)	3 (2.5)	9 (10.5)	
Exercise				
Sports participation[3]	105 (40.2)	50 (34.0)	55 (48.2)	0.023*
Walking or cycling	104 (39.8)	63 (42.9)	41 (36.0)	
None	36 (13.8)	24 (16.3)	12 (10.5)	

Data are expressed as mean ± SD or as absolute and percentage. BSA=Body Surface Area; ARB= Angiotensin II receptor blocker; ACEi= Angiotensin Converting Enzyme inhibitor; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome; LDS 3= Loeys-Dietz Syndrome type 3 (SMAD3 mutation).

[1] Only patients without previous aortic surgery.

[2] Current employment= Paid job or volunteer work.

[3] Defined as: Participating in any sport other than daily walking or cycling at any level at least once a week.

* Significant at the 0.05 level

** Significant at the 0.01 level

SUPPLEMENTAL FILE 3

Stratified analysis for male-female differences in TAD-patients and screening-participants.

Table 2a Male-female scores of screening-participants on all questionnaires.

	Total (n=114)	Males (n=43)	Females (n=71)	p-value
RDSQ				
Total score	44.0 (29.5-68.3)	40.0 (28.0-65.0)	47.0 (32.0-70.0)	0.185
SF-36				
Physical Functioning	90.0 (75.0-100.0)	100.0 (85.0-100.0)	90.0 (60.0-95.0)	0.001*
Role Physical	100.0 (50.0-100.0)	100.0 (75.0-100.0)	100.0 (25.0-100.0)	0.257
Bodily Pain	90.0 (57.5-100.0)	100.0 (77.5-100.0)	77.5 (57.5-100.0)	0.002*
General Health	62.5 (40.0-81.3)	75.0 (55.0-90.0)	55.0 (35.0-70.0)	0.003*
Vitality	62.5 (45.0-85.0)	75.0 (65.0-90.0)	55.0 (35.0-75.0)	<0.001*
Social Functioning	87.5 (62.5-100.0)	100.0 (87.5-100.0)	87.5 (62.5-100.0)	0.004*
Role Emotional	100.0 (66.7-100.0)	100.0 (100.0-100.0)	100.0 (33.3-100.0)	0.021
Mental health	84.0 (67.0-92.0)	84.0 (76.0-92.0)	80.0 (60.0-92.0)	0.030
PCS	53.0 (42.1-57.9)	54.6 (45.5-58.5)	49.5 (36.4-56.9)	0.026
MCS	52.3 (44.2-56.9)	55.4 (49.2-58.1)	49.4 (42.6-55.7)	0.004*
HADS				
Anxiety score	4.0 (2.0-7.0)	4.0 (1.0-5.0)	5.0 (2.0-9.0)	0.028
Depression score	2.0 (0.8-3.0)	1.0 (0.0-3.0)	2.0 (1.0-5.0)	0.004*
Total score	5.5 (3.0-10.3)	5.0 (2.0-7.0)	6.0 (4.0-16.0)	0.014*

Data are expressed as medians (IQR).
RDSQ= Rotterdam Disease Specific Questionnaire; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale; PCS= Physical Component Summary; MCS= Mental Component Summary.
* Significant after Bonferroni correction.

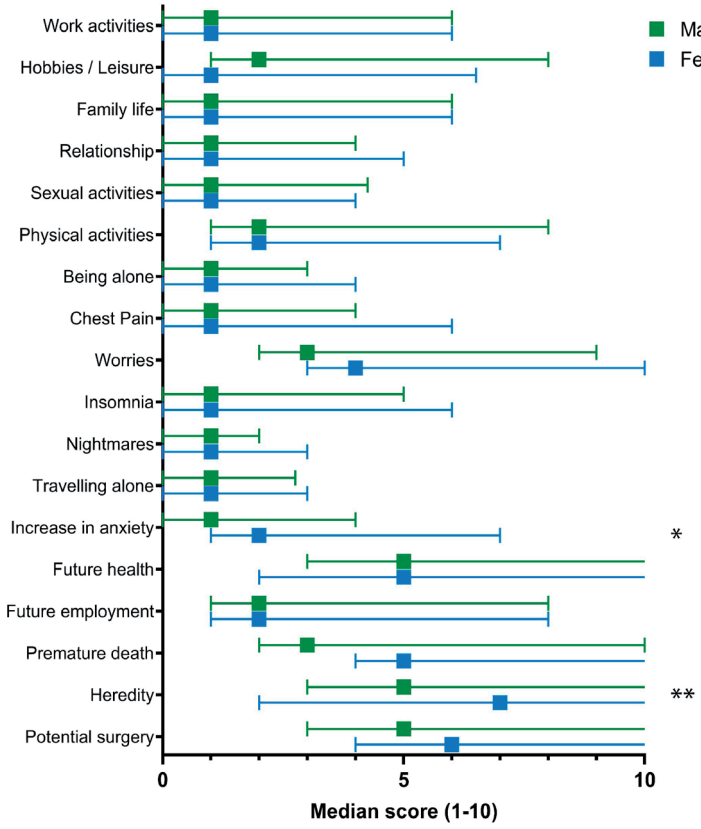
TABLE 2b Male-female scores of TAD-patients on all questionnaires.

	Total (n=147)	Males (n=93)	Females (n=54)	p-value
RDSQ				
Total score	59.0 (34.0-89.0)	54.0 (31.0-81.5)	67.5 (39.0-98.5)	0.057
SF-36				
Physical Functioning	80.0 (55.0-95.0)	85.0 (65.0-95.0)	72.5 (43.8-90.0)	0.001*
Role Physical	75.0 (25.0-100.0)	100.0 (37.5-100.0)	37.5 (0.0-100.0)	0.001*
Bodily Pain	80.0 (57.5-100.0)	90.0 (67.5-100.0)	67.5 (45.0-92.5)	0.003*
General Health	50.0 (35.0-70.0)	50.0 (37.5-75.0)	50.0 (33.8-65.0)	0.233
Vitality	60.0 (40.0-75.0)	65.0 (47.5-80.0)	47.5 (33.8-61.3)	0.002*
Social Functioning	87.5 (62.5-100.0)	100.0 (62.5-100.0)	75.0 (50.0-100.0)	0.004*
Role Emotional	100.0 (58.3-100.0)	100.0 (100.0-100.0)	66.7 (25.0-100.0)	<0.001*
Mental health	80.0 (60.0-88.0)	80.0 (64.0-88.0)	72.0 (56.0-88.0)	0.019
PCS	47.3 (37.3-53.0)	49.3 (40.1-53.7)	41.7 (35.0-50.6)	0.010
MCS	57.8 (39.4-56.9)	54.0 (46.4-57.2)	45.7 (36.3-53.7)	0.003*
HADS				
Anxiety score	4.0 (2.0-7.0)	4.0 (2.0-6.0)	4.0 (2.0-8.0)	0.204
Depression score	2.0 (1.0-5.0)	2.0 (0.0-5.0)	2.0 (1.0-5.0)	0.509
Total score	6.0 (3.0-12.0)	6.0 (3.0-11.0)	6.5 (4.0-13.8)	0.320

Data are expressed as medians (IQR).
TAD= Thoracic aortic aneurysm ≥ 40 mm; RDSQ= Rotterdam Disease Specific Questionnaire; SF-36= Short Form 36; HADS= Hospital Anxiety and Depression Scale; PCS= Physical Component Summary; MCS= Mental Component Summary.
* Significant after Bonferroni correction.

SUPPLEMENTAL FILE 4

Male-female scores on the Rotterdam Disease Specific Questionnaire



* Significant at the 0.05 level

** Significant at the 0.01 level

SUPPLEMENTAL FILE 5

Univariable and multivariable analyses

Univariable analysis screening-participants and TAD-patients						
	RDSQ score		HADS anxiety score		HADS depression score	
Variable	**Coefficient**	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**
Age - y	-0.04	0.770	-0.04	0.024*	-0.01	0.535
Sex	5.31	0.209	1.47	0.003**	0.74	0.114
Length - m	-0.10	0.482	-0.02	0.263	-0.01	0.725
Weight - kg	-0.11	0.335	-0.02	0.186	0.00	0.985
BSA	-9.84	0.313	-1.64	0.151	-0.01	0.996
Hypertension	2.70	0.525	-0.12	0.817	0.21	0.661
Hyperlipidemia	0.39	0.937	-0.32	0.578	0.05	0.923
Smoking	2.72	0.717	1.23	0.169	1.57	0.056
Diabetes	13.56	0.241	2.12	0.120	3.97	0.002**
Renal dysfunction	8.02	0.603	0.66	0.717	-1.30	0.449
Depression	-1.34	0.879	2.05	0.048*	2.44	0.013*
Anxiety	15.61	0.364	6.14	0.002**	7.59	<0.001**
Beta blocker use	6.91	0.169	-0.46	0.437	0.94	0.092
ARB use	9.52	0.129	0.32	0.662	0.36	0.608
ACEi use	1.04	0.857	-0.62	0.355	0.04	0.950
Diagnosis						
Marfan Syndrome	8.75	0.432	-1.10	0.402	-1.34	0.284
Loeys-Dietz Syndrome	-6.98	0.531	-2.14	0.102	-2.07	0.097
Ehlers-Danlos Syndrome	-39.62	0.105	-2.58	0.373	-2.40	0.381
Other	-12.40	0.224	-0.50	0.680	-0.05	0.964
Positive family history aortic disease	-4.86	0.252	-0.27	0.593	-0.48	0.308
Abdominal aortic aneurysm	-11.18	0.334	-0.53	0.699	1.10	0.396
Maximal diameter aortic root	0.62	0.106	-0.06	0.164	-0.01	0.873
Indexed diameter aortic root[1] (mm/BSA)	2.13	0.010**	0.04	0.684	0.01	0.890
Maximal diameter ascending aorta	0.90	0.004**	-0.01	0.815	0.014	0.694
Indexed diameter ascending aorta[1] (mm/BSA)	1.85	0.002**	0.07	0.344	0.04	0.551
Maximal diameter descending aorta	0.26	0.483	-0.03	0.568	0.03	0.437
Indexed diameter descending aorta[1] (mm/BSA)	1.04	0.187	0.04	0.657	0.136	0.131
Previous aortic surgery	7.90	0.214	-0.12	0.872	1.70	0.016*
Previous dissection	11.63	0.118	-0.14	0.873	0.41	0.62
Current partner	13.04	0.034*	1.98	0.009**	1.52	0.035*
Current employment	7.35	0.125	0.16	0.774	0.01	0.988
Exercise	-5.614	0.200	-0.10	0.851	-0.34	0.498

BSA=Body Surface Area; ARB= Angiotensin II receptor blocker; ACEi= Angiotensin Converting Enzyme inhibitor; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome.

* Significant at the 0.05 level

** Significant at the 0.01 level

[1] Aortic diameter indexed for Body Surface Area.

Univariable analysis partners						
	RDSQ score		HADS anxiety score		HADS depression score	
Variable	**Coefficient**	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**
Age - y	0.16	0.581	0.05	0.252	0.07	0.097
Sex	0.78	0.915	-0.82	0.339	-0.36	0.658
Length - m	-0.30	0.375	-0.00	0.910	-0.03	0.518
Weight - kg	-0.26	0.263	0.01	0.750	-0.00	0.970
BSA	-18.62	0.268	0.395	0.845	-0.52	0.792
Hypertension	9.12	0.220	0.00	0.998	1.01	0.226
Hyperlipidemia	16.82	0.023*	1.60	0.067	1.83	0.026*
Smoking	42.81	0.004**	1.41	0.500	4.24	0.042*
Diabetes	36.79	0.031*	1.76	0.370	3.90	0.034*
Renal dysfunction	-	-	-	-	-	-
Depression	12.44	0.287	-0.54	0.705	-0.69	0.611
Anxiety	-	-	-	-	-	-
Beta blocker use	13.59	0.076	0.82	0.362	1.37	0.103
ARB use	10.75	0.284	-1.81	0.128	0.60	0.599
ACEi use	-1.58	0.848	1.62	0.085	0.93	0.301
Diagnosis						
Marfan Syndrome	-28.88	0.097	-0.68	0.735	-2.42	0.201
Loeys-Dietz Syndrome	-15.05	0.325	0.65	0.711	-1.21	0.466
Ehlers-Danlos Syndrome	-3.92	0.896	-	-	-	-
Other	-19.16	0.522	2.40	0.482	2.41	0.455
Positive family history aortic disease	7.16	0.321	0.28	0.739	-0.11	0.891
Abdominal aortic aneurysm	25.43	0.040*	-0.17	0.904	0.42	0.759
Maximal diameter aortic root	0.85	0.191	0.07	0.382	0.02	0.810
Indexed diameter aortic root[1] (mm/BSA)	2.92	0.016*	0.14	0.336	0.08	0.571
Maximal diameter ascending aorta	1.18	0.061	0.14	0.095	0.11	0.140
Indexed diameter ascending aorta[1] (mm/BSA)	2.46	0.021*	0.24	0.074	0.20	0.119
Maximal diameter descending aorta	0.88	0.251	-0.00	0.975	0.05	0.590
Indexed diameter descending aorta[1] (mm/BSA)	2.96	0.045*	-0.08	0.643	0.14	0.409
Previous aortic surgery	18.73	0.036*	1.32	0.203	1.75	0.073
Previous dissection	21.77	0.080	2.97	0.035*	1.16	0.394
Current employment	-4.27	0.594	-0.33	0.670	-0.60	0.448
Exercise	-11.74	0.134	-0.34	0.719	-0.37	0.679

BSA=Body Surface Area; ARB= Angiotensin II receptor blocker; ACEi= Angiotensin Converting Enzyme inhibitor; LVEF= left ventricular ejection fraction; MFS= Marfan Syndrome.

* Significant at the 0.05 level

** Significant at the 0.01 level

[1] Aortic diameter indexed for Body Surface Area.

Multivariable analyses in screening participants and TAD-patients			
HADS anxiety score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	4.26		0.044
Sex	1.81		0.058
Age	-0.03		0.279
History of depression	-2.17		0.275
History of anxiety disorder	6.89		0.006
HADS depression score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	-1.19		0.651
Sex	0.89		0.364
Age	-0.04		0.180
History of depression	-1.90		0.42
History of anxiety disorder	9.80		<0.001
Previous aortic surgery	3.55		0.016
Diabetes Mellitus	6.38		0.009
Indexed descending aortic diameter[1]	0.36		0.028
RDSQ score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	30.68		0.093
Sex	11.36		0.142
Age	0.06		0.786
History of depression	-4.42		0.783
History of anxiety disorder	6.10		0.756
Employment	17.28		0.023

Multivariable analyses in partners			
HADS anxiety score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	1.31		0.666
Age	0.06		0.200
Sex	-0.40		0.667
Previous aortic dissection	7.42		<0.001
ARB use	-5.79		0.007
HADS depression score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	-4.15		0.198
Age	0.06		0.241
Sex	1.60		0.085
Previous aortic surgery	3.30		0.010
RDSQ score			
Covariate	**Coefficient**	**95% CI**	**p-value**
Intercept	-14.95		0.692
Age	0.75		0.183
Sex	12.64		0.247
Previous aortic dissection	36.41		0.049

HADS= Hospital Anxiety and Depression Scale; RDSQ= Rotterdam Disease Specific Questionnaire; TAD= Thoracic aortic disease; ARB= Angiotensin Receptor Blocker; CI= Confidence Interval.

[1] Aortic diameter indexed for Body Surface Area.

SUPPLEMENTAL FILE 6

Coding tree and full version results of in-depth interviews.

In the third phase of the content analysis procedure of all 11 interviews, SD and EG analyzed the codes together to construct the narrative syntheses (i.e., selective coding) and the final coding tree.

Coding tree

- Psychological distress
  - (Fairly) No psychological distress
  - Moderate level of psychological distress
  - Prominent level of psychological distress
- Communication
  - Communication within healthcare team
  - Communication within familial context
- Sense of control
  - Sense of control through disease-related knowledge
  - Sense of control in unpredictable and uncertain prognosis
- Coping styles
  - Coping style in relation to the self
  - Coping style in relation to partner, family and environment
- Expressions of depressive feelings because of the condition
- Physical complaints
- Sense of loss

- Sense of loss in daily life, spare time and social life
- Sense of loss in personality and professional choice
- Sense of loss in future and thoughts about family planning.

Figure 4 is based on the results of this coding tree. In this tree the pronunciations of the interviewees were divided under the different subjects. These pronunciations were analysed and summarized in the result section below.

Psychological distress rather than feelings of fear

Fear did not appear as the main topic in our analyses as was hypothesized at the start of this study. All participants did, however, express some level of emotional (di)stress related to their condition, although a large variability between interviewees was observed. While some patients expressed feelings of being overwhelmed by the condition and experienced daily, persistent and paralyzing emotional distress, others only encountered distress when an outpatient check-up was approaching. Hence, the concept of psychological/emotional

distress is deemed more in line with patients' expression in contrast to the concept of 'fear'. Furthermore, three different groups could be described in our sample based on their respective level of experienced psychological distress: (i) (fairly) no psychological distress; (ii) moderate level of psychological distress; and (iii) prominent level of psychological distress.

The majority of patients (n=5/11) in our sample, expressed (fairly) no psychological distress. The explanation of this absence of fear appeared to be found in relation to regularly check-ups performed at the outpatient clinic, the confirmation of a stable aorta diameter and a specific, down-to-earth and rational personality. The only time these patients reported some distress was a short period before an outpatient check-up. Within this group, patients did not report having fear of being alone or getting complications after an operation in the future. Furthermore, they did not spontaneously express any concerns about the hereditary nature of their condition in relation to their children.

Three participants experienced variable levels of distress at different points in time (i.e., moderate level of psychological distress). Distress was not experienced on a daily basis, nor was it predominant in patients' daily. One patient said: "*It's fine that I know my diagnosis, but it's also terrible to know*!". In this group, patients were not afraid of being alone. Their annual check-up of the aorta diameter resulted in a feeling of safety. However, experiences of bodily pain and symptoms during exercise caused uncertainties, thinking: "*Is it my heart? My aorta?".*

In three out of 11 participants, the level of psychological distress was prominent. These patients experienced a significant level of psychological distress on a daily basis. They described constantly being aware of the fact that they have an aortic aneurysm that could dissect or rupture. One participant said: "*It feels like having a 'time bomb', because you don't know when it goes off. And… you have to live with that knowledge*". Two of the three were women; both diagnosed with a genetic predisposition for thoracic aortic aneurysm, positive family history of familial aneurysm and both already underwent surgery. The other patient was a man, without any known genetic disorder or familial aneurysm and with a thoracic aortic diameter of 50 mm. For these patients the diagnosis of the disease had been shocking, especially for the patient who had received surgery a short time after receiving the diagnosis. This patient expressed thoughts such as: "*Will the surgery be performed in time, what if the aorta will rupture before it's my turn?*".

These feelings of prominent distress were triggered by bodily pain and symptoms, as expressed by one patient: "*I am feeling pain, does this mean there is something wrong with my aorta?*". Two patients did not feel comfortable being alone, because they were afraid that something might happen. One of the patients, experienced distress especially

when family members expressed their fear. In one participant religion played an important role, thinking: "*Do I take good care of my 'borrowed' body?*". While another patient who experienced moderate psychological distress, felt supported by her religion.

Communication

Communication with their healthcare team had little influence on the level of distress expressed by patients. However, when patients experienced having a 'positive' conversation with the physician, during which confirmation was given that the diameter of the aorta remained stable, this was reassuring. Receiving additional information by the physician about the disease and prognosis, was very much appreciated.

The communication within the familial context appeared to have a bigger influence on the level of psychological distress as compared to communication with the healthcare team. Eight out of 11 participants had an 'open' communication style about their disease with family members. In these cases, patients could freely talk about their worries with family members, which resulted in decreased feelings of distress. However, such an 'open' communication climate in the family was also found to be stressful for the whole family. For example, when posing the question if there is any kind of fear having this aorta disease, a family member replied: "*Do they really think we don't have any fear, of course we have fear!*". Three participants did not talk about their disease with their family members, as they deliberately did not want them to worry about their condition. Although most patients had a network of friends whom they could talk to about their disease, these conversations were experienced as superficial by patients.

Sense of control

Disease-related knowledge

Patients described that having more knowledge about their disease could give them a stronger feeling of control resulting in decreased levels of distress. On the one hand, a lack of disease-related knowledge of the participant or the family physician, gave a loss of control resulting in an increased level of distress. Some participants self-fulfilled this condition and increased their level of disease-related knowledge by reading about the disease, attending scientific meetings or participating in a patient association. On the other hand, some patients described that 'having more knowledge about the disease' resulted into more awareness and subsequently generated more distress.

Unpredictable and uncertain prognosis

Almost all participants reported that the unpredictable and uncertain evolution of the disease triggered feelings of loss of control and thereby increased levels of psychological distress. Some participants said: "*They can't guarantee that the aorta will not rupture.*

If the aorta will rupture, than you will die at once". This uncertainty again plays a major role in the degree of distress expressed by patients. "*If something will happen, is there a chance that I can have surgery on time and that I can make it?*" Shortly before a scheduled check-up of the aorta diameter, all patients expressed increased feelings of distress, which mostly disappeared when they received confirmation that the diameter had remained stable.

Coping strategies

Coping strategies employed by our sample can be divided in two categories: (i) related to how the individual (the participant) handles his/her disease and (ii) in relationship with their partner, family member(s) and environment.

Coping style in relation to the self

Two participants seemed to have an inadequate coping style, resulting in a daily state of emotional distress due to their altered future perspectives. They experienced problems because they can't live their life the way they had planned before being diagnosed with their aortic disease. They said: "*Honestly, I don't feel good at all, I'm always tired, I can't sleep and at my work I forget everything". "I can't be myself like I was in the past*". Any proposal to talk about their problems with a healthcare professional was, however, refused because they believed nobody could take away the fear they experienced. Other participants eventually accepted their disease, although most of them first experienced a period of shock, anger and sadness, having to change their sport practice or profession. For example: "*Then you have to adjust yourself, I couldn't play soccer anymore, that was really a bummer*". Feelings of acceptance were also encountered by some patients, as expressed by this patient "*I can worry, but I live now and when I continue to worry, I may live shorter*". Some patients have a generally more positive attitude towards life because of their aortic disease, they felt like they are living in spare time. These patients were grateful that they could be operated in time, increasing their changes to live a longer life.

Coping style in relation to partner, family and environment

Coping with the disease in relation to the partner, family and environment was seen as something individual by the participants. Patients carry their own worries and uncertainties, as if it was their individual responsibility. Illustrated by this quote: "*I know it can be hereditary, but I don't want to burden my children with it", "Don't want to bother them in their fantasies, life and stress*". In contrast, sharing with family members made them take over some tasks to relieve the participant.

Feelings of depression

Two participants expressed depressive thoughts, although these patients experienced these feelings in a very different way. One patient expressed depressive complaints at the

moment of the interview. In this patient, the depressive thoughts were partly related to the aorta disease, although not exclusively. Other factors were: physical complaints not related to the aorta; being confronted with a partner who was depressed; having no other family members to rely on; and the recent suicide of a family member. In this participant, a constructive coping strategy for his disease was totally lacking and he explicitly did not want any professional help for his emotional problems. The other participant, however, described experiencing depressive thoughts in the past, shortly after receiving aortic surgery and losing a family member. At the moment of the interview, these thoughts were not present anymore. Many family members of this patient were diagnosed with aortic pathology, underwent surgery and were confronted with death originating from the aortic disease. "*I know I was ehhh tired of life, when my third brother….than I thought, arrggh, I don't have the energy for it, for mourning, I don't want to anymore*". This patient sought professional help from a psychologist who helped her tackle these difficult circumstances and described that those negative thoughts disappeared largely. Meanwhile, this participant developed a very good coping strategy to live with her disease.

Physical complaints

All participants reported experiencing some physical complaints, like thoracic pain, dyspnea or tachycardia. These complaints often triggered increased levels of distress. Most patients described an unsettling feeling when having physical complaints, because they wondered whether these complaints could by directly linked to their aortic disease or the heart.

Sense of loss

The aortic disease had an impact on the patient's daily life, their spare time and social life. Furthermore, the majority of patients reported that the diagnosis itself had a significant impact on their personality, their professional choice and future, and thoughts about family planning. "*Yes, that's though, you suddenly have to adjust yourself, I wasn't allowed to play soccer anymore. I had many friends there, which I lost, because I stopped*". Another participant could not do his job anymore, because he was not allowed to lift weights. One participant felt angry towards life when she had to work fewer hours, and have less responsibility. "*The biggest problem of this disease is that I couldn't do the things that I have always done*". Three of the 11 participants informed their sports instructor about their disease, in case something happened during exercise. This makes them less free to do sports anywhere, limited their personal space and freedom.

On the other hand, five participants reported living without limits and doing everything they wanted to do. They deliberately choose not to let their disease determine what they can or cannot do. The participants who underwent surgery in the past expressed a significant decline of their physical health condition, shortly after their operation, but also

many years later. Three participants said they are not themselves anymore; they changed into a different personality due to the condition, being more emotional or easily triggered by certain events.

One participant even described that her diagnosis had a significant impact on her decision not to have children and start a family. However, two out of seven patients who had already children before they knew about their heredity disease, did not know what they would have done if they knew about their diagnosis beforehand.

CHAPTER 10

10

Long term health-related quality of life after acute type B aortic dissection: a cross-sectional survey study

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European Journal of Vascular & Endovascular Surgery, 2023

ABSTRACT

Background

Acute type B aortic dissection (ATBD) is a rare yet serious cardiovascular event, which potentially has impact on health-related quality of life (HRQoL). However, long-term follow-up data on this topic are scarce. This study aimed to review the long term HRQoL among patients treated for ATBD.

Methods

In this multicentre cross sectional survey study, consecutive treated patients with ATBD between 2007-2017 in four referral centres in the Netherlands were retrospectively included and baseline data was collected. Between 2019-2021 the Short-Form 36 (SF-36) questionnaire was sent to all surviving patients (n=263) and was compared to validated SF-36 scores in the Dutch general population stratified by age and sex.

Results

In total, 144 patients out of 363 surviving patients completed the SF-36 questionnaire (response rate 55%). The median age was 68 [IQR:61,76] at completion of the questionnaire and 40% (n=58) was female. Initial treatment was medical in 55% (n=79), endovascular in 41% (n=59) and surgical in 4% (n=6) of ATBD patients. The median follow-up time was 6.1 (range: 1.7-13.9, IQR: 4.0-9.0) years. Compared to the general population, patients scored significantly worse on 6/8 SF-36 subdomains, particularly physical domains. Apart from bodily pain no substantial differences in HRQoL between male and female ATBD patients were found. When compared to the sex-matched normative data, females scored significantly worse on 5/8 subdomains, whereas males scored significantly lower on 6/8 subdomains. Younger patients aged 41-60 seemed more severely impaired in HRQoL when compared to the age-matched general population. Treatment strategy did not influence HRQoL outcomes. Follow-up time was associated with better physical and mental component summary scores.

Conclusions

Long-term HRQoL was impaired in ATBD patients compared to the Dutch general population, especially concerning the physical status. This warrants more attention for HRQoL during clinical follow-up. Rehabilitation programs including exercise and physical support might improve HRQoL and increase patients' health understanding.

INTRODUCTION

Acute thoracic aortic dissection (TAD) is a rare yet highly lethal disease [1], affecting 4.6-6.0 cases per 100.000 inhabitants annually [2,3]. Acute Stanford type B aortic dissection (ATBD), which does not involve the ascending aorta [4], comprises around 27% of all TAD cases [5]. In the acute phase, anti-impulse medication is recommended for ATBD, while endovascular or surgical repair is advised in complicated cases [4].

Regardless of chosen treatment in the early phase, survivors of ATBD have a poor prognosis with considerable mortality and morbidity, and require close surveillance [6,7]. In the conservatively treated patient group aneurysm formation is common in the chronic phase [8], whereas reinterventions are frequently observed in repaired ATBD [9]. These factors, along with the impact of the acute dissection itself, might trigger anxiety and psychological stress as well as a decrease in physical activity, as described in surviving TAD patients [10]. ATBD patients tend to live with uncertainty in their daily activities such as exercise or travelling, as there might be a risk of worsening the dissection. Communication regarding these issues by physicians is not always optimal, also because medical knowledge on these issues is poor. Unfortunately, literature on health-related quality of life (HRQoL) after ATBD is scarce and encompasses only small study populations focusing on a specific treatment group [11,12]. Previous studies have investigated HRQoL in TAD in general or in type A aortic dissection (ATAD) [10,13,14]. As ATBD has a different clinical presentation, treatment options and outcomes than ATAD, investigation of the impact on HRQoL focussed on ATBD is warranted.

Furthermore, patient-specific information on HRQoL, in particular male-female differences, is needed to optimize treatment and rehabilitation after ATBD. HRQoL is known to differ between males and females in the general population and in patients with thoracic aortic disease [15,16] Although male-female differences in clinical presentation and outcomes have been identified in TAD [17], no published study to date has examined male-female differences in HRQoL yet.

Therefore, this study aimed to assess the long-term HRQoL in patients after ATBD in a large multicentre cross-sectional survey study based on a retrospective cohort and make a comparison with the Dutch normative population. Secondary objectives were to compare HRQoL stratified by sex, treatment strategy and age category and to study associations with HRQoL scores and patients characteristics. We hypothesized that ATBD patients would have an impaired HRQoL when compared to the general population.

METHODS

Study design and study population

A cross-sectional survey study in a large multicentre retrospective cohort was conducted following the STROBE guidelines for cross-sectional studies [18]. All consecutive patients (18 years old) who were diagnosed with ATBD in 4 tertiary referral centres in the Netherlands (the Erasmus University Medical Centre in Rotterdam, the Catharina Medical Centre in Eindhoven, Radboud University Medical Centre in Nijmegen and St. Antonius Hospital in Nieuwegein) between 2007 and 2017 were eligible for inclusion. Patients with non-acute, traumatic or iatrogenic ATBD were excluded. This multicentre study was designed, conducted and controlled complying local and international good clinical practice guidelines and was approved by the local medical ethics committees (MEC-2018-1535). Eligible patients were sought with national diagnostic codes for thoracic aortic disease used by the cardiology, cardiothoracic surgery and vascular surgery departments and verified with existing local research databases in each centre. In Appendix I the diagnostic codes and search strategy are explained.

A sample size calculation was performed based on estimates of two SF-36 domains comparing thoracic aortic disease patients with the normative Dutch population [16] using a web-based calculator [19] (see Appendix II for more details). With a desired power of 0.80 and level of significance of .05, the required sample size ranged between 109 and 209 patients.

Data collection

Both the retrospective data of the total cohort and the questionnaire data were documented in an anonymized standardized case report form using OpenClinica (OpenClinica, LLC, version 3.6). Retrospective data collection of patient characteristics, presentation and treatment was performed using patient files. All included variables with their definitions are shown in Appendix III. A mortality check was performed in the municipal data registry before sending the questionnaires. Between July 2019 and February 2021 the 36-Item Short Form Survey (SF-36) [20-22] including an informed consent form on paper was sent to the patients still alive in all the four participating study centres. In order to increase the response rate, all patients who had not returned the questionnaire, were contacted by telephone. If the patient did not respond after all attempts mentioned, they were deemed “non-responder”. For the retrospective data collection, informed consent was waived.

HRQoL questionnaire

The SF-36 questionnaire is a widely used HRQoL questionnaire with 36 items that highlights eight domains: Physical Functioning, Role limitations due to the Physical health problems,

Bodily Pain, General Health perceptions, Vitality, Social Functioning, Role limitations due to Emotional problems, and general Mental Health (psychological distress) [15,22]. The first four domains together form the Physical Component Summary (PCS) and the last four domains form the Mental Component Summary (MCS). All SF-36 subdomains have a score range of 0-100, with higher scores reflecting a better quality of life. The SF-36 has been used in previous studies on HRQoL in patients with type A aortic dissection and in thoracic endovascular repair (TEVAR) patients [13,14,23]. The SF-36 has been translated, validated and normed in the Dutch population, also categorized by sex and age groups, which can be considered as normative data [15].

Statistical analysis

Data were analysed using statistical and computing program *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 4.1.2). Continuous data were presented as mean and standard deviation (SD) when normally distributed and as median with interquartile range (IQR) when skewed. Normality was checked visually with histograms and tested with use of the Shapiro-Wilk test. Group comparisons were done using unpaired Student's t-test when normally distributed, and a Mann Whitney U test was used when data was not normally distributed. Categorical data were presented as frequencies with percentages and compared with χ^2 test or Fisher's exact test, as appropriate. Additionally, the male and female subdomain scores were compared to the male and female norm values of the national general Dutch population and per age category [15], using the age at completion of the questionnaire of ATBD patients. Comparing the patient with the normative data, means and standard deviations were reported and a one-sample Student's t-test was used. Univariable linear regression analyses were performed to study associations with the follow-up time, age, sex, initial treatment strategy, comorbidities and late (re) intervention during follow-up with the PCS and MCS separately in a complete case analysis. Multicolinearity was assessed with a correlation matrix. Additionally, variables with $p<.10$ in univariable analysis were entered into a backward selection process to obtain the final models. In the backward selection, a threshold of $p<0.10$ was used to keep relevant variables in the final model. To investigate non-responder and survival bias, the patient characteristics of responders were compared with non-responders and non-survivors of the total cohort. If data in one or more questions in a subdomain were not filled in by the participant, that complete subdomain was considered as missing. All patients with any missing subdomain consequently missed the end score of the PCS and the MCS. In case the date of completion of the questionnaire was not filled in by the participant, the date was estimated by using the median date in that study centre. A two-sided p-value of $<.05$ was considered statistically significant.

RESULTS

The flow-chart of the patient selection is depicted in Figure 1. In total, 263 SF-36 questionnaires were sent to all ATBD patients who were alive, and 144 completed questionnaires were returned, resulting in a response rate of 55%. The median follow-up time from admission to completing the questionnaire was 6.1 years (range: 1.7-13.9 years, IQR: 3.96, 8.99 years). Table 1 shows the patient and treatment characteristics stratified by sex. Of the total 144 patients the median age at time of the questionnaire was 68 years [IQR: 61, 76 years] and 40% (n=58) was female. For one patient the date of completing the questionnaire was not reported, and was estimated. In this selected patient group, 26% (35/137) patients had received a (re)intervention during follow-up before completing the questionnaire, for 7 patients it was unknown.

Table 2 shows the scores on all sub-domains of the SF-36 and the physical and mental component summary for the whole study population and stratified by sex. Female patients scored significantly lower on bodily pain than males (p=0.028). In Figure 2 mean SF-36 subdomain scores are compared with the general Dutch population for the whole study population and stratified by sex, the crude data is shown in Appendix IV. On 6/8 SF-36 subdomains, ATBD patients scored lower than the general population. A similar pattern was observed when comparing females and males with the sex-matched normative population.

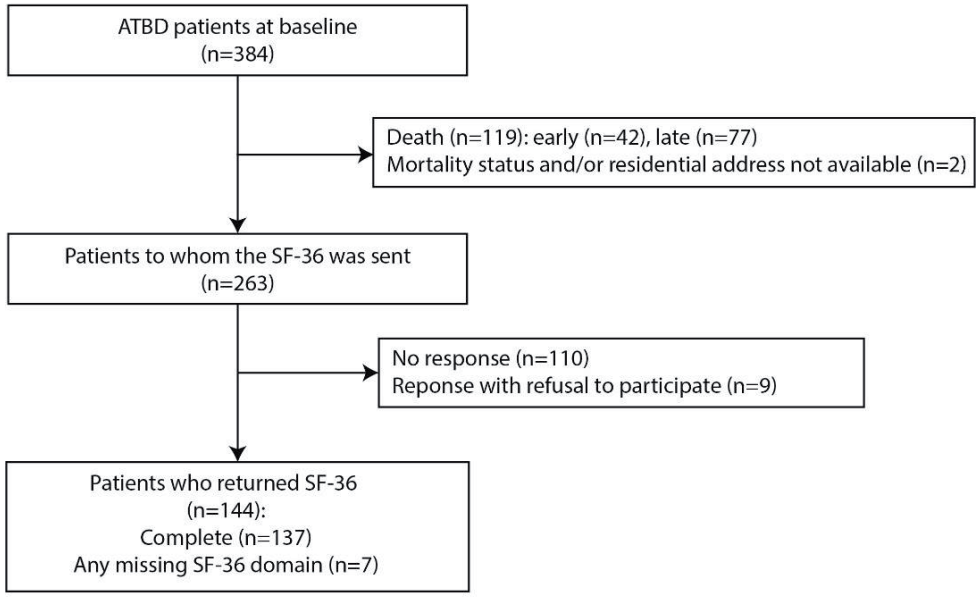

Figure 1 Flowchart of patient selection.
ATBD = acute type B aortic dissection; SF-36 = 36 Item Short Form Health Survey.

In Figure 3 ATBD HRQoL scores are compared with the age-matched normative population, the crude data is reported in Appendix IV. Figure 3 shows impaired HRQoL in the youngest age group (41-60 years) when compared to the general population.

In Table 3 the HRQoL scores are depicted for the patients who initially received medical treatment compared to endovascular or surgical treatment, which showed no significant differences between treatment groups.

Table 4 shows the univariable and multivariable analyses with the Physical Component Score (PCS) and the Mental Component Score (MCS) for the whole study population. A longer follow-up time (> median) was associated with better scores for both the PCS and the MCS on univariable analysis. A history of hypertension, chronic kidney disease, and prior aortic surgery were independently associated with impaired PCS scores, whereas hypertension was independently associated with impaired MCS scores. No significant associations were found with treatment groups or (re)intervention during follow-up.

In Table 5 responders (n=144) were compared with non-responders (n=119). In Appendix VI responders (n=144) were compared with non-survivors (n=119), showing a difference in age (61 ± 11 years in responders vs. 69 ± 11 in non-survivors) and a higher proportion of comorbidities in non-survivors.

Table 1 Patient and treatment characteristics at presentation of acute type B aortic dissection (ATBD)

	All patients (n=144)	**Females (n=58)**	**Males (n=86)**	**P-value**	**Missing %**
Follow-up time (median (range, IQR)) - years	6.11 (1.66-13.9), [3.96, 8.99]	5.43 (1.68-12.7), [4.03, 8.84]	6.63 (1.66-13.9), [3.93, 9.06]	0.494	0.7
Patient demographics					
Age at ATBD (mean ± SD) - years	61.5 ± 10.6	62.3 ± 10.7	59.3 ± 10.4	0.096	0.0
Age at questionnaire (median[IQR]) - years	68.3 [61.0, 75.6]	69.1 [63.5, 76.2]	67.3 [58.6, 74.3]	0.149	0.0
BMI (median [IQR]) – kg/m^2	25.6 [22.9, 28.1]	24.2 [22.5, 28.1]	26.2 [24.1, 28,1]	**0.040**	18.1
BSA (median [IQR]) – m^2	1.95 [1.83, 2.09]	1.79 [1.70, 1.88]	2.03 [1.94, 2.15]	**<0.001**	18.1
History of hypertension (%)	71 (49.3)	31 (53.4)	40 (46.5)	0.518	0.0
Hyperlipidaemia (%)	25 (17.4)	11 (19.0)	14 (16.3)	0.847	0.0
Diabetes mellitus (%)	5 (3.5)	1 (1.7)	4 (4.7)	0.648[i]	0.0
COPD (%)	10 (6.9)	4 (6.9)	6 (7.0)	1.000[i]	0.0
History of CVA (%)	9 (6.2)	5 (8.6)	4 (4.7)	0.485[i]	0.0
History of MI (%)	2 (1.4)	0 (0.0)	2 (2.3)	0.516[i]	0.0
Chronic kidney disease (%)[†]	4 (2.8)	3 (5.2)	1 (1.2)	0.303[i]	0.0
Prior TAA (%)	6 (4.2)	2 (3.4)	4 (4.7)	1.000[i]	0.0
Prior AAA (%)	12 (8.3)	1 (1.7)	11 (12.8)	**0.028**[i]	0.0
Prior aortic dissection (%)	3 (2.1)	1 (1.7)	2 (2.3)	1.000[i]	0.0

Table 1 Continued

	All patients (n=144)	Females (n=58)	Males (n=86)	P-value	Missing %
Prior cardiac surgery (%)	5 (3.5)	0 (0.0)	5 (5.8)	0.082[i]	0.0
Prior aortic surgery (%)	13 (9.0)	3 (5.2)	10 (11.6)	0.242[i]	0.0
Connective tissue disease (%)*	6 (4.7)	5 (10.0)	1 (1.3)	**0.035**[i]	11.8
Treatment strategy					0.0
Medical (%)	79 (54.9)	30 (51.7)	49 (57.0)	0.692	
Endovascular (%)	59 (41.0)	26 (44.8)	33 (38.4)		
Surgical (%)	6 (4.2)	2 (3.4)	4 (4.7)		
Endovascular or surgical treatment	**All patients (n=65)**	**Females (n=28)**	**Males (n=37)**	**P-value**	**Missing %**
Urgency treatment (%)				0.518[i]	3.1
Acute	30 (47.6)	11 (39.3)	19 (54.3)		
Urgent	30 (47.6)	15 (53.6)	15 (42.9)		
Elective	3 (4.8)	2 (7.1)	1 (2.9)		
Indication invasive treatment (%)				**0.028**[i]	1.5
Uncomplicated (study)	1 (1.6)	1 (3.6)	0 (0.0)		
Occlusion of major aortic branch leading to ischemia	22 (34.4)	7 (25.0)	15 (41.7)		
Persistent severe pain	4 (6.2)	3 (10.7)	1 (2.8)		
Extension of dissection	1 (1.6)	0 (0.0)	1 (2.8)		
Aneurysmal expansion	8 (12.5)	4 (14.3)	4 (11.1)		
Expanding hematoma	4 (6.2)	4 (14.3)	0 (0.0)		
Rupture	9 (14.1)	3 (10.7)	6 (16.7)		
Multiple	8 (12.5)	1 (3.6)	7 (19.4)		
Other	7 (10.9)	5 (17.9)	2 (5.6)		

Normally distributed continuous variables are expressed as mean ± SD, skewed continuous variables are expressed as median and 25^{th}-75^{th} percentile, and categorical values are expressed as percentages. For follow-up time, the 25^{th}-75^{th} percentile as well as the range are reported. P-values < 0.05 are depicted in bold.

*Connective tissue disease diagnosed before or after acute type B aortic dissection. [i] = Fisher's exact test. ┼ None of the patients known with CKD was requiring dialysis at presentation with ATBD. ATBD: acute type B aortic dissection; BMI: body mass index; BSA: body surface area; MI: myocardial infarction; TAA: thoracic aortic aneurysm; AAA: abdominal aortic aneurysm

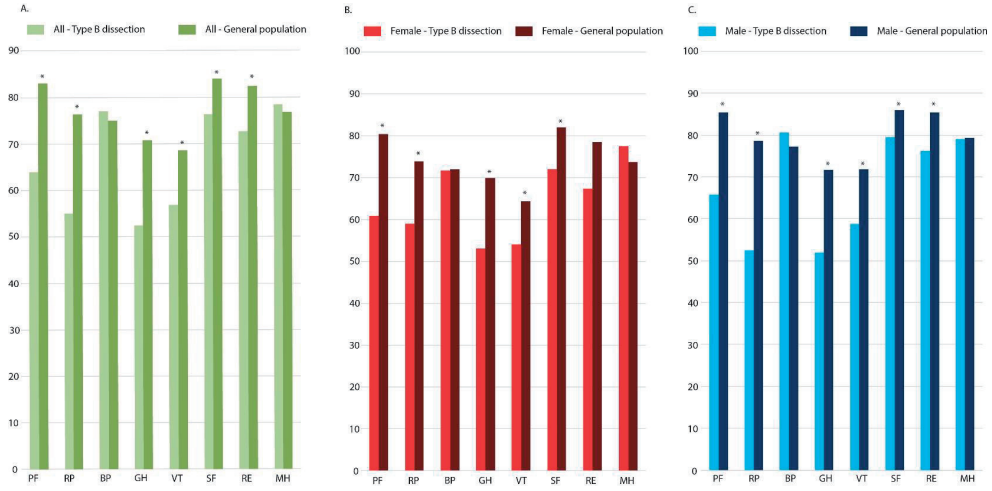

Figure 2. Comparison of mean SF-36 scores for (A) the whole study population and (B,C) stratified by sex for female (B) and male (C) acute type B aortic dissection patients compared with the general population.

SF-36 subdomain scores are presented as mean in order to compare the data with the general population data which was reported as mean. *P value < 0.05 in one-sample Student's t-test compared to the general population.
PF: Physical Functioning; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health

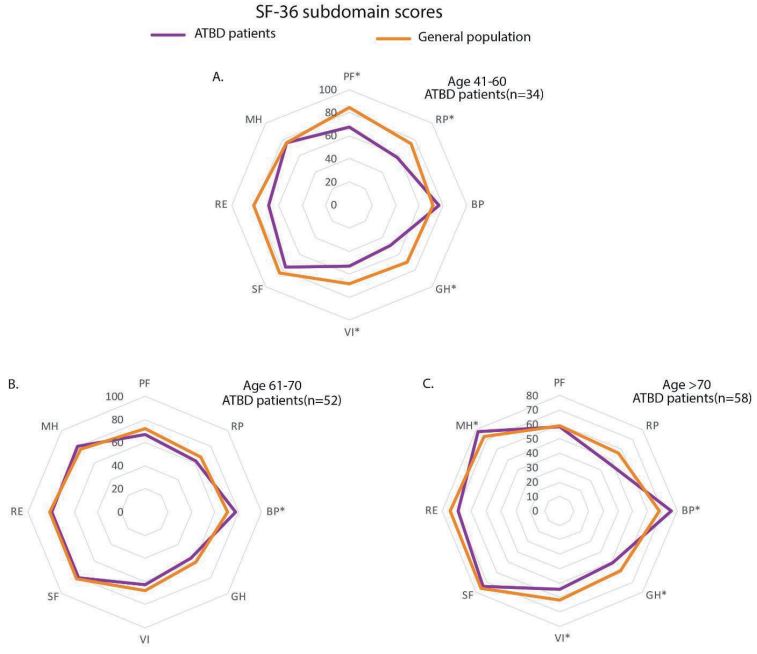

Figure 3. Comparison of the mean SF-36 scores of ATBD patients to the general population according to age category (age at time of questionnaire).

SF-36 subdomain scores are presented as mean in order to compare the data with the general population data which was reported as mean. *P value < 0.05 in one-sample Student's t-test compared to the general population in that age category.
PF: Physical Functioning; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health

Table 2 Long term health-related quality of life scores after acute type B aortic dissection for the Short Form-36 health survey

	All patients (n=144)	Females (n=58)	Males (n=86)	P-value	Missing (%)
Physical Functioning	70.0 (45.0-85.0)	60.0 (45.0-80.0)	75.0 (40.0-85.0)	0.152	0.7
Role Physical	75.0 (0.0-100.0)	75.0 (0.0-100)	62.5 (0.0-100.0)	0.339	2.8
Bodily Pain	78.8 (56.9-100.0)	67.5 (50.0-100.0)	90.0 (67.5-100.0)	**0.028**	0.0
General Health	50.0 (35.0-70.0)	50.0 (40.0-68.8)	52.5 (35.0-70.0)	0.700	0.0
Vitality	60.0 (40.0-75.0)	50.0 (40.0-75.0)	60.0 (40.0-75.0)	0.266	0.7
Social Functioning	87.5 (62.5-100.0)	75.0 (50.0-100.0)	87.5 (62.5-100.0)	0.230	1.4
Role Emotional	84.0 (68.0-92.0)	100.0 (0.0-100.0)	100.0 (58.3-100.0)	0.179	2.1
Mental Health	84.0 (68.0-92.0)	80.0 (68.0-88.0)	84.0 (68.0-92.0)	0.296	0.7
PCS	45.4 (33.5-51.0)	45.8 (35.7-48.5)	45.2 (33.3-52.2)	0.466	4.9
MCS	53.5 (41.4-57.9)	52.4 (36.9-57.6)	55.0 (45.5-58.0)	0.219	4.9

SF-36 subdomain scores and the Physical Component Summary and the Mental Component Summary are presented as median and 25^{th}-75^{th} percentile.
P-values < 0.05 are depicted in bold.
PCS: Physical Component Summary; MCS: Mental Component Summary.

Table 3 Comparison of long term Short Form-36 health survey scores between initial endovascular or surgical treatment and medical treatment in acute type B aortic dissection

All patients (n=144)	Medical treatment (n=79)	Endovascular or surgical treatment (n=65)	P-value	Missing %
Physical Functioning	65.0 (42.5-85.0)	75.0 (45.0-85.0)	0.386	0.7
Role Physical	50.0 (0.0-100.0)	100.0 (0.0-100.0)	0.084	2.8
Bodily Pain	77.5 (52.5-100.0)	87.5 (65.0-100.0)	0.575	0.0
General Health	45.0 (35.0-70.0)	55.0 (40.0-70.0)	0.263	0.0
Vitality	55.0 (35.0-75.0)	60.0 (40.0-75.0)	0.554	0.7
Social Functioning	75.0 (62.5-100.0)	87.5 (75.0-100.0)	0.071	1.4
Role Emotional	100.0 (33.3-100.0)	100.0 (83.3-100.0)	0.085	2.1
Mental Health	80.0 (66.0-92.0)	84.0 (68.0-92.0)	0.234	0.7
PCS	44.3 (32.9-50.4)	46.5 (35.4-51.5)	0.305	4.9
MCS	51.8 (37.3-57.5)	54.5 (47.5-58.1)	0.215	4.9

SF-36 subdomain scores and the Physical Component Summary and the Mental Component Summary are presented as median and 25^{th}-75^{th} percentile.
P-values < 0.05 are depicted in bold.
PCS: Physical Component Summary; MCS: Mental Component Summary.

Table 4 Associations of patient and treatment characteristics of type B aortic dissection patients physical and mental component summary in linear regression analysis

	Physical component summary				Mental component summary			
	Univariable beta estimate (95% CI)	P-value	Multivariable beta estimate (95%CI)	P-value	Univariable beta estimate (95% CI)	P-value	Multivariable beta estimate (95%CI)	P-value
Follow-up time (per year)	0.542 (-0.003-1.087)	0.051	0.450 (-0.067-0.968)	0.088	0.516 (-0.002-1.087)	0.076	-	-
Follow-up time > median	0.543 (0.086-6.922)	0.050	-	-	4.097 (0.531-7.662)	**0.025**	-	-
Age at ATBD (per year)	-0.195 (-0.360—0.030)	**0.021**	-	-	-0.008 (-0.360—0.030)	0.932	-	-
Female sex	-0.935 (-4.471-2.600)	0.602	-	-	-2.079 (-4.471-2.600)	0.267	-	-
History of hypertension	-4.636 (-8.015—1.256)	0.008	-3.734 (-7.108—0.359)	**0.030**	-4.066 (-8.015-1.256)	**0.026**	-4.084 (-7.678—0.489)	**0.026**
History of hyperlipidaemia	-4.591 (-9.014—0.168)	**0.042**	-	-	-5.839 (-9.014—0.168)	**0.013**	-	-
Diabetes	-4.531 (-13.750-4.688)	0.333	-	-	2.704 (-13.750-4.688)	0.581	-	
COPD	-5.331 (-11.937-1.277)	0.113	-	-	-4.640 (-11.938-1.277)	0.188	-	-
History of CVA	-7.275 (-14.167—0.383)	**0.039**	-	-	-6.235 (-14.167—0.383)	0.092	-	-
History of MI	12.289 (-2.023-26.600)	0.092	14.153 (0.589-27.718)	**0.041**	6.772 (-2.023-26.600)	0.377	-	-
Chronic kidney disease	-15.189 (-26.757—3.620)	**0.011**	-15.072 (-26.095—4.050)	**0.008**	1.664 (-26.757—3.620)	0.791	-	-
Known TAA	-8.836 (-17.179—0.493)	**0.038**	-	-	-0.232 (-17.179—0.493)	0.959	-	-
Prior AAA	-8.077 (-14.057—2.096)	**0.009**	-	-	-7.150 (-14.057—2.096)	**0.027**	-	-
Prior AD	-10.831 (-22.541-0.878)	0.070	-	-	-7.624 (-22.541-0.878)	0.224	-	-

Table 4 Continued

	Physical component summary				Mental component summary			
	Univariable beta estimate (95% CI)	**P-value**	**Multivariable beta estimate (95%CI)**	**P-value**	**Univariable beta estimate (95% CI)**	**P-value**	**Multivariable beta estimate (95%CI)**	**P-value**
Prior aortic surgery	-7.844 (-13.611—2.076)	**0.008**	-5.848 (-11.547—0.1493)	**0.044**	-5.689 (-13.611—2.077)	0.068	-	-
Prior cardiac surgery	0.549 (-8.702-9.800)	0.907	-	-	3.445 (-8.702-9.800)	0.482	-	-
Connective tissue disease	-4.332 (-12.999-4.335)	0.324	-	-	-1.109 (-12.999-4.335)	0.807	-	-
Endovascular/surgical vs. Medical treatment	1.831 (-1.646-5.308)	0.299	-	-	3.154 (-1.646-5.308)	0.087	-	-
(Re)intervention during follow-up	-0.293 (-4.428-3.842)	0.889	-	-	0.815 (-3.469-5.098)	0.707	-	-

Beta coefficients and corresponding 95% CI are shown. Interpretation for beta coefficients: if the beta coefficient is positive, for every unit increase in the predictor variable, the outcome variable (PCS or MCS score) will increase by the beta coefficient value. "-" means the variable was not included in the final multivariable model after backward selection. P-values < 0.05 are depicted in bold. COPD: Chronic obstructive pulmonary disease; CVA: cerebrovascular accident; MI: myocardial infarction; TAA: thoracic aortic aneurysm; AAA: abdominal aortic aneurysm; AD: aortic dissection.

Table 5 Sensitivity analysis: comparing type B aortic dissection patients characteristics between responders and non-responders

	Responders (n=144)	Non-responders (n=119)	P-value	Missing %
Patient demographics				
Sex, female (%)	58 (40.3)	49 (41.2)	0.983	0.0
Age at ATBD (mean ± SD) - years	60.5 (10.6)	60.1 (14.1)	0.784	0.0
BMI (median [IQR]) – kg/m^2	25.6 [22.9-28.1]	25.9 [23.2-28.8]	0.467	23.2
BSA (median [IQR]) – m^2	1.95 [1.83-2.09]	1.99 [1.81-2.14]	0.427	23.2
History of hypertension (%)	71 (49.3)	55 (46.2)	0.708	0.5
Hyperlipidaemia (%)	25 (17.4)	26 (22.0)	0.427	1.0
Diabetes mellitus (%)	5 (3.5)	5 (4.2)	1.000	0.5
COPD (%)	10 (6.9)	6 (5.0)	0.702	0.5
History of CVA (%)	9 (6.2)	12 (10.1)	0.361	0.5
History of MI (%)	2 (1.4)	9 (7.6)	0.026[i]	0.8
Chronic kidney disease (%)	4 (2.8)	5 (4.2)	0.736[i]	0.5
Prior TAA (%)	6 (4.2)	9 (7.6)	0.360	0.8
Prior AAA (%)	12 (8.3)	7 (5.9)	0.600	0.3
Prior aortic dissection (%)	3 (2.1)	4 (3.4)	0.705[i]	0.5
Prior cardiac surgery (%)	5 (3.5)	13 (10.9)	0.033	0.5
Prior aortic surgery (%)	13 (9.0)	16 (13.4)	0.347	0.3
Connective tissue disease (%)*	6 (4.7)	10 (9.7)	0.224	15.1
Treatment strategy				
Medical (%)	80 (55.6)	58 (48.7)	0.543	0.0
Endovascular (%)	58 (40.3)	55 (46.2)		
Surgical (%)	6 (4.2)	6 (5.0)		

Normally distributed continuous variables are expressed as mean ± SD, skewed continuous variables are expressed as median and 25^{th}-75^{th} percentile, and categorical values are expressed as percentages. P-values < 0.05 are depicted in bold.

*Connective tissue disease diagnosed before or after acute type B aortic dissection. [i] = Fisher's exact test. BMI: body mass index; BSA: body surface area; MI: myocardial infarct; TAA: thoracic aortic aneurysm; AAA: abdominal aortic aneurysm

DISCUSSION

This multicentre cross-sectional survey study examines long-term health-related quality of life (HRQoL) in all consecutive patients treated for acute type B aortic dissection (ATBD), as first published study to date. Compared to the Dutch normative population, HRQoL was significantly lower in ATBD patients, for both females and males. In our ATBD study population, no male-female differences were found except for bodily pain, that was more common in females than males. No significant differences were observed in HRQoL between treatment groups. The impairments seemed mostly concerning patients' physical status and our study suggested HRQoL in younger patients was more severely

affected when compared to the general population. Follow-up time was associated with better HRQoL scores.

When comparing the patient population to the general population, both males and females scored lower on almost all SF-36 subdomains. In a selected group of uncomplicated ATBD patients, Winnerkvist et al. observed no substantial differences with the normative Swedish population in terms of functioning and well-being with a follow-up of 5.4 years (range 1.9-12.7 years) [12]. A possible reason for this is the relatively small study population (n=53) and thereby limited statistical power of the study. Similar to our findings, several other studies concerning thoracic aortic aneurysms (TAA) observed impaired HRQoL [16,24]. In the study by Winnerkvist et al. no significant association was found with the follow-up duration and HRQoL scores [12], while our study showed that a longer follow-up duration was associated with better HRQoL. In a longitudinal study on HRQoL after treatment for abdominal aortic aneurysms (AAA), a strong decrease in HRQoL was observed immediately after treatment, reaching a plateau phase during follow-up [25]. The event of ATBD might also have large impact on the mental and physical well-being of patients in the short term, while over time it increases to a stable level - although lower than in the general population.

In our study the physical domains seemed particularly impaired: physical functioning, role physical, general health and vitality. In Olsson et al. TAA patients scored lower on mostly the physical domains [24], also found in a study among patients treated for AAA [25]. Since most of the questions in the physical subdomains cover impairments of daily living activities, patients might benefit from physical rehabilitation programs such as cardiac rehabilitation or support of paramedics in physical activities. Although we did not observe significant differences in mental health with the general population, these might still be existent and not captured in the SF-36 questionnaire, as depression and anxiety have been reported to be increased in previous studies on TAD survivors and TAA patients [10,16]. Qualitative research on the mental health in ATBD patients could provide more information and meaningful cues for clinicians to account for in daily practice. Furthermore, the SF-36 does not take into account the disease specific impact of ATBD on their daily activities. In future studies, a quantitative questionnaire tailored for ATBD patients including questions on exercise, travelling and sexual activity, might increase our understanding.

Furthermore, no significant differences were observed in HRQoL when stratified per treatment regime (conservative versus interventional) and (re)intervention during follow-up did not seem to be associated withHRQoL scores. In a study on thoracic endovascular repair (TEVAR) in acute and subacute type B dissections, comparable or improved HRQoL was observed when comparing pre- and postoperative HRQoL [11]. In our study no statistical difference in HRQoL was observed between treatment groups, however our study had a limited sample size as it was not designed for this purpose. Therefore, we encourage to

prospectively study HRQoL in larger study populations among different ATBD treatment groups and possible associations with (re)interventions during follow-up, preferably using multiple HRQoL measurements. In patients with uncomplicated ATBD, the debate regarding the most accurate timing and management is ongoing. Regarding clinical outcomes such as mortality and reinterventions, no significant differences between TEVAR compared to conservative medical treatment in the acute phase exist [26]. Patient-reported outcomes and cost-effectiveness might offer more insight into a favourabletiming and management of uncomplicated ATBD.

In this population, a comparable pattern in HRQoL was observed among females and males when compared to the general population. Contrariwise, in Winnerkvist et al. female chronic type B dissection patients tended to score worse on physical functioning [12], and in Thijssen et al. female patients had lower scores on 8/8 subdomains when compared to male TAA patients [16]. In our own study population, female patients scored lower solely on bodily pain in comparison to males. This difference might reflect the existing male-female difference in the general population, as females score significantly lower on 7/8 subdomains including bodily pain [15]. Another explanation might be a different perception of pain or the way of coping with pain in female ATBD patients. In acute type A aortic dissection, females tend to report a more tearing pain, whereas male patients experienced sharp pain more frequently [27]. During follow-up the impact of ATBD on pain might be different in females and males, and worth discussing during clinical visits.

Nevertheless, age might be of more importance in ATBD: compared to the general population, especially ATBD patients in the younger age range from 41-61 years seemed to have impaired HRQoL on predominantly physical subdomains. Younger patients might have higher expectations of their physical functioning and therefore feel more deterioration due to the disease. Interestingly, a study on HRQoL after acute type A aortic dissection showed that especially younger patients had a greater deterioration in the mental component summary of the SF-36 [14]. ATBD might cause more anxiety and impact on the social environment and job functioning in younger patients, when compared to older patients. Several other patient-specific associations with the physical component summary were observed: hypertension, a history of myocardial infarction, chronic kidney disease and prior aortic surgery were negatively associated. Patients with a younger age and patients with the aforementioned comorbidities require extra attention during follow-up and might benefit from tailored physical rehabilitation programs.

In clinical practice, the study findings should lead to more awareness for long-term HRQoL to the healthcare providers and physicians, especially in young patients. Further investigation of cardiac rehabilitationfor ATBD patients could be in both clinicians' and patients' best interests. Furthermore, studies investigating the effect on daily activities

such as exercise, travelling and sexual activity, could give more insight into the impaired HRQoL and are clearly warranted. We believe that if patients would be better informed with the risks of complications and what activities they are (not) allowed to do, anxiety and stress could be reduced.

Limitations

Several limitations apply to this study. In this cross-sectional observational study no baseline HRQOL scores at the time of onset of disease were available and HRQOL was assessed at one time point during follow-up. As a result, no time-trend analysis could be performed. The response rate in our study was 55%, comparable to other (online) questionnaires[28]. Nonetheless, some non-responder bias was present: the sensitivity analysis showed that although the groups were largely comparable, non-responders more often had a history of myocardial infarction and cardiac surgery. Also, survival bias might be present: a higher age and proportion of comorbidities was observed comparing non-survivors with responders. Thus, patients in a worse cardiovascular status might have been excluded from this study, resulting in overestimated HRQOL scores. These scores were compared with age-matched individuals in the general population, which accentuates the impact of this disease. Due to the retrospective baseline data collection, we could not collect data on important matters associated with HRQOL such as psychiatric conditions and cognitive abilities. The results of the subgroup analyses and linear regression analyses should be interpreted with caution, due to limited statistical power. Lastly, as the participating centres were tertiary referral centres, the proportion of uncomplicated ATBD might be lower than in clinical practice, limiting the generalizability of our findings.

CONCLUSION

In this multicentre cross-sectional survey study, HRQOL was impaired in both male and female ATBD patients compared to the Dutch normative population. In particular the physical domains were affected and HRQOL seemed especially impaired in younger patients. No substantial associations with sex and HRQOL were found apart from bodily pain, and initial treatment strategy did not seem to be associated with HRQOL. HRQOL should be an integrative part of the clinical follow-up care of patients with ATBD.

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APPENDIX I

Search strategy

As there are no specific diagnostic codes for type B dissections, we set up a broad search strategy to avoid missing any patients. For the surgical departments the national diagnostic code 403: “Thoracic aortic aneurysm, rupture”, which is applied to acute type B dissection patients, was used. The patient files of the cardiology departments were sought with national diagnostic code 601: “Arterial vascular abnormality/stenosis”. Consequently, all patient files were checked manually for the in- and exclusion criteria. The search strategy could slightly vary per centre due to differences in the local information technology search methods.

APPENDIX II

Sample size calculation

A sample size calculation was performed based on the estimates of the physical functioning and social functioning domain of the SF-36 comparing thoracic aortic disease patients with the normative Dutch population using a web based calculator: https://statulator.com/SampleSize/ss2M.html.

The mean value of the SF-36 subdomain score of the normative Dutch population was used as mean of the reference group, and the estimate of the study by Thijssen et al. as the mean of the test group. The pooled standard deviation was calculated using the standard deviations and number of participants of the study by Thijssen et al. and the normative Dutch population of Aaronson et al.

The settings for the calculation were the default: a desired power of 0.80, level of significance 0.05, alternate hypothesis two-sided. As the study size of the normative population was around 6 times greater than the study size of Thijssen et al., the ratio of the reference to the test group was set at 6.

This resulted in an estimated sample size of 109 for physical functioning and 209 for social functioning.

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APPENDIX III

Variable definitions

Variables	Unit	Definition
Follow-up time	Years	Time from admission to completion of questionnaire
Patient characteristics		
Age at ATBD	Years	Age at presentation calculated from date of birth
Age at questionnaire	Years	Age at time of completion questionnaire
Sex		As reported in patient file
Body mass index		
Body surface area		Dubois-Dubois formula
History of hypertension		Medical treatment for hypertension or described in patient history
Hyperlipidaemia		Medical treatment for hyperlipidaemia or described in patient history
Diabetes mellitus		Medical treatment for diabetes mellitus or described in patient history
Chronic obstructive pulmonary disease (COPD)		Any history of COPD that required medical treatment or FEV1<70%)
History of cerebrovascular disease (CVA)		History of TIA (transient ischemic attack) or stroke in patient history
History of myocardial infarction (MI)		As described in patient history
Chronic kidney disease		As described in patient history
Prior thoracic aortic aneurysm (TAA)		Thoracic aorta > 40 mm or treated for thoracic aortic aneurysm
Prior abdominal aortic aneurysm (AAA)		AAA > 30 mm or treated for AAA
Prior aortic dissection		As described in patient history
Prior cardiac surgery		As described in patient history
Prior aortic surgery		As described in patient history
Connective tissue disease		Diagnosed before or after onset of the dissection
Treatment characteristics		
Medication		Conservative treatment with medication
Thoracic endovascular repair (TEVAR)		Endovascular procedure with access through blood vessels
Open surgical repair		Thoracotomy
Urgency of operation		Duration from diagnosis until surgery
Indication for endovascular/surgical treatment		As described in patient file
Late intervention (only for initial medical treatment group)		Endovascular or surgical intervention on thoracic aorta or side branches, related to the aortic dissection
Late reintervention (only for initial endovascular or surgical treatment group)		Endovascular or surgical intervention on thoracic aorta or side branches, related to the aortic dissection

APPENDIX IV

Scores of the study population compared with the general Dutch population stratified by sex

	All patients (n=144)	General population	P-value	Female (N=58)	General female population	P-value	Male (N=86)	General male population	P-value
Physical Functioning	63.9 ± 25.9	83.0 ± 22.8	<0.001	60.9 ± 24.1	80.4 ± 24.2	<0.001	65.8 ± 27.0	85.4 ± 21.0	<0.001
Role Physical	55.0 ± 44.9	76.4 ± 36.3	<0.001	58.9 ± 44.3	73.8 ± 38.5	0.015	52.4 ± 45.4	78.7 ± 34.1	<0.001
Bodily pain	77.0 ± 24.1	74.9 ± 23.4	0.306	71.7 ± 24.8	71.9 ± 23.8	0.957	80.5 ± 23.1	77.3 ± 22.7	0.202
General Health	52.4 ± 21.4	70.7 ± 20.7	<0.001	53.0 ± 19.5	69.9 ± 20.6	<0.001	52.0 ± 22.7	71.6 ± 20.6	<0.001
Vitality	56.8 ±24.0	68.6 ± 19.3	<0.001	54.0 ± 22.8	64.3 ± 19.7	0.001	58.7 ± 24.6	71.9 ± 18.3	<0.001
Social Functioning	76.4 ± 26.2	84.0 ± 22.4	<0.001	72.0 ± 30.2	82.0 ± 23.5	0.014	79.5 ± 22.7	86.0 ± 21.1	0.010
Role Emotional	72.6 ± 41.3	82.3 ± 32.9	0.006	67.3 ± 43.9	78.5 ± 35.7	0.058	76.2 ± 39.3	85.5 ± 29.9	0.033
Mental Health	78.4 ± 17.7	76.8 ± 17.4	0.297	77.5 ± 15.8	73.7 ± 18.2	0.072	78.9 ± 18.9	79.3 ± 16.4	0.839

SF-36 subdomain scores are presented as mean ± SD in order to compare the data with the general population data which was reported as mean ± SD.

APPENDIX V

Scores of the study population compared with the general Dutch population stratified by age category

	Age 41-60			Age 61-70			Age > 70		
	ATBD patients (n=34)	General population	P-value	ATBD patients (n=52)	General population	P-value	ATBD patients (n=58)	General population	P-value
Physical Functioning	67.8 ± 24.9	84.0 ± 19.6	<0.001	67.1 ± 25.9	71.7 ± 25.6	0.208	58.5 ± 26.0	58.9 ± 30.8	0.910
Role Physical	58.1 ± 45.1	74.5 ± 36.8	0.041	62.0 ± 43.5	67.3 ± 40.9	0.393	46.9 ± 45.5	56.9 ± 44.0	0.105
Bodily pain	76.6 ± 25.6	71.8 ± 24.1	0.281	77.8 ± 22.5	70.5 ± 24.6	0.023	76.4 ± 24.9	68.1 ± 27.4	0.014
General Health	49.9 ± 21.1	69.7 ± 20.6	<0.001	55.8 ± 23.2	61.7 ± 20.2	0.071	50.9 ± 19.8	58.9 ± 21.1	0.003
Vitality	52.7 ± 22.3	68.6 ± 20.2	<0.001	62.5 ± 24.7	67.7 ± 19.6	0.136	54.3 ± 23.7	61.8 ± 23.6	0.019
Social Functioning	76.1 ± 22.8	83.5 ± 22.1	0.073	79.8 ± 26.9	82.0 ± 24.6	0.556	73.5 ± 27.6	75.6 ± 27.0	0.561
Role Emotional	68.6 ± 42.6	81.6 ± 33.2	0.085	79.1 ± 38.9	81.1 ± 35.0	0.713	69.1 ± 42.6	74.5 ± 38.2	0.342
Mental Health	75.7 ± 21.7	75.6 ± 18.5	0.99	80.5 ± 15.9	76.9 ± 17.9	0.116	78.1 ± 16.6	73.0 ± 19.9	0.024

SF-36 subdomain scores are presented as mean ± SD in order to compare the data with the general population data which was reported as mean ± SD.
P-values < 0.05 are depicted in bold

APPENDIX VI

Sensitivity analysis: comparing patient characteristics between responders and non-survivors

	Responders (n=144)	Non-survivors (n=119)	P-value	Missing %
Patient demographics				
Sex, female (%)	58 (40.3)	49 (41.2)	0.983	0.0
Age at ATBD (mean ± SD) - years	60.5 ± 10.6	68.5 ± 11.2	<0.001	0.0
BMI (median [IQR]) – kg/m^2	25.6 [22.9, 28.1]	27.0 [22.9, 29.8]	0.290	23.2
BSA (median [IQR]) – m^2	1.95 [1.83, 2.09]	1.91 [1.77, 2.09]	0.333	23.2
History of hypertension (%)	71 (49.3)	76 (65.0)	0.016	0.5
Hyperlipidaemia (%)	25 (17.4)	32 (27.6)	0.067	1.0
Diabetes mellitus (%)	5 (3.5)	6 (5.1)	0.724	0.5
COPD (%)	10 (6.9)	19 (16.2)	0.029	0.5
History of CVA (%)	9 (6.2)	14 (12.0)	0.161	0.5
History of MI (%)	2 (1.4)	8 (6.9)	0.026[i]	0.8
Chronic kidney disease (%)	4 (2.8)	9 (7.7)	0.088[i]	0.5
Prior TAA (%)	6 (4.2)	19 (16.4)	0.002	0.8
Prior AAA (%)	12 (8.3)	23 (19.5)	0.014	0.3
Prior aortic dissection (%)	3 (2.1)	4 (3.4)	0.704[i]	0.5
Prior cardiac surgery (%)	5 (3.5)	17 (14.5)	0.003	0.5
Prior aortic surgery (%)	13 (9.0)	28 (23.7)	0.002	0.3
Connective tissue disease (%)*	6 (4.7)	6 (6.4)	0.812	15.1
Treatment strategy				
Medical (%)	80 (55.6)	55 (47.8)	0.455	1.0
Endovascular (%)	58 (40.3)	55 (47.8)		
Surgical (%)	6 (4.2)	5 (4.3)		

Normally distributed continuous variables are expressed as mean ± SD, skewed continuous variables are expressed as median and 25^{th}-75^{th} percentile, and categorical values are expressed as percentages. P-values < 0.05 are depicted in bold.

*Connective tissue disease diagnosed before or after acute type B aortic dissection. [i] = Fisher's exact test. BMI: body mass index; BSA: body surface area; MI: myocardial infarct; TAA: thoracic aortic aneurysm; AAA: abdominal aortic aneurysm

Epilogue

SUMMARY

There are clear differences between males and females with thoracic aortic aneurysms (TAA). For starters, TAA is known to have a higher incidence in males. Furthermore, females seem to present with thoracic aortic aneurysm at an older age. However, little is known about possible differences between male and female TAA patients in presentation, management and outcomes. Worse outcomes in females after thoracic aortic dissection and elective thoracic aortic surgery have been reported, which lead to uncertainties about optimal timing of preventive thoracic aortic surgery in male and female patients. The mechanisms underlying these male-female differences in outcome remain unclear. As a result, there has been debate about the appropriateness of the use of absolute aortic diameter for the timing of surgery. Currently, sex and body size are not taken into account when timing preventive aortic surgery. However, male-female specific cut-off values for maximal aortic diameter might be helpful. Furthermore, the risk of aortic dissection causes stress and anxiety in TAA patients, which could impact quality of life. The effect of TAA on quality of life might be different in males and females, since male-female differences in emotional functioning, coping strategies and stress (i.e. anxiety/depression) are well known to exist in the general population. Moreover, limited information is available on the safety of daily activities, such as exercise and sports participation in both male and female patients with thoracic aortic disease. All these male-female differences have largely been neglected in patients with heart disease in general and aortic disease in particular. Therefore, research in all these aspects of aortic disease is essential.

This thesis is part of the 'Size Matters' project, funded by ZonMW, aims to identify male-female differences and other patient specific insights into thoracic aortic aneurysm diagnosis, treatment and outcomes. More accurate identification of patients at risk for thoracic aortic dissection allows for better timing of intervention, and will hopefully contribute to better survival, as well as stress reduction and better quality of life.

Part 1 - Characteristics of thoracic aortic disease

Part one describes several aspects of the normal thoracic aorta and of the aorta in patients with thoracic aortic aneurysm and hereditary thoracic aortic disease. In order to define pathological aortic dilatation, it is important to explore normal variation in aortic dimensions during the adult life-course. Therefore, in **chapter 1** we studied changes of thoracic aortic diameters in participants from the prospective population-based Rotterdam Study. All 943 participants (median age at baseline 65 years) underwent serial non-enhanced cardiac computed tomography (CT) on which the ascending and descending aorta were measured with a mean scan interval of 14 years. It was concluded that progression of ascending and descending aortic diameters in the general population is very limited. Although, aortic dilatation rate was higher in males, the differences

seemed clinically irrelevant. Factors associated with more rapid thoracic aortic dilatation rate were higher age, higher body mass index and higher diastolic blood pressure. Therefore, these factors seem important for prevention of thoracic aortic aneurysm formation and progression. As rapid thoracic aortic growth and aneurysm formation are often asymptomatic, diagnosis is challenging. Biomarkers may have potential diagnostic and prognostic value in TAA patients. Ideally, biomarkers might be used for diagnosis, follow-up assessment and clinical decision making regarding preventive intervention for TAA. In **chapter 2**, we studied potential biomarkers associated with thoracic aortic disease severity in a prospective cohort study including clinically stable TAA patients from our outpatient clinic. After venous blood sampling, we performed a batch-wise analysis of 92 biomarkers. With these data we explored the association between a broad spectrum of cardiovascular biomarkers with clinical characteristics and thoracic aortic diameter. Our results showed Matrix Metalloproteinase-3 (MMP-3) to be associated with absolute maximal thoracic aortic diameter, and insulin-like growth factor binding protein 2 (IGFBP-2) showed a significant association with thoracic aortic diameter indexed for body surface area. Fatty acid-binding protein 4 (FABP4) showed a significant association with absolute descending aortic diameter. Patients with hereditary thoracic aortic disease had higher Trem-like transcript protein 2 (TLT-2) which might indicate inflammatory involvement. These biomarkers and their biochemical pathways seem to play a role in assessing TAA severity, enabling the investigation of the specific pathways involved.

Hereditary thoracic aortic disease accounts for about 20% of all patients with thoracic aortic disease. Each of the known syndromes can cause a variety of vascular abnormalities. Loeys-Diets Syndrome type III, caused by pathogenic SMAD3 variants, is an autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with osteo-arthritis. Neurovascular abnormalities have been described in other heritable aortic syndromes, however data on neurovascular involvement in Loeys-Dietz syndrome type III was lacking. In **chapter 3** we described neurovascular findings in patients with Loeys Dietz syndrome type III and their possible clinical impact. Our results revealed abnormalities such as cerebral aneurysm, tortuosity, coiling and kinking in the vast majority of patients. Neurovascular abnormalities were equally present in males and females, although, clinical events were rare during the mean follow-up period of nine years. Longer follow-up is necessary to investigate further the clinical relevance of our findings. For now, neurovascular screening and follow up should be considered in all adult patients with Loeys Dietz syndrome type III.

Part 2 - Thoracic aortic dissection and surgery

Knowledge about age and sex as determinants of outcome after elective thoracic aortic surgery and acute aortic dissection is important for providing patient-tailored treatment and facilitate well informed shared decision-making. In **chapter 4** we studied

male-female differences in presentation, treatment and post-operative outcomes after elective ascending aortic surgery using data form the Netherlands Heart Registration. This nation-wide cohort study showed clear differences between males and females in patient presentation, procedural characteristics and in-hospital outcomes after elective ascending aortic surgery. In-hospital mortality was significantly higher in females, and being female was an independent risk factor for mortality. This study indicates male-female differences are an important factor in elective aortic surgery. Another factor to consider in elective thoracic aortic surgery is age. As elderly often have many comorbidities, aortic surgery might impose greater risks for them. In order to further explore these patient specific aspects in elective thoracic aortic surgery and acute thoracic aortic dissection (Stanford type A and B) we started a nationwide retrospective cohort study called the disSEXion study. For this study we included patients from four centers in the Netherlands: Radboud University Medical Center (Nijmegen), Catharina hospital (Eindhoven), Sint Antonius hospital (Nieuwegein) and Erasmus Medical Center (Rotterdam). This project provided the data for the next chapters. In **chapter 5** we studied male-female differences in acute Stanford type A thoracic aortic dissection. Females with aortic dissection presented at an older age and more often presented with nausea and severe hypotension. Although this study provided several important differences in presentation between males and females with aortic dissection, aortic diameter at presentation and short-term mortality after aortic dissection surgery were not different. In **chapter 6** we investigated differences between elderly and nonelderly TAA patients. This study showed that elderly patients (aged ≥70 years), and especially elderly females, received surgery at larger thoracic aortic diameters compared to nonelderly (aged <70 years), and larger than the threshold for elective aortic surgery as mentioned in current guidelines. Procedural characteristics differed from nonelderly including more supracoronary replacements and more concomitant procedures. Despite these differences, short-term morbidity and mortality were not higher in elderly TAA patients.

Part 3 - Living with thoracic aortic aneurysm or heritable thoracic aortic disease

Living with thoracic aortic aneurysm or heritable thoracic aortic disease imposes many uncertainties, especially when it comes to exercise and sports participation. **Chapter 7** provides an up-to-date systematic review of the available evidence on risks and benefits of exercise and sports participation in patients with thoracic aortic disease. The first important finding was the absolute lack of high-quality studies in this field. There is no longitudinal data on the risk of acute aortic dissection due to exercise in patients with thoracic aortic disease. Larger aortic diameters in athletes seem to result from higher cardiac output (presumably associated with sports) and difference in body size. More importantly, we found no evidence supporting the theory of static exercise being more prone to inducing acute thoracic aortic dissections than dynamic exercise, although considering the massive

increase in blood pressure resulting from static exercise this seems plausible. The current recommendations and reservations concerning exercise are mainly based on case reports and expert opinion. Based on theoretical knowledge, participation in heavy static exercise should likely be avoided. However, regular exercise should probably be encouraged for its known positive effects on overall health, survival and quality of life. In **chapter 8** we evaluated health-related quality of life in males and females with hereditary thoracic aortic disease and Marfan Syndrome in particular. This prospective cohort study showed patients with hereditary thoracic aortic disease had subnormal quality of life, especially females. Interestingly, factors such as employment, coping style, and disease acceptance seemed to have more impact on quality of life than disease related factors in both males and females. This highlights the importance of counselling and guidance for patients with hereditary thoracic aortic disease. Since this may help to develop effective coping strategies, which could improve daily functioning and quality of life. In **chapter 9** we evaluated health-related quality of life in a broader population of patients with (or screened for) hereditary and non-hereditary (sporadic) thoracic aortic disease and their partners in a cross-sectional study. Additionally, we performed in-depth interviews to explore lived experiences and feelings of anxiety or depression using a mixed methods design. This study showed that quality of life in screening-participants was affected to a lesser extent compared to patients with confirmed thoracic aortic aneurysm. Especially female and younger patients reported lower quality of life. Partners' quality of life was also reduced. Disease-related factors negatively influencing quality of life were an increase in thoracic aortic diameter, need for thoracic aortic surgery and a lower level of disease-related knowledge. However, interviewed patients mentioned several other important factors influencing their quality of life, namely: loss of identity, restrictions in sports participation and vocational choice, physical complaints and communication within their family. These might be valuable leads for further study which can hopefully be improved by counselling and result in HRQOL improvement. In **chapter 10** we evaluated health-related quality of life in patients who suffered Stanford type B aortic dissection. This study had a median follow-up time of 6.1 years after presentation with aortic dissection at four referral centers in the Netherlands. Quality of life in this specific population was impaired in both male and female patients, especially the physical components were reduced. However, quality of life in males and females was not significantly different. Moreover, quality of life was not different in conservatively treated patients compared to surgically treated patients, but did seem more reduced in younger patients. These results emphasize it is important for clinicians to consider quality of life in patients who suffered type B aortic dissection, even after many years. These patients might benefit from rehabilitation programs, since the physical components were most reduced in this population. More research is needed to illuminate this, in particular qualitative research could provide meaningful clues for quality of life improvement.

DISCUSSION

Currently, patient specific factors such as sex, age and body size are largely neglected in the diagnosis and management of thoracic aortic disease. This thesis aimed to improve patient specific insights into thoracic aortic disease, and in particular to investigate male-female differences. In part one, aortic diameters, biomarkers and other vascular abnormalities in both patients with and without (hereditary) thoracic aortic aneurysm were studied, in order to define pathological findings. Part two aimed to find male-female and age-related factors associated with outcomes after thoracic aortic surgery and dissection, in order to identify factor that should be considered in the timing of thoracic aortic surgery. In part three quality of life including exercise in males and females with sporadic as well as hereditary thoracic aortic disease and acute aortic dissection was evaluated. In this chapter clinical implications of these findings will be discussed, followed by future perspectives including implications for future research. In addition to the three parts as described above, male-female differences identified in this thesis and their clinical implications will be discussed. Exploring male-female differences in thoracic aortic disease is of great value for daily clinical practice, allowing for tailoring of treatment to the individual patient, and therefore this is a common thread throughout this thesis.

What defines thoracic aortic disease?

In clinical practice, a thoracic aortic diameter of ≥ 40 mm is often considered pathological[1,2]. However, little information has been available on physiological changes in thoracic aortic dimensions throughout the adult life course. The use of absolute aortic diameter irrespective of body size, has been questioned. Especially since high quality evidence on the association between aortic diameter corrected for body size and the occurrence of thoracic aortic dissection is hard to obtain. This thesis highlights another factor to be considered. Changes in thoracic aortic diameters in the general population were very limited, which indicates it is important not to only define pathological aortic disease by aortic diameter measured at one time-point. Rapid changes in thoracic aortic diameter over time are also an important factor to consider when defining thoracic aortic disease. This means thoracic aortic dimensions need to be compared between at least two time-points in order to identify rapid growth, in addition to the measurement of absolute thoracic aortic diameter. Based on this thesis aortic dilatation of more than 3 mm per decade is already abnormal (Chapter 1). The association between more rapid changes thoracic aortic diameters and complications such as thoracic aortic dissection or rupture remains to be investigated. However, rapid changes in thoracic aortic diameters in patients with known TAA is already considered a risk factor for aortic dissection[3]. Similarly, measuring aortic diameters at multiple time-points, in order to quantify aortic growth rate, might improve identification of patients at risk for aneurysm formation or even acute aortic dissection.

The use of aortic diameter for risk prediction is especially debatable in hereditary thoracic aortic disease, which is nowadays often diagnosed genetically. Most importantly, genetic screening for hereditary thoracic aortic diseases should always be considered in patients who fulfill the criteria[2]. Hereditary thoracic aortic disease can cause a great variety of vascular abnormalities as well as other systemic symptoms. In order to prevent serious complications such as aortic or peripheral arterial dissection, it is important to know the prevalence of different vascular abnormalities in every hereditary form of thoracic aortic disease. In this thesis the prevalence of neurovascular abnormalities and events in Loeys-Dietz type III patients is reported (Chapter 3), and neurovascular screening in all patients with this type of hereditary thoracic aortic disease is recommended. Since we observed no major events during follow-up, the role of imaging in the prevention of acute cerebral events remains to be determined. In order to gain more insight into the prevalence of neurovascular abnormalities and acute cerebral events, neurovascular imaging should be performed in all patients with LDS type III. Furthermore, neurovascular imaging might need to be considered in other hereditary thoracic aortic diseases in which the prevalence of neurovascular abnormalities is unknown.

What factors should be considered in timing of elective aortic surgery?

Currently, the timing of preventive surgery for patients with thoracic aortic disease is almost solely based on absolute maximal thoracic aortic diameter, since this has been associated with the risk of acute thoracic aortic dissection[4]. In this regard, no patient specific factors are considered for the timing of elective aortic surgery, with the exception of patients with bicuspid aortic valve and hereditary thoracic aortic diseases[3]. In this thesis we report several patient specific factors which might be important in the decision making process for timing of preventive aortic surgery.

First, being female seems an important factor. Females are significantly older at the time of elective aortic surgery, receive different surgical procedures and suffer higher in-hospital mortality. Being female is independently associated with outcomes after aortic surgery, as has previously been reported[5]. The factors underlying these male-female differences remain unclear (Chapter 4). Socio-cultural factors related to gender such as patient and/or physician delay may play a role in this. For example, these gender related factors might contribute to a delayed presentation and recognition in females with thoracic aortic aneurysm.

Second, contradictory evidence has been reported on outcomes after thoracic aortic surgery in elderly. Outcomes after contemporary elective aortic surgery seem very acceptable in elderly patients. Although elderly received surgery at a larger aortic diameter, and procedural characteristics were different, they seem to suffer mainly from minor complications (Chapter 5). These findings are in contrast with several previous

reports[6,7].This thesis indicates elderly age alone might not need to be a contra-indication for surgery. However, elderly females who received elective thoracic aortic surgery had much larger aortic diameters, far above the current threshold for elective thoracic aortic surgery. No explanation for this difference could be identified in the cardiovascular risk factors of male and female elderly. It is uncertain whether socio-economic factors play a role in this as well.

Third, there has been debate about the use of absolute or corrected aortic diameters for the timing of elective aortic surgery, since aortic diameter indexed for body surface area was found to better predict dissection than aortic diameter alone[8]. In this thesis we have found no unequivocal evidence to support correcting absolute thoracic aortic diameter for body size. Body size was not found to be associated with outcomes after elective aortic surgery. Furthermore, absolute aortic diameter was not different in males and females with acute thoracic aortic dissection, despite differences in body size. Although absolute thoracic aortic diameter seems comparable in males and females, differences in aortic diameter relative to body size exist. Aortic diameter corrected for body size is significantly larger in females. More research is needed to further illuminate the factors underlying female sex as a risk factor for worse outcomes after aortic surgery.

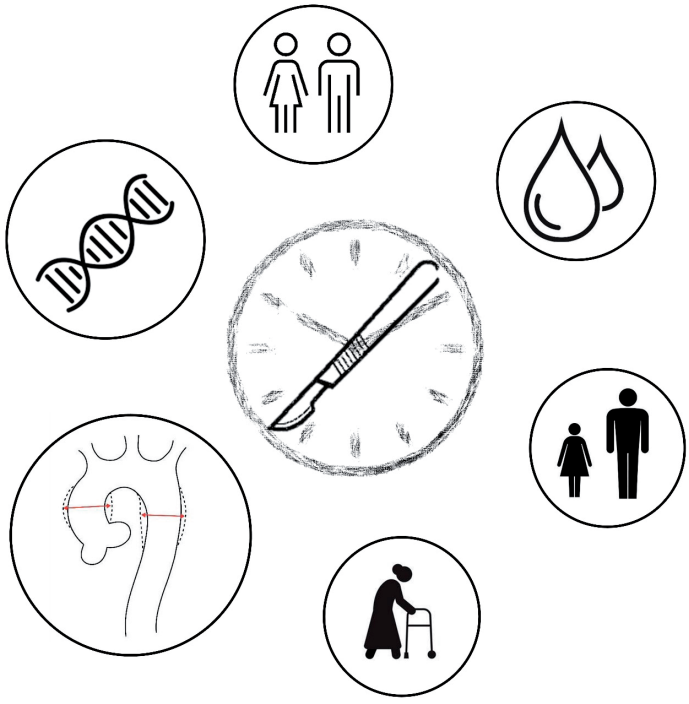

Figure 1. Factors to consider in the timing of thoracic aortic surgery
Clockwise from left bottom: Absolute maximal thoracic aortic diameter, hereditary thoracic aortic diseases including bicuspid aortic valve, sex, blood biomarkers, body size, higher age.

Last, biomarkers are a promising addition in risk prediction for patients with thoracic aortic disease, and provide an interesting avenue for future studies. As mentioned above, diagnosis as well as timing of preventive surgery are currently based on measurements of absolute aortic diameters, but aortic diameter is not the only parameter defining the risk of thoracic aortic dissection. More readily available and cheap tools can facilitate risk prediction in thoracic aortic disease. Several studies showed circulating biomarkers are promising in this regard[9]. In this thesis two biomarkers were selected which were associated with maximal thoracic aortic diameter (Matrix Metalloproteinase-3 and Insulin-like growth factor binding protein 2), descending aortic diameter (fatty acid-binding protein 4) and one biomarker associated with hereditary thoracic aortic disease (Trem-like transcript protein 2) (Chapter 2). Circulating plasma biomarkers could be of great value for risk prediction in TAA patients. However, currently there are no biomarkers that can accurately predict the presence or severity of either sporadic or hereditary thoracic aortic disease.

Ideally, all abovementioned factors combined might eventually be candidates for a risk prediction model in order to predict a patients individual risk of thoracic aortic dissection.

How does thoracic aortic disease affect quality of life?

A large part of this thesis focussed on evaluating health-related quality of life in patients with thoracic aortic disease and their partners. Previously, quality of life had mainly been investigated in patients with hereditary thoracic aortic disease and in patients who received aortic surgery, and was found to be suboptimal. Patients with thoracic aortic disease, patients being screened for thoracic aortic disease and partners of patients with thoracic aortic disease had not been investigated. As presented in this thesis, they all suffer from impaired quality of life (Chapter 8, 9 and 10), which is why it is important for clinicians to be aware of the fact that thoracic aortic disease significantly impairs quality of life of patients and their partners. Currently, international guidelines do not mention health related quality of life[3,10,11]. More attention for quality of life is clearly needed, as treatment of patients with thoracic aortic disease should ideally aim for quality of life improvement in addition to providing optimal medical treatment. Therefore, patients with thoracic aortic disease and partners should be systematically screened with standardized questionnaires both before and after elective thoracic aortic surgery, in order to identify the patients with symptoms of depression and anxiety, which would be the first step towards quality of life improvement. Based on this thesis not only disease-related factors are important for quality of life improvement. Counselling patients to employ constructive coping strategies and good communication within the family might reduce psychological distress and improve quality of life in this population, as was also reported by Moon et al. who stated social support (e.g. family / friends support) and bio-behavioral factors (e.g.

anxiety, depression, fatigue, pain) significantly influence quality of life in patients with Marfan Syndrome[12].

Exercise and sports participation are important factors when it comes to improving both mental and physical well-being. Patients with thoracic aortic disease are often refrained from performing strenuous exercise, even though evidence on this subject is very scarce. Altogether, there is no unequivocal evidence to support discouragement of exercise and sports participation in patients with thoracic aortic disease (Chapter 7). Therefore, mild to moderate regular exercise should be encouraged. Rather than imposing restrictions on sports participation. Clinicians should focus on guidance of patients in order to find the right type and intensity of exercise they can perform. This could be aided by performing cardio-pulmonary exercise testing, combined with counselling on the importance of exercise, in order to create full understanding of risks and benefits and reach a shared decision on sports participation.

Male-female differences in thoracic aortic disease

It has been suggested that females are underrepresented in studies because of a lower prevalence of cardiovascular disease compared to males, as is the case in thoracic aortic disease. However, it has been reported that even after correction of sex-specific prevalence, trials include a proportionally low percentage of female participants[13]. As a result, trial evidence is largely based on data mainly concerning male patients. Moreover, in many manuscripts the terms male and man, and female and woman, are used interchangeably. This is not correct, as the terms refer to sex, respectively gender. Inappropriate use of these terms can make it harder to identify existing male-female specific data. Therefore the term male-female differences, which incorporates the broader aspects of both sex and gender, was used consistently throughout this thesis. In order to provide more female specific data, inclusion criteria were based on a minimum number of females to include whenever possible; all analyses were performed for the total population as well as males and females separately throughout this whole thesis; and male-female differences were discussed as much as possible. From this we can conclude several male-female differences.

Thoracic aortic diameters and dilatation rate

Previous studies showed the absolute thoracic aortic diameter to be substantially larger in males[14]. However, the indexed thoracic aortic diameter is larger in females[14]. Thoracic aortic dilation rate in the general population was found to be significantly faster in males (Chapter 1). However, the absolute difference is so small, this seems clinically irrelevant.

Dissection

In this thesis we found that females present with acute thoracic aortic dissection at a higher age than males. However, males and females had comparable aortic diameters

at the time of aortic dissection (Chapter 5). Furthermore, some important information on presentation was obtained: Females more often present with nausea and severe hypotension reflecting hemodynamic instability. In the end these male-female differences do not seem to result in higher short-term mortality in females. All of these findings are remarkably similar to a recent study of the international registry of aortic dissection (IRAD). Despite the fact that mortality and morbidity does not seem that different in males and females, there clearly are differences between males and females presenting with thoracic aortic dissection that should be considered in clinical practice. In particular, females seem to present with hemodynamic instability and shock more often, which has been associated with worse outcomes. Therefore timely recognition and diagnosis is especially important in female patients.

Quality of life

In general, females are known to suffer more from depression and anxiety compared to males, and a lower overall quality of life as measured by questionnaires[15]. In this thesis, patients with (hereditary) thoracic aortic disease and their partners were found to have lower health-related quality of life compared to the general population (Chapters 8, 9 and 10). Female patients showed higher rates of anxiety and depression compared to male patients, which seems logical since females in the general population are already closer to pathological values. However, the question remains whether females actually experience a lower quality of life. The male-female difference in quality of life might partially be explained by the measurement methods used, as quality of life is usually measured by self-reported questionnaires. Females might self-report their feelings and anxieties differently than males, as they might experience their functional capacity and quality of life in a different manner.

Future perspectives

In recent years male-female differences in thoracic aortic disease have been increasingly studied, especially since a higher mortality in females after thoracic aortic surgery and dissection had been reported. We expect this increase in sex and gender oriented research to continue in the upcoming years. However, a correct choice of words is vital in order to identify, extrapolate and reproduce this evidence. In many scientific research articles the terms sex, respectively gender are used interchangeably. 'Male' and 'female' are the more appropriate term to use, as the variables included in most studies can be associated with both sex and gender. We encourage efforts to increase the body of knowledge concerning both males and females with thoracic aortic disease, but encourage authors to keep in mind the correct nomenclature.

From this thesis we can formulate several implications for further research. In Part I we aimed to define pathological thoracic aortic diameters and dilatation. More imaging

research in both the general population and patients with thoracic aortic aneurysm is needed to establish accurate sex and age specific reference values for normal thoracic aortic diameters and aortic growth rate at different locations of the thoracic aorta. Long term follow-up will be needed to study the association between more rapid aortic dilatation and the formation of thoracic aortic aneurysm or the occurrence of acute aortic complications.

In part II we reported male-female and age-differences in thoracic aortic dissection and elective aortic surgery. Timing of elective thoracic aortic surgery, and the prevention of acute thoracic aortic dissection remains challenging. Since the factors underlying male-female differences in outcomes after elective aortic surgery remain unclear, future research should report on male-female differences and age-differences in short-term and long-term outcomes after thoracic aortic surgery and dissection. This is needed to provide insight into male-female specific and age-related determinants of outcome after surgery. With this information recommendations can be provided on how exactly timing of elective surgery should be tailored to an individual patient. This information could be incorporated into male-female and age-sensitive information portals and decision-aids, to improve shared decision making. Hopefully, this will lead to improved outcomes, especially in females with thoracic aortic disease. Biomarkers seem promising in this regard as they might aid in risk prediction. We would like to encourage researchers investigate the biochemical pathways associated with the biomarkers that were identified and their potential clinical benefit.

In part III we studied several aspects of life with thoracic aortic disease, and especially quality of life in this population. Concerning quality of life research: females might report their feelings and anxieties differently, as females experience their functional capacity and quality of life different from males. From experience, it is best to combine both qualitative and quantitative research methods in order to properly assess quality of life in both males and females.

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NEDERLANDSE SAMENVATTING

Dit proefschrift focust zich op het onderzoeken van man-vrouw verschillen en de invloed van andere patiënt specifieke kenmerken zoals lichaamsgrootte en leeftijd bij mensen met een thoracaal aorta aneurysma (TAA). Een TAA is een lokale verwijding van de grote lichaamsslagader (de aorta), in het gedeelte van de aorta dat door de borstkas loopt. In de dagelijkse praktijk wordt vaak een diameter van maximaal 40 mm aangehouden als grens voor een abnormale verwijding van de thoracale aorta, daarboven wordt gesproken van een TAA. Een TAA geeft meestal geen klachten, en is daarom vaak ongemerkt aanwezig. We weten dat een aneurysma over de tijd langzaam in diameter toeneemt. Bij het groter worden van een aneurysma neemt de kans op het ontstaan van een scheur in de wand van de aorta toe. Het ontstaan van een scheur, ook wel aorta dissectie genoemd, levert een levensbedreigende situatie op met een hoge kans op sterfte (ongeveer een op de drie patiënten overlijdt hieraan). Omdat bekend is dat bij een diameter boven de 55 mm de kans op een scheur exponentieel toeneemt, wordt rond deze diameter meestal preventief een interventie uitgevoerd om het aangedane deel van de aorta te vervangen.

Meestal ontstaat een en TAA spontaan. In ongeveer 20% van de gevallen speelt er echter een erfelijke oorzaak. Inmiddels zijn meerdere erfelijke bindweefsel aandoeningen bekend die een aorta aneurysma of aneurysma op een andere plaats in het lichaam kunnen veroorzaken. Vanwege het eerder genoemde risico op een scheur, kan het hebben van een TAA en/of een erfelijke bindweefsel aandoening leiden tot veel onzekerheden, stress en angst. Dit heeft vermoedelijk gevolgen voor de kwaliteit van leven bij de patiënten met een al dan niet erfelijk aorta aneurysma. Daarnaast zijn er duidelijke verschillen in het voorkomen van een TAA bij mannen en bij vrouwen met een hogere incidentie bij mannen (3:1). Vrouwen lijken zich met dit ziektebeeld te presenteren op een hogere leeftijd. Helaas is er slechts weinig bekend over man-vrouw verschillen in presentatie, behandeling en uitkomsten bij patiënten met een TAA. Sommige onderzoeken die laten zien dat vrouwen een slechtere uitkomst hebben na een dissectie en na aorta chirurgie. Hierdoor zijn er onzekerheden ontstaan over de timing van een preventieve interventie bij vrouwen.

Dit proefschrift is onderdeel van het ‘Size Matters’ project, gesponsord oor ZonMW. Dit project heeft als doel man-vrouw verschillen en andere patiënt specifieke inzichten met betrekking tot TAA te vergaren, zodat er een betere inschatting kan worden gemaakt welke patiënten een risico lopen op een scheur in de aorta en een preventieve operatie op het goede moment kan worden uitgevoerd. Dit zou kunnen leiden tot betere overleving en een vermindering van de stress die zij ervaren, met en een verbetering van de kwaliteit van leven tot gevolg.

Deel 1 – Karakteristieken van het thoracale aorta aneurysma

In deel 1 worden karakteristieken van de normale aorta, de aorta bij patiënten met een TAA, en vasculaire afwijkingen bij patiënten erfelijke bindweefsel aandoeningen beschreven. Om te kunnen definiëren wanneer een toename in diameter van de aorta pathologisch is, is het belangrijk om inzicht te hebben in de normale toename van de dimensies van de aorta bij het ouder worden. In **Hoofdstuk 1** worden veranderingen van aorta diameters geëvalueerd bij deelnemers aan de prospectieve Rotterdam Studie. Hierin werden 943 deelnemers uit de algemene bevolking geïncludeerd (mediane leeftijd op baseline 65 jaar) welke twee CT-scans zonder contrast ondergingen om de aorta diameters te meten. Op deze scans met een gemiddeld scan interval van 14 jaar werden het stijgende deel van de aorta (aorta ascendens) en dalende deel van de aorta (aorta descendens) in de borstkas gemeten. We konden hieruit concluderen dat de toename van de diameters van de aorta ascendens en descendens in de algemene bevolking minimaal is. Hoewel de toename van aorta diameters iets groter was bij mannen dan bij vrouwen, blijkt het verschil niet klinisch relevant. Enkele factoren bleken geassocieerd te kunnen worden met een snellere toename van de aorta diameter, namelijk: hogere leeftijd, hogere body mass index (BMI) en hogere diastolische bloeddruk. Deze factoren zouden van belang kunnen zijn voor het voorkomen van een TAA en progressie hiervan.

Aangezien snellere groei van de aorta diameter en de vorming van een aneurysma vrijwel altijd asymptomatisch zijn, is het moeilijk een (beginnend) aneurysma te diagnosticeren. Biomarkers zijn stofjes in het bloed die meetbare indicatoren zijn van een biologische toestand of conditie, en die wellicht gebruikt kunnen worden voor de diagnose van een TAA, het opvolgen hiervan en het stellen van de indicatie voor preventieve interventie. In **Hoofdstuk 2** hebben we daarom een groot scala aan cardiovasculaire biomarkers bestudeerd in relatie tot het TAA. In veneus bloed werden 92 biomarkers bepaald, om uit te zoeken welke geassocieerd waren met de aorta diameter en enkele klinische karakteristieken bij patiënten met een TAA. De resultaten toonden aan dat *Matrix Metalloproteinase-3* (MMP-3) geassocieerd was met de absolute maximale aorta diameter. *Insulin-like growth factor binding protein 2* (IGFBP-2) was geassocieerd met maximale aorta diameter geïndexeerd voor body surface area (BSA). *Fatty acid-binding protein 4* (FABP4) was geassocieerd met absolute diameter van de aorta descendens. *Trem-like transcript protein 2* (TLT-2) was hoger bij patiënten met een erfelijke bindweefsel aandoening. Dit zou een aanwijzingen kunnen zijn voor een vorm van ontsteking die aanwezig is bij deze patiënten. Deze vier biomarkers en de biochemische cascades waartoe zij behoren, lijken een rol te spelen bij de ernst van het TAA. De identificatie van deze biomarkers maakt verder onderzoek naar de cascades waartoe zij behoren en hun betrokkenheid bij het ziekteproces mogelijk.

Erfelijke bindweefsel aandoeningen kunnen naast een TAA een scala aan andere vasculaire problemen veroorzaken. Het Loeys-Dietz syndroom type III, veroorzaakt door pathogene

SMAD3 genetische varianten, is een zeldzaam autosomaal dominant overervend syndroom, dat wordt gekenmerkt door een combinatie van aneurysmata en kronkelige vaten (arteriële tortuositeit) in combinatie met gewrichtsontstekingen (osteoartritis). Bij sommige erfelijke bindweefsel aandoeningen komen ook afwijkingen voor van de slagaders in het hoofd (neurovasculaire afwijkingen). Tot op heden is er geen bewijs voor het voorkomen van neurovasculaire afwijkingen bij patiënten met Loeys-Dietz type III. In **Hoofdstuk 3** worden neurovasculaire afwijkingen beschreven bij patiënten met Loeys-Dietz type III die bekend zijn in ons expertisecentrum (Erasmus MC Rotterdam). Onze resultaten lieten zien dat afwijkingen zoals verwijde slagaders in het hoofd (cerebrale aneurysmata), tortuositeit met kronkelende en knikkende vaten in het grootste deel van de patiënten met Loeys-Dietz type III voorkomen. Deze afwijkingen kwamen evenveel voor bij mannen als bij vrouwen. Acute problemen waren zeer zeldzaam gedurende onze follow-up periode van negen jaar. Desondanks lijkt het verstandig patiënten met Loeys-Dietz syndroom type III altijd te screenen op neurovasculaire afwijkingen en waarschijnlijk ook om deze regelmatig te blijven controleren middels beeldvorming.

Deel 2 – Thoracale aorta dissecties en chirurgie

Om een patiënt een specifieke behandeling te kunnen bieden, is het belangrijk wetenschappelijk bewijs te hebben voor factoren als leeftijd en geslacht als voorspellers van uitkomsten na preventieve chirurgie van de thoracale aorta en als voorspellers van uitkomsten na een aorta dissectie. In **Hoofdstuk 4** onderzoeken we de verschillen tussen mannen en vrouwen in presentatie, behandeling en post-operatieve uitkomsten na preventieve chirurgie van de aorta ascendens. Daarvoor zijn data van de Nederlandse Hart Registratie (NHR) gebruikt, een landelijk cohort. Deze studie toonde duidelijke verschillen tussen mannen en vrouwen in presentatie, procedurele karakteristieken en korte termijn uitkomsten. De in-hospital sterfte was significant hoger bij vrouwen en vrouw zijn was onafhankelijk geassocieerd met hoge kans op korte termijn sterfte. Dit benadrukt dat man-vrouw verschillen aandacht verdienen als het preventieve aorta chirurgie betreft.

Een andere belangrijke factor is leeftijd. Ouderen hebben vaak meerdere ziekten waardoor preventieve chirurgie voor hen meer risico's met zich mee brengt. Om eerder genoemde patiënt karakteristieken beter te kunnen onderzoeken, hebben we een landelijke retrospectieve cohort studie opgezet genaamd disSEXion studie. Voor deze studie zijn patiënten geïncludeerd die een preventieve aorta operatie hebben ondergaan of een acute aorta dissectie hebben gehad in vier grote cardiovascularie centra in Nederland: Radboud Universitair medisch Centrum (Nijmegen), Catharina Ziekenhuis (Eindhoven), Sint Antonius ziekenhuis (Nieuwegein) en Erasmus Medisch Centrum (Rotterdam). De data uit deze studie maakten het mogelijk enkele patiënten karakteristieken te onderzoeken die worden beschreven in de volgende hoofdstukken. In **Hoofdstuk 5** worden man-vrouw verschillen bij patiënten met een acute type A aorta dissectie beschreven. Vrouwen met

een aortadissectie presenteerden zich op hogere leeftijd en vaker met misselijkheid en ernstige hypotensie. Echter de aorta diameter bij presentatie en korte-termijn mortaliteit na aortadissectie waren niet significant verschillend. In **Hoofdstuk 6** worden de verschillen tussen oudere (≥70 jaar) en niet-oudere (<70 jaar) patiënten beschreven die een preventieve thoracale aorta operatie hebben ondergaan. Ouderen, met name oudere vrouwen, bleken pas bij grotere aorta diameters geopereerd te worden (de diameters waren groter dan in de huidige richtlijnen voor interventie aangegeven). Ouderen kregen vaker een supra coronaire ascendens vervanging evenals een bijkomende operatieve procedure. Desondanks was de korte termijn morbiditeit en mortaliteit niet significant verschillend.

Deel 3 – Leven met een thoracaal aorta aneurysma of erfelijke bindweefsel aandoening

Het leven met een TAA of erfelijke bindweefsel aandoening gaat gepaard met veel onzekerheden, vooral als het gaat over fysieke inspanning en sportieve activiteiten. **Hoofdstuk 7** betreft een systematische review over de actuele wetenschappelijke stand van zaken betreffende risico's en voordelen van sport en fysieke inspanning bij patiënten met een TAA of een erfelijke bindweefsel aandoening. De eerste belangrijke bevinding was dat er vrijwel geen kwalitatief hoogstaande studies over dit onderwerp zijn gerapporteerd. Met name vonden wij geen longitudinale studies in deze populatie die het risico op een aortadissectie onderzoeken als gevolg van fysieke inspanning. Grotere aorta diameters werden gerapporteerd bij sporters. Dit lijkt vooral het gevolg van een hoger hartminuut volume en verschillen in lichaamsgrootte. Evenmin waren er onderzoeken die de theorie ondersteunen dat statische inspanning een hoger risico zou geven op een acute aorta dissectie dan dynamische inspanning. Echter gezien de enorme stijging in bloeddruk die samengaat met statische inspanning lijkt dit wel aannemelijk. Huidige richtlijnen en aanbevelingen zijn vooral gebaseerd op case-reports en deskundige meningen. Gebaseerd op de huidige kennis wordt het verstandig geacht voor patiënten met een TAA of erfelijke bindweefsel aandoening om zware statische inspanning te vermijden. Regelmatige inspanningen worden wel aangemoedigd vanwege de bekende positieve effecten van sporten voor de algehele gezondheid, overleving en kwaliteit van leven.

In **Hoofdstuk 8** wordt dieper ingegaan op de kwaliteit van leven bij mannen en vrouwen met erfelijke bindweefsel aandoeningen en het Syndroom van Marfan in het bijzonder. De prospectieve cohort studie laat zien dat patiënten met een erfelijke bindweefsel aandoening een verminderde kwaliteit van leven rapporteren, met name de vrouwen. Factoren zoals werk, coping stijl en ziekte-acceptatie lijken een grotere impact op de kwaliteit van leven dan ziekte-gerelateerde factoren bij zowel mannen als vrouwen. Dit benadrukt het belang van een goede begeleiding van patiënten met een erfelijke bindweefsel aandoening. Het gebruiken van effectieve coping strategieën zou kunnen helpen het dagelijks functioneren

en de kwaliteit van leven te verbeteren. In **Hoofdstuk 9** wordt de kwaliteit van leven middels een cross-sectionele studie bij een bredere populatie geëvalueerd. Het betreft zowel patiënten met een TAA, als patiënten met een erfelijke bindweefsel aandoening, alsook patiënten die gescreend worden op het bestaan van een TAA (screening patiënten) en de partners van deze patiënten. Er werden zowel vragenlijsten als diepte-interviews gebruikt om ervaringen en gevoelens van angst en depressie in beeld te brengen. De kwaliteit van leven bij screening patiënten bleek minder aangedaan dan bij patiënten met een bekend TAA of erfelijke bindweefsel aandoening. Vrouwen en jongere patiënten rapporteerden juist een lagere kwaliteit van leven. De kwaliteit van leven van partners was ook verminderd ten opzichte van de algemene populatie. Ziekte-gerelateerde factoren die de kwaliteit van leven beïnvloeden waren een toename van de aorta diameter, het moeten ondergaan aorta chirurgie en minder kennis over het ziektebeeld. Uit de interviews kwamen enkele andere factoren naar voren die de kwaliteit van leven ook sterk leken te beïnvloeden zoals het verlies van de eigen identiteit, restricties in sport beoefening en beroepskeuze, fysieke ongemakken en communicatie met familie leden. Deze factoren lijken waardevol voor toekomstige studies en het begeleiden van patiënten, wat hopelijk zal leiden tot een verbetering van de kwaliteit van leven. Tot slot wordt in **hoofdstuk 10** de kwaliteit van leven onderzocht bij patiënten die een acute type B dissectie hebben gehad. Deze studie had een mediane follow-up duur van 6.1 jaar na het vaststellen van de dissectie. Kwaliteit van leven in deze patiënten was verminderd bij zowel mannen als vrouwen in vergelijking met de algemene populatie. Vooral de fysieke componenten waren verminderd. De kwaliteit van leven bij mannen en vrouwen was niet significant verschillend. De kwaliteit van leven was niet verschillend tussen patiënten die conservatief werden behandeld en patiënten die een ingreep ondergingen. De kwaliteit van leven van de jongere patiënten bleek wel verminderd te zijn. Deze resultaten benadrukken ook voor patiënten die een type B aortadissectie hebben gehad het belang van aandacht voor kwaliteit van leven in de dagelijkse praktijk, zelfs nog na enkele jaren. Gezien de fysieke aspecten het meest aangedaan leken te zijn, zouden deze patiënten wellicht voordeel kunnen hebben van een revalidatie programma. Meer onderzoek is nodig om hier duidelijkheid over te verkrijgen en de kwaliteit van leven in deze populatie te verbeteren.

PHD PORTFOLIO

General courses	Year	ECTS
Basic training LimeSurvey	2017	0.15
Basic training GemsTracker	2017	0.15
TedTalk Masterclass (Bayer, DebatNL)	2017	0.5
Basic training Open Clinica	2018	0.3
Basic course on Regulations and Organisation for clinical investigators (BROK)	2018	1.5
MolMed Basic course on SPSS	2018	1.0
Integrity in Science	2018	0.3
MolMed Workshop Adobe Photoshop an Illustrator	2018	0.3
MolMed Workshop InDesign	2018	0.15
Consultation Center for Patient Oriented research (CPO) course	2018	0.3
NIHES Biostatistical Methods I: Basic principles	2018	5.7
NIHES Biostatistical Methods II: Classical regression models	2019	4.3
MolMed Biomedical English Writing	2020	2.0
	Total	*16.65*
In-depth courses		
COEUR: sex and gender in cardiovascular research	2018	0.5
COEUR: congenital heart disease	2018	0.5
COEUR: vascular clinical epidemiology	2018	0.5
COEUR: PhD day	2019	0.3
	Total	*1.8*
Seminars and workshops		
COEUR: Encanging precision medicine through biomarkers profiling	2017	0.15
Aorta Masterclass	2018	0.6
Libin international trainee symposium: Research is better with Sec & Gender	2020	0.6
ExCOEURsie tuchtcollege	2018	0.2
	Total	*1.55*
Oral presentations		
Size Matters project kick-off meeting	2017	0.3
NVVC Najaarscongres	2018	0.6
Size matters consortium meeting	2018	0.3
Davos Wintermeeting	2018	1.5
Davos Wintermeeting	2019	1.5
Size Matters consortium meeting 2x	2019	0.6
Size Matters consortium meeting	2020	0.3
Meeting disSEXion study participating centres	2020	0.2
	Total	*5.3*
Poster presentations		
EuroGUCH	2018	0.9
ESC Munich	2018	2.0
EuroGUCH	2019	0.9
ACHD symposium	2019	1.3
EuroGUCH	2020	0.9
ESC the digital experience	2020	2.0
	Total	*8.0*

Conference attendance		
NVVC najaarscongres	2017	0.3
NVVC voorjaarscongres	2018	0.3
NVVC najaarscongres	2021	0.3
NVVC najaarscongres	2022	0.3
	Total	*1.2*
Teaching activities		
Lecture ECG education, minor CHD	2020	0.2
Supervising master thesis: Male-female differences in elective aortic root and ascending aortic surgery (Tamin Noordam, 6 months)	2020	1.2
Supervising master thesis: Treatment and outcomes after elective thoracic aortic aneurysm surgery in the elderly (Feyza Memis, 6 months)	2020	1.2
Supervising master thesis: Male-Female Differences in Type B Aortic Dissection (Frederike Meccanici, 12 months)	2019	2.4
Supervision systematic review bachelor students: Quality of life after type A aortic dissection	2019	0.6
Supervising student team disSEXion study including students from: Erasmus University, Radboud University and Groningen University and Maastricht University.	2019-2020	2.4
	Total	*8.0*
Other		
ACE meetings aortic disease	2018-2020	1.0
Total ECTS		43.5

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ABOUT THE AUTHOR

Carlijn Gerlinde Elise Thijssen was born on the 29th of June 1992 in Rotterdam, the Netherlands. After spending the first years of her childhood in Rotterdam, her family moved to Eindhoven. Here she completed high school in 2010 (VWO, Pleincollege Bisschop Bekkers), after which she moved to Maastricht to study Medicine at Maastricht University. In 2013, she received her Bachelor of Science degree. When studying for her Masters degree she spent two internships abroad, one in Kampala, Uganda (surgery) and one in Jakarta, Indonesia (gyneacology and pediatric care). She devoted several internships to her interest in cardiology (research internship, senior internship and pediatric cardiology). In 2016 she graduated from Maastricht University medical school, after which she gained more clinical experience working at the cardiology department of the Amphia hospital in Breda. In 2017 she started her PhD at the Erasmus Medical Center as part of the 'Size Matters' project on male-female differences in thoracic aortic diseases, supervised by prof.dr. J.W. Roos-Hesselink, prof.dr. J.J.M. Takkenberg and dr. R.R.J. van Kimmenade. During her PhD project she was closely involved in patient care at the aorta outpatient clinic, where she consulted patients once a week and participated in various multidisciplinary team meetings. Furthermore, she had the opportunity to present her work at various international conferences, and to publish manuscripts in peer-reviewed journals. In addition to this, she supervised many bachelor and master degree students. During medical school and while working as a PhD candidate, Carlijn played the guitar at 'Studententen Gitaar Ensemble Nederland (SGEN)', and participated in two album recordings as well as many concerts both in the Netherlands and abroad. In 2022 she joined a new guitar ensemble called 'Gitaar Camerata Utrecht', in which she still plays with great joy. As of November 2020, Carlijn is working at the Amphia hospital in Breda again where she is now a resident in training to become a cardiologist.

ACKNOWLEDGEMENTS

Het waren enkele onstuimige jaren, maar eindelijk is het zover: mijn proefschrift is af! Graag wil ik iedereen bedanken die mij in deze tijd heeft gesteund, op wat voor manier dan ook.

Prof.dr. Roos-Hesselink, Lieve Jolien. Wat een voorrecht om onderdeel te mogen zijn van jouw onderzoeksteam! Als mijn dagelijks begeleider wist je vaak precies de juiste handvaten en instructies te geven zodat ik er weer tegenaan kon. Heel bijzonder hoe jij voor iedereen aandacht hebt, en hoe we altijd bij je terecht kunnen. Bedankt voor de fijne begeleiding tijdens dit traject en de mogelijkheden die je hebt geboden om mijzelf verder te ontwikkelen op alle vlakken. Ik heb enorm veel geleerd en genoten van alle mooie momenten: congressen, borrels, zeil, golf en wandel uitjes. Van jou en mijn tweede promotor **Prof.dr. Takkenberg** (Hanneke) leerde ik niet alleen over wetenschappelijk onderzoek, maar ook over jullie visie op de geneeskundige en wetenschappelijke wereld. Hanneke, je passie voor een patiënt specifieke gezondheidszorg en in het bijzonder man-vrouw verschillen is inspirerend! Jullie hebben mij veel geleerd over de positie van vrouwen als patiënt, maar ook de positie van vrouwen in het werkveld. Dat is iets dat ik de rest van mijn carrière zal meenemen. **Roland van Kimmenade**, jouw nuchtere (en letterlijke en figuurlijk verder afstaande) blik was altijd verfrissend. Je humor en positieve ondersteuning waren vaak precies wat ik nodig had. Bedankt dat je altijd bereikbaar was voor vragen en adviezen. Ik kom graag nog een keer langs in Nijmegen voor een kopje koffie.

Uiteraard wil ik **prof.dr. Widdershoven**, **dr.ir. Wentzel** en **prof.dr. Kluin** bedanken voor het het plaatsnemen in de leescommissie en het beoordelen van mijn proefschrift. **Prof. dr. Verhagen, dr. Kavousi en dr. Geuzebroek** hartelijk dank voor het plaatsnemen in de grote commissie. **Prof.dr. Kemps**, Hareld, bij jou deed ik als geneeskunde student mijn eerste ervaringen op met wetenschappelijk onderzoek. Daarvoor wil ik je bedanken, want dankzij die positieve ervaring ben ik aan dit traject begonnen.

Arjen, samen hebben wij ons in dit project gestort en vele hordes genomen. De berg werk leek soms oneindig, en we hebben heel wat hobbels moeten overwinnen. We wisselden elkaar mooi af met onze pieken en dalen, en boden elkaar zowel mentaal als praktisch gezien altijd de hoognodige ondersteuning of afleiding. Een betere partner had ik me voor dit project niet kunnen wensen! Inmiddels heeft je carrière een hele andere wending genomen waardoor we elkaar niet meer zo veel tegen komen. Ik wens je heel veel succes en geluk.

Gelukkig kwam **Frederike** ons bij dit project ondersteunen. Freddie, het was geweldig om te zien hoe jij je van 'net master student' ontpopte tot epidemioloog met een enorme bak aan statistische kennis (en een heleboel handige R scripts) bij wie ikzelf terecht kan met vragen. Zo ontwikkelde je je langzaam tot een belangrijke 'spar partner' voor nieuwe ideeën en problemen. Ik ben ervan overtuigd dat jij mij net zoveel (of meer) geleerd hebt als ik jou, maar daarnaast kan ik ook gewoon enorm met je lachen! Hopelijk kunnen we dat nog een tijdje voortzetten. Daarnaast wil ik al onze andere studenten van het disSEXion project bedanken. In het bijzonder **Max** en **Feyza**, die zich enorm hebben ingezet voor dit project (en nog steeds). Maar ook **Tamin, Marie, Mark, Guy, Jort, Jolien, Rick, Annemijn en Sanne**: zonder jullie hulp hadden we het nooit gered. Ik heb genoten van jullie enthousiasme en jullie hebben me verbaasd met de hoeveelheid verslagen en papers die er uit het project zijn gekomen.

Natuurlijk zou mijn promotie tijd niet hetzelfde zijn geweest zonder mijn collega's van de congenitale research groep (aka congenitaaltjes). Jullie gezelligheid zorgde ervoor dat het drie fantastische jaren waren. Ontelbare borrels, koffietjes, sportieve activiteiten en reizen hebben we samen ondernomen. Tijdens de laatste maanden van mijn PhD-tijd, in de corona crisis, heb ik ervaren dat het onderzoeksleven echt niet hetzelfde was geweest zonder jullie. **Lidia**, van jou mocht ik de aortapoli met bijbehorende inclusie overnemen, samen met wat welgemeende adviezen voor de toekomst. Ook na je vertrek uit de kantoortuin kon ik regelmatig bij je terecht als ik mijn verhaal even kwijt moest. Bedankt daarvoor! **Roderick**, als vroege vogel van Ba-308 was je altijd beschikbaar voor vragen, koffie, loopjes en natuurlijk borrels. Jouw betrouwbare aanwezigheid heeft mij op weg geholpen in dit traject. Ik zal nog vaak aan je denken als ik met de taxi naar een congres ga. **Laurie**, mijn eerste NVVC congres met jou was meteen onvergetelijk, maar ook daarna hebben we samen nog heel wat congressen onveilig gemaakt, inclusief het zeepaardje uiteraard. **Lucia**, jouw relativeringsvermogen en eigen wil waren heerlijk verfrissend, en zorgden voor leven in de brouwerij. **Allard**, altijd in voor een wat competitie of een dansje om de zinnen te verzetten. Heerlijk om ons af en toe uit te leven! Dat hierbij enkele (bijna) crashes kwamen kijken laten we hier maar even buiten beschouwing… (steenbok?). **Savine**, allebei hadden wij een project waarbij het publiceren soms wat moeizamer ging. Hierdoor konden we wel altijd onze problemen bij elkaar kwijt. Je bent een ongelofelijk harde werker, een super gezellige borrelaar, maar een nog beter skiër. Inmiddels zijn we opnieuw collega's, en ook borrel buddy's zijn we gebleven. Hopelijk gaan we dat nog jaren voorzetten, en kunnen we samen ook Breda een beetje op z'n kop zetten! **Karishma**, **Paul**, **Chiara** en **Zoë** de nieuwe generatie aka 'congenitale clowns'. Jullie hebben de tradities ondanks een zware corona periode in ere weten te houden. Respect voor de manier waarop jullie je onderzoek en ook zo veel mogelijk de sociale events voort hebben weten te zetten. Samen hebben we desondanks een mooie tijd beleefd, vooral de Juicy

Lucy was om nooit te vergeten! Graag wil ik alleen nog wel even benadrukken dat blokje twee met de koffie bar toch echt de 'place to be' is…

Martijn, **Judith** en **Annemien**, bedankt voor het altijd inpassen van de poli supervisie. Van jullie heb ik vooral op klinisch vlak veel geleerd over de aorta pathologie. Onder jullie leiding leerde ik steeds meer zelfstandig de aortapoli te doen. Lieve **Silvy**, op de poli was jij mijn steun en toeverlaat. We konden het altijd samen hebben over onze gedeelde patiënten en de lastige casuïstiek die we soms tegenkwamen. Ook in het onderzoek vulden we elkaar aan wat heeft geleid tot meerdere mooie publicaties. Ik bewonder je enorme inzet, die ervoor zorgt dat zowel de zorg als het onderzoek vooruit gaan, en daarom ben ik blij om te horen dat je weer binnen de cardiologie werkzaam bent. Hopelijk tot snel.

Daarnaast de andere PhD's die ik heb mogen leren kennen: **Jesse, Sumant, Roy, Stefan, Rafi, Elke, Marie, Amira, Fay, Nikki, Eline, Michelle, Hannah** en **Kevin**. We hebben samen gewerkt aan projecten en ons samen door moeilijke cursussen weten te worstelen. Mooi om te zien hoe ieder nu zijn eigen weg gaat. Ik zie ernaar uit jullie weer tegen te komen.

Collega's van de cardiologie in Breda (**Amphianen**), met jullie ben ik inmiddels begonnen aan het volgende avontuur. Toen ik net uit de schoolbanken kwam hebben jullie mijn enthousiasme voor de cardiologie aangewakkerd, ik ben dan ook heel erg blij en dankbaar dat ik bij jullie ben mogen terug komen.

Mijn mede gitaristen van het *Studenten Gitaar Ensemble Nederland* en inmiddels ook van *Gitaar Camerata Utrecht*, en **Susana** in het bijzonder: bij jullie kan ik me even begeven in een hele andere wereld. Hoewel het qua (reis)tijd voor mij soms passen en meten is, ben toch altijd blij om me even op iets anders te kunnen richten. Susana, jouw eindeloze energie en passie drijven inmiddels meerdere ensembles vooruit en bezorgen ons allemaal heel veel mooie memorabele momenten. Bedankt dat ik hier deel van mag uitmaken! Ik hoop nog lang samen met jullie muziek te mogen maken. Ook de leden van *schaatsvereniging Ballangrud* zorgen ervoor dat mijn werk-privé balans in evenwicht blijft. Jullie hebben mijn enthousiasme voor de schaatssport weer helemaal aangewakkerd, en mij inmiddels ook op de fiets gekregen. Hopelijk kunnen we samen nog vele tochtjes en wedstrijden meemaken. **Evelien**, als vrouwen van dezelfde leeftijd, met hetzelfde beroep en dezelfde hobby's hadden wij elkaar al snel gevonden. Jij sleepte me gelijk enthousiast mee in alle Ballangrud activiteiten en bedacht er zelf nog een paar bij. Ondanks je eigen drukke gezinsleven vinden we altijd wel weer een momentje om bij te kletsen. **Herman**, jij hebt me meteen vanaf het begin enthousiast gemaakt voor Ballangrud en hebt me altijd welkom laten voelen. Bedankt daarvoor, mede dankzij jou voel ik me nu helemaal thuis op de ijsbaan en daarbuiten.

Lieve **Hanneke**, **Bianca** en **Daphne**, aan het begin van onze studie geneeskunde in Maastricht leerden wij elkaar kennen in het 'nageplaatsten' groepje. Een onwaarschijnlijk kwartet dat wellicht in andere omstandigheden nooit zo close was geworden. Samen hebben we een onvergetelijke studententijd beleefd met vele avonturen. Ook nu kan ik altijd bij jullie terecht. Met jullie kan ik heerlijk alle perikelen uit de medische wereld bespreken, maar daar toch net een andere visie op krijgen. Hopelijk kunnen we nog veel gezellige wandelingen maken, totdat we oud en gepensioneerd zijn.

Annemieke, ook jou ken ik al sinds onze studententijd, alleen is het pas daarna dat het lot ons weer bij elkaar bracht. De gemeenschappelijke liefde voor zeilen zorgt ervoor dat we elkaar iedere zomer weer opzoeken voor het volgende avontuur. Helaas ga je binnenkort verhuizen, maar desondanks hoop ik dat we nog vele avonturen samen mogen beleven.

Lieve buurtjes: **Cléo**, **Jorgo**, **Lenny**, **Marianne** en **Anne-Sophie**, wat een gezellig verdieping hebben wij! Heerlijk om altijd iemand in de buurt te hebben voor een wandeling of theetje en een goed gesprek. Jullie gezelligheid en borrels met eten in overvloed zijn geregeld een goede afwisseling geweest en hebben mij in deze drukke periode echt goed gedaan.

Dan mijn paranymfen **Eric Thijssen** (pap) en **René Gilhuis** (Gil): voor mij was het wel duidelijk dat jullie dit moesten worden. De afgelopen jaren, tijdens mijn studie en promotie, hebben jullie altijd voor me klaar gestaan met jullie wijze raad en advies. Wat een goed gevoel om twee ervaren rotten in het vak te hebben die er altijd voor je zijn, ongeacht wat er goed (of slecht) gaat. Daarmee kan ik de (medische) wereld aan. Pap, al mijn hele leven roep jij dat dokter zijn het mooiste vak is. Wat er uiteraard toe leidde dat ik eerst 15 jaar van mijn leven heb gezegd dat ik dat niet ging doen. Maar blijkbaar lijk ik toch meer op je dan ik dacht, want het is vast geen toeval dat de cardiologie ook heel goed bij mij lijkt te passen. Dus vooruit, bij deze: je had gelijk. René, bij jou lag dit wat anders, na jaren van toenemende regelzucht in de zorg kwam jij juist met het advies om GEEN dokter te worden. Maar na mijn beslissing om dat toch te doen, vormde deze gemeenschappelijke interesse toch al snel een brug tussen ons. Tel daar een voorliefde voor golf en muziek bij op, en je hebt het samen erg gezellig! Hopelijk mag ik nog vele jaren profiteren van jullie uitgebreide ervaring en gewenste of ongewenste adviezen. Maar ik wil jullie nu alvast heel erg bedanken voor de nooit aflatende steun.

Marianne, bij jullie in Achel is het heerlijk thuiskomen. Jij staat altijd voor ons klaar, en zorgt dat het niemand aan iets ontbreekt. Bedankt voor alle jaren goede zorgen. Als je af en toe wat hulp nodig hebt om die mannen in huis tot bezinning te brengen, dan weet je me te vinden ;).

Sebas, wat geweldig om te zien hoe ook jij je nu in het studentenleven stort. Nadat wij jaren ons best hebben gedaan jou van alles te leren, begin jij ons nu steeds vaker te vertellen hoe de vork in de steel zit. Hopelijk worden de gesprekken en de wijn alleen maar beter, en kunnen we ervaringen blijven uitwisselen over onze totaal verschillende werelden en carrières.

Lieve **mam**, jouw rol als moeder zou ik bijna beschouwen als vanzelfsprekend. Je staat altijd voor me klaar op alle mogelijke manieren. Maar eigenlijk heb ik natuurlijk gewoon enorm geluk met zo'n geweldige moeder! Bedankt voor alles dat jij en pap hebben gedaan om mij en Evelijn te krijgen waar we nu zijn. Dat jullie zo hard hebben gewerkt aan een mooie toekomst is geen vanzelfsprekendheid, en ik ben er erg dankbaar voor. Hopelijk hebben we nog vele jaren samen als moeder en dochter, maar vooral ook als maatjes en gesprekspartners.

En tot slot: Lieve **Eef**, wat fijn en bijzonder om jou in mijn leven te hebben! Als iemand er iemand is die echt begrijpt hoe ik het leven zie en waarom, dan ben jij het wel. Samen hebben we immers al heel wat meegemaakt… Je bent altijd te porren voor een reis, borrel, lekker eten, of gewoon een goed gesprek onder het genot van een glas wijn. Laten we dat vooral vaak blijven doen!

FINANCIAL SUPPORT

Financial support for publication of this thesis was generously provided by:

Department of cardiology, Erasmus University Medical Center Rotterdam
Erasmus Universiteit Rotterdam
Chipsoft
Boehringer Ingelheim
Nederlandse hartstichting
Abbott, met dank aan Joost-Jan Waanders