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Screening of first-degree relatives of patients with an aortic aneurysm and/or bicuspid aortic valve: is it worthwhile?

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1. Abstract

Introduction: The estimated incidence of ascending aortic aneurysms is 2,8% in individuals over 50 years. A bicuspid aortic valve (BAV) is the most common hereditary congenital heart anomaly and an important risk factor for aneurysm development, which can ultimately lead to acute aortic syndromes. Timely management is key since urgent surgery has a poor prognosis. The aim of this study was to determine the yield of pro-active screening for thoracic aortic disease (TAD) in patients' relatives. **Materials and methods:** We retrospectively screened 526 probands attending the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases between May 2013 and June 2020 and their relatives. Inclusion criteria were the presence of a BAV or an ascending aortic/aortic root diameter over 40mm. Patients with incomplete medical records or poor transthoracic echocardiographic (TTE) images were excluded. Pedigree construction of the 526 probands resulted in a study population of 1689 patients. In total 121 families and 384 relatives accepted screening, consisting of thorough cardiac familial anamnesis, physical examination in search of extra-aortic identifiers (XAI) of connective tissue weakness and TTE. All predicted values were calculated using peer-reviewed formulas. Statistical analysis was done using IBM® SPSS® statistics version 27. **Results:** Of 1163 relatives included, 384 were screened. Main reasons of non-screening were non-proposal (56,1%) and refusal (15,5%). In 43,8% of screened families a new TAD-relative was found (mean 1,42 per family). A positive familial history (FH) for TAD did not result in significantly more diagnosed TAD in relatives ($p > 0,05$). Presence of XAI resulted in significantly greater aortic diameters in minors ($p < 0,05$). Z-scores of the largest aortic diameter did not differ significantly either with XAI presence in all age and gender groups ($p > 0,05$). An aortic diameter larger than the upper limit of normal was significantly more common when XAI were present in minors ($p < 0,05$). XAI presence was not pathognomonic for TAD or relatives at risk for TAD. **Conclusion:** Systematic screening of relatives of patients with a presumed isolated thoracic aortic aneurysm (TAA) recategorizes the aneurysm towards at least a familial thoracic aortic aneurysm and dissection (FTAAD) syndrome in a substantial proportion (43,8%). This yield is more pronounced as compared to previous reports. A known FH should not exclusively increase the level of suspicion for FTAAD, since pedigree screening of patients with presumed isolated TAA identified new cases and renders negative FHs into positive ones. Indexation of aortic diameters increases detection of patients at risk for development of a TAA later in life. The systematic assessment of XAI, especially in youngsters, increases the identification of patients at risk of TAD even more. Therefore, a snapshot screening at a young age should be followed by repeat imaging throughout the individual's lifetime. This study emphasizes the need for standardized screening programs for TAD-relatives in dedicated Aortic Centers. **Keywords:** TAA, BAV, FTAAD, screening, relatives.

2. Abbreviations

ULON: upper limit of normal

TTE: transthoracic echocardiography

CT: computed tomography

MRI: magnetic resonance imaging

TAD: thoracic aortic disease

BSA: body surface area

BAV: bicuspid aortic valve

FDR: first-degree relative

XAI: extra-aortic identifiers

SDR: second-degree relative

TDR: third-degree relative

>TDR: more-than-third-degree relative

TAV: tricuspid aortic valve

FTAAD: familial thoracic aortic aneurysm and dissection

FH: familial history

TAA: thoracic aortic aneurysm

3. Introduction

Aneurysms of the ascending aorta are defined as an abnormal dilatation by more than 50% of its normal predicted diameter.(1) The incidence of ascending aortic aneurysms is estimated at 2,8% in individuals aged over 50 years.(2) When left untreated, an aortic aneurysm will keep on growing and will ultimately lead to aortic dissection or rupture with imminent death of the patient. If urgent surgery can be done, the mortality rate is still higher compared to elective surgery.(3) Hence, the importance of a timely diagnosis and follow-up.

The expected diameter of the ascending aorta and its upper limit of normal (ULON) can be calculated based on age, sex, height and weight using established formulas and nomograms.(4-6) Alternatively, the diameter of an ascending aorta can be presented by using z-scores.(5) Whatever the age, sex, height or weight of the patient, a diameter of more than 40mm is always considered abnormally dilated and warrants investigation and follow-up.(7, 8)

Transthoracic echocardiography (TTE) is the primary method to diagnose an ascending aortic aneurysm. Incidentally, the diagnosis is made on a computed tomography (CT) scan or on magnetic resonance imaging (MRI), often for another indication. Once diagnosed, the extend of the aortic involvement is analyzed by a total aortic CT scan.(9)

The treatment of an ascending aortic aneurysm and therefore preventing aortic dissection, is surgical replacement of the involved segments.(10) Elective surgery has a lower mortality rate compared to urgent surgery, indicated when an aortic dissection occurs. In high-volume aortic surgery centers, the operative mortality of elective surgery is below 2,5%.(3) When comparing to the general population, health-related quality of life in patients with thoracic aortic disease (TAD) is lower when treatment is conservative but reaches similar levels after elective surgery.(11) Medium-term survival on the other hand is slightly worse than in the general population but significantly higher than in non-operated patients. In the present era, surgical mortality has declined for elective surgery while, despite advances in peri-operative care, the mortality of surgery performed for aortic dissection did not.(12)

The indication for aortic surgery is largely based on the absolute diameter of the aneurysm. Briefly, cut-off diameters are 55mm in normal circumstances or 50mm or lower in patients with genetically triggered aneurysms, syndromic aneurysms, presence of risk factors (*i.e.*, hypertension, familial history of aortic dissection, etc.) or when the possibility of valve preservation is present.(7, 13) However, in recent years, the observation was made that 97% of the aortic dissections occurred at

diameters below 55mm and 92% with a diameter below 50mm.(14) Explanation of these observations is twofold, firstly, because the guidelines are based on the diameter of already dissected aortas (the diameter of the aorta increases with the occurrence of an aortic dissection) and, secondly, because aortic aneurysms at high risk for dissection are not identified based on crude diameter solely. In order to account for this second argument, in recent years the aortic diameter is indexed to body surface area (BSA) or height of the patient (Aortic Size Index and Aortic Ratio). Furthermore, there is also an influence of the presence of a bicuspid aortic valve (BAV) lowering the threshold for elective surgery. Guidelines have been varying throughout the years regarding the suggested diameter for which surgery is indicated and the influence of risk factors on the surgical indication.(1, 3, 14, 15)

Figure 1: Graph representing normal aortic diameters according to the body surface area (BSA). In this example, an aortic diameter of 4,7cm is clearly above expected aortic diameters for this BSA, regardless of gender.(16)

Aortic aneurysms can be categorized into three subtypes: syndromic aortic aneurysms, non-syndromic familial aneurysms and isolated aortic aneurysms.(17-19) When the aneurysm is genetically triggered and is part of a syndrome with other extra-aortic manifestations of the genetic mutation, it is a syndromic aortic aneurysm. Examples are Marfan syndrome, Loeys-Dietz syndrome and Ehlers-Danlos syndrome.(18) Non-syndromic familial aneurysms are a category that includes aneurysms with familial occurrence but without known syndrome-associated manifestations. Although most familial thoracic aortic aneurysms are not identified as being familial due to the lacked

notion of them being familial, it is estimated in the literature that in 20% of these cases, a pathogenic mutation in one of the 20-some known causative genes is responsible.(10, 20) Whenever no causative genetic mutation is diagnosed this is due to the fact the responsible genes are not identified yet. Most non-syndromic aneurysms are inherited in an autosomal dominant matter with incomplete penetrance. As a consequence, theoretically 50% of the offspring inherits the specific mutation while incomplete clinical penetration (mainly in females) is responsible for the phenotypic manifestation of aortic aneurysms in less than 50% of the offspring.(17) Finally, isolated aortic aneurysms are found in patients with an ascending aortic aneurysm with apparently no familial history of aortic aneurysms or other extra-aortic manifestation.

In recent years, there seems to exist an overlap between isolated aortic aneurysms and familial non-syndromic aneurysms on the one hand and between familial non-syndromic aneurysms and syndromic aneurysms on the other hand. In the former, omitting familial anamnesis and pedigree analysis is mostly responsible. The latter is due to the fact that a substantial number of aneurysms caused by a syndrome-specific genetic mutation, do not manifest the characteristic extra-aortic syndromic features or more subtle extra-aortic manifestations are not looked for. Consequently, they are not recognized as such. They are referred to as *formes frustes*. As such, many aneurysms are misclassified.(10, 21, 22)

In terms of guidelines and recommendations, screening relatives of aortic aneurysm patients is attributed a low level of evidence in the American and European cardiovascular guidelines except when a BAV is present, in which case screening first-degree relatives (FDR) carries a class I recommendation.(7, 13) However, in clinical practice, screening is often not performed.

A subset of FDRs at particular risk are children of patients with an aortic aneurysm. They are often minors or young adults and, when eventually screened, they do not manifest aortic pathology. In these cases, the presence of extra-aortic manifestations and calculating the z-score becomes very important, as to identify patients at risk for developing an aortic aneurysm later in life. If only screened superficially with TTE without calculating z-scores or actively searching for XAI, these patients will remain undetected throughout their next generation.(8, 17)

When a patient presents for screening, besides measuring the different parameters of the aorta and identifying the cuspidity of the aortic valve, three aspects are of paramount importance. Firstly, the familial history must be gauged for the presence of congenital aortic valve abnormalities (e.g., BAV), the presence of thoracic aortic, peripheral or cerebral aneurysms, surgery for the aortic and mitral

valve and/or aneurysms, proven aortic dissection and sudden death of possible cardiac origin.(8) Secondly, during anamnesis, emphasis should be on seemingly unrelated comorbidities which, however, can be silent witnesses of generalized connective tissue disease and are frequently associated with thoracic aortic aneurysms. These are, among others, spontaneous joint dislocations, pes planus, ocular lens dislocations, extreme myopia, history of cerebral or other peripheral aneurysms, herniae (e.g., inguinal, umbilical, gastric, discal), renal cysts, varicose veins and hemorrhoids. Thirdly, a general physical examination must be performed. Hereby, certain manifestations deserve special attention because of their high likelihood of coexistence with thoracic aortic aneurysms: hyperflexibility and hyper-extensibility in the joints (e.g., fingers, elbows, knees) and skeletal malformations (e.g. scoliosis, pectus excavatum/carinatum). In order to stratify, to a certain extent, the hyperflexibility, three clinical tests are performed: the touch thumb to forearm sign; the Steinberg test, *i.e.*, the distal phalanx of the adducted thumb extends beyond the ulnar border of the palm; and the Walker-Murdoch test, *i.e.*, the thumb and the fifth finger overlap when wrapped around the contralateral wrist.(23)

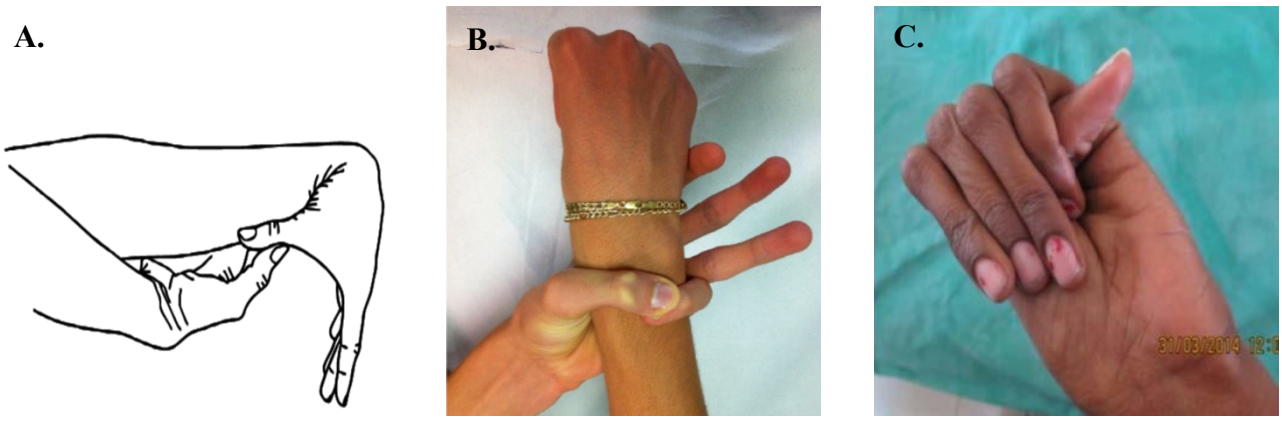

Figure 2: A. Touch thumb to forearm sign.(24) B. Walker-Murdoch sign.(25) C. Steinberg sign.(26)

These comorbidities and clinical signs described above are called extra-aortic identifiers (XAI). Specifically, the tests assessing joint hypermobility are established clinical signs in patients with syndromic aneurysms, like Marfan syndrome and Ehlers-Danlos syndrome. The importance of these XAI lies in the fact that they might increase suspiciousness in patients with only slight dilatation of the ascending aorta or children who did not (yet) develop a dilatation of their aorta. Furthermore, the presence of XAI in relatives might reveal a possible familial inheritance form of TAD.(27)

As mentioned above, genetically triggered ascending aortic aneurysms have an increased risk for dissection. They are identified by analyzing the familial history for aortic aneurysm and dissection. Therefore, the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases deployed

a pro-active screening program. Every proband presenting with an aortic aneurysm or dilatation and/or a BAV is questioned thoroughly for a positive familial history, an extensive pedigree is reconstructed, and every patient is examined extensively in search for XAI. We specifically adopted the attitude to assess systematically and bilaterally the three tests assessing joint hypermobility, described above. These clinical tests are "borrowed" from syndromic aneurysm patients and applied in patients with presumed isolated ascending aortic aneurysms and in their relatives. We hypothesized these tests might have an orienting potential as to whether these signs might add some arguments of suspiciousness to these patients and their relatives. Every screened patient undergoes an extensive TTE measuring the four classical aortic diameters, *i.e.*, the aortic annulus, the sinuses of Valsalva, the sinotubular junction and the tubular ascending aorta, looking for aortic coarctation, assessing aortic valve cuspidity, mitral valve involvement and other left sided congenital vessel malformations.(28) As such patients are categorized as being diagnosed with an aortic dilatation and/or BAV, suspicious because of abnormal z-scores, suspicious because of manifest XAI or indeterminate. Every screened patient is invited for a follow-up TTE of which the interval is determined by the level of suspicion, *i.e.*, after one, three, five or 10 years.

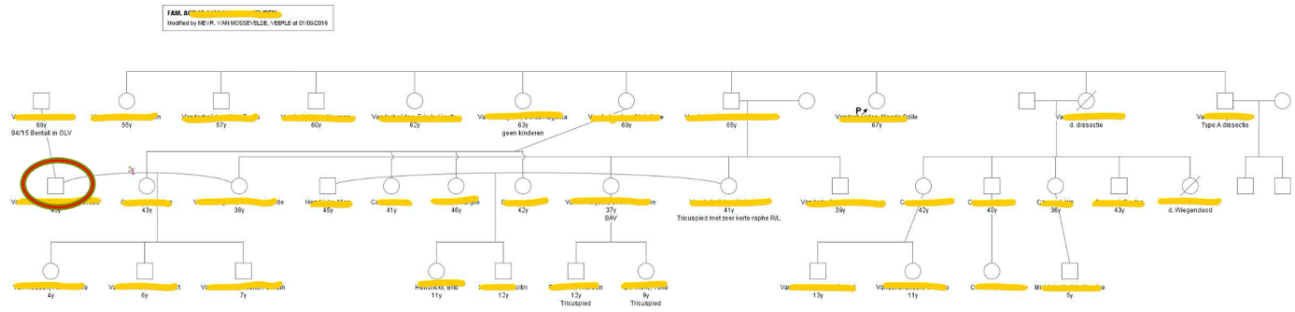

Figure 3: Reconstruction of an extensive pedigree by the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases. Note: two families with thoracic aortic disease meet.

In the present study, we aimed to analyze whether this strategy of proactive screening relatives of patients with an ascending aortic aneurysm indeed identifies new cases of aortic dilatation, aneurysm or BAV. We also analyze if patients at potential risk are identified, for which interval imaging is indicated as to rule out future development of aortic dilatation, based on the actual ascending aortic diameter and/or the presence of XAI. In other words, we examine whether active screening of FDRs and even second-degree relatives (SDR) has a yield that is important enough to underscore the importance of screening.

4. Materials and methods

For this retrospective study, patients in the working list of the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases were reviewed. All patients that had undergone a TTE between May 2013 and June 2020 were retained for further retrospective analysis. Definitive inclusion depended on the presence of TAD defined as demonstrating an aortic root/ascending aortic aneurysm, *i.e.* an aortic diameter over 40mm, or the presence of a BAV. No exclusion criteria based an age, sex or ethnicity were defined. When TTE results were unavailable in the electronic medical record or were judged to be of poor quality by the echocardiographist, inclusion criteria were considered not met and the patient was not retained. Also, an incomplete medical record was an exclusion criterium. These selection criteria led to a total of 526 probands included in this study.

In the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases, all probands underwent a thorough familial anamnesis as well as a physical examination, beyond cardiac, as to identify the presence of XAI (Steinberg sign, Walker-Murdoch sign and pathologies like gastro-intestinal reflux disease (GERD), cerebral aneurysms, osteo-arthritis). Presence of these clinical markers led to increased urge to perform screening of FDRs, SDRs and sometimes third-degree relatives (TDR), including children. Not every relative was screened however, as every person asked could refuse. Reasons for non-screening were documented.

Permission to retrospectively review all selected probands was granted by the UZ Brussels's Ethical Committee (file number 2020-303). This analysis consisted in systematically collecting the following data in the patients' electronic medical records: age, gender, height, weight, aortic valve cuspidity, hypertension values, anti-hypertensive medication if applicable, other cardiac and vascular abnormalities, presence of XAI for aortic disease, genetic screening results if performed and familial history for cardiac disease. Insight into the genetic charts was approved by the UZ Brussels's Department of Genetics.

If depicted in the genetic pedigree, FDRs, SDRs, TDRs and more-than-TDRs (>TDR) were included in the study and screened for the same parameters as described for the probands. As such, 1689 patients were reviewed.

In the medical records, age, gender, weight, height, the aortic root diameter at the sinus of Valsalva level and the ascending aorta diameter of every patient was collected in order to calculate the BSA, the z-score of the largest aortic diameter, the expected aortic diameter and the ULON of the aortic

diameter. These parameters were calculated using peer-reviewed formulas. (i) BSA following the Dubois and Dubois method where BSA = $0.007184 \times H^{0,725} \times W^{0,425}$ [m^2]; with H the height in cm, W the weight in kg.(4) (ii) The z-score of the largest aortic diameter was calculated using the online z-score calculation tool of the Marfan Foundation based on Devereux *et al.* formula approved by van Kimmenade *et al.* where Z = (measured diameter – predicted AD)/SD with SD the standard deviation of 0.261 cm, AD the aortic diameter in cm and the predicted AD for BSA = 2.423 + (age × 0.009) + (BSA × 0.461) − (sex × 0.267), with sex = 1 when male and 2 when female.(4, 5) (iii) The expected aortic diameter = 2,423 + (age x 0.009) + (BSA x 0.461) - (sex x 0,267), with age in years, BSA in m^2 and sex = 1 when male and 2 when female.(4) (iv) The ULON of the thoracic aorta diameter, ULON = 31 + 0,16 x age.(6)

All statistical analysis was done using IBM® SPSS® statistics version 27. Univariate descriptive statistics was used when considering one variable and bivariate descriptive statistics when considering two variables. Multivariate descriptive statistics were used when considering three or more variables.

5. Results

In this study, 526 probands, of which 10 were children under 18 years, were screened which led to an equal number of included families. There were 408 male and 118 female probands. The proband was defined as the first family member known to have an aortic aneurysm or a BAV and was therefore not always the first patient consulting the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases. In total, 1163 relatives were identified by pedigree analysis. With probands included, this led to a study population of 1689 patients; 1011 were male and 678 were female. Of these 1163 relatives, 384 were screened by the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases and 779 were not. Reasons for non-screening were documented. In 56,1% further familial screening was not (yet) proposed to the proband. In 15,5%, screening did not happen because of a lack of consent for no specific reason. In 15,1%, relatives were considered too young for screening in order to have a normal childhood. In 4,1%, relatives couldn’t be screened because they lived in remote locations. In 3,4%, relatives were too old or had a limited life expectancy. In 2,6%, relatives were dead. In 1,8%, the proband refused contacting family members due to the lack of family contact. Finally, 1,4% where young adults waiting for socio-economic stability before screening.

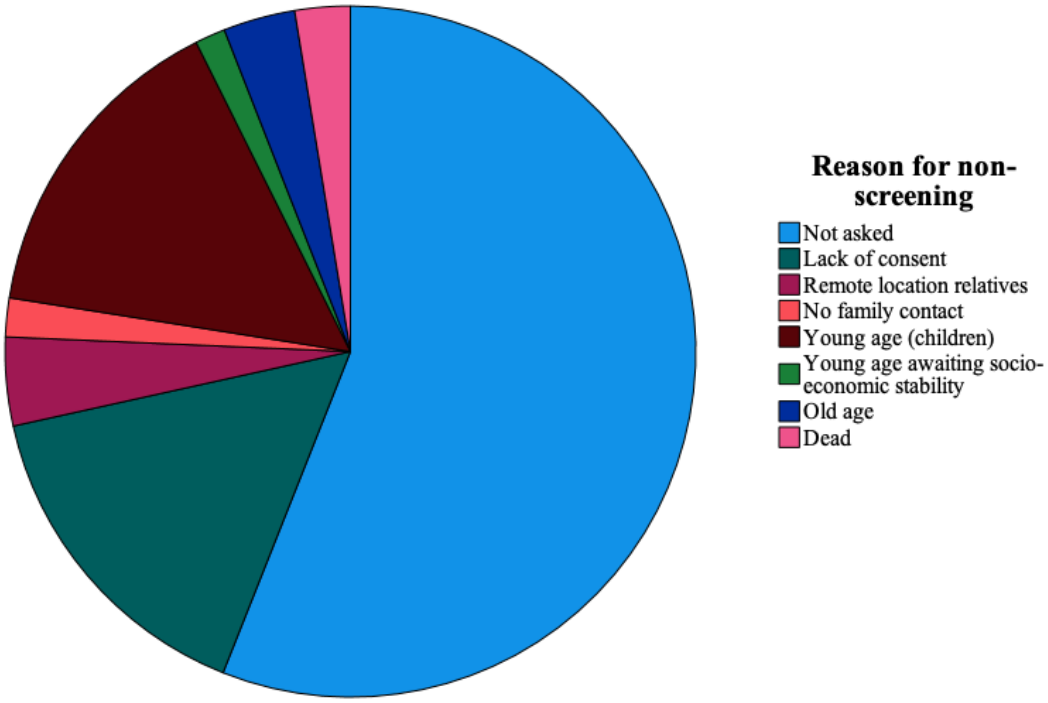

Figure 4: Pie chart representing the reasons for non-screening in probands' relatives.

Probands were referred to the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases mostly by a cardiologist. This accounted for 88,0%. Referral was also done by the general practitioner in 4,6%, by a member of the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases in 2,7% and by a geneticist in 0,7%. Self-referral or referral by other patients accounted for 4%.

The reasons for initial presentation of probands were also documented. Mostly, probands presented themselves with anxiousness about phenotypic traits of TAD, this accounted for 47,6%. Other reasons for initial presentation were probands seeking a second opinion for the management of a known aortic aneurysm or BAV. This was the case in 29,4%. A familial history of sudden death or aortic (valve) surgery accounted for 21,9%. Finally, referral by a geneticist because of positive genetic testing for or suspicion of diseases leading to cardiovascular events accounted for 1,1%.

In total, 298 FDRs, 61 SDRs, 16 TDRs and 9 >TDRs were identified, of which 17,2% were aged under 18 years. The mean number of relatives per family was 3,14 FDRs, 1,28 SDRs and 0,27 TDRs. These 384 screened relatives were used for all further analyses.

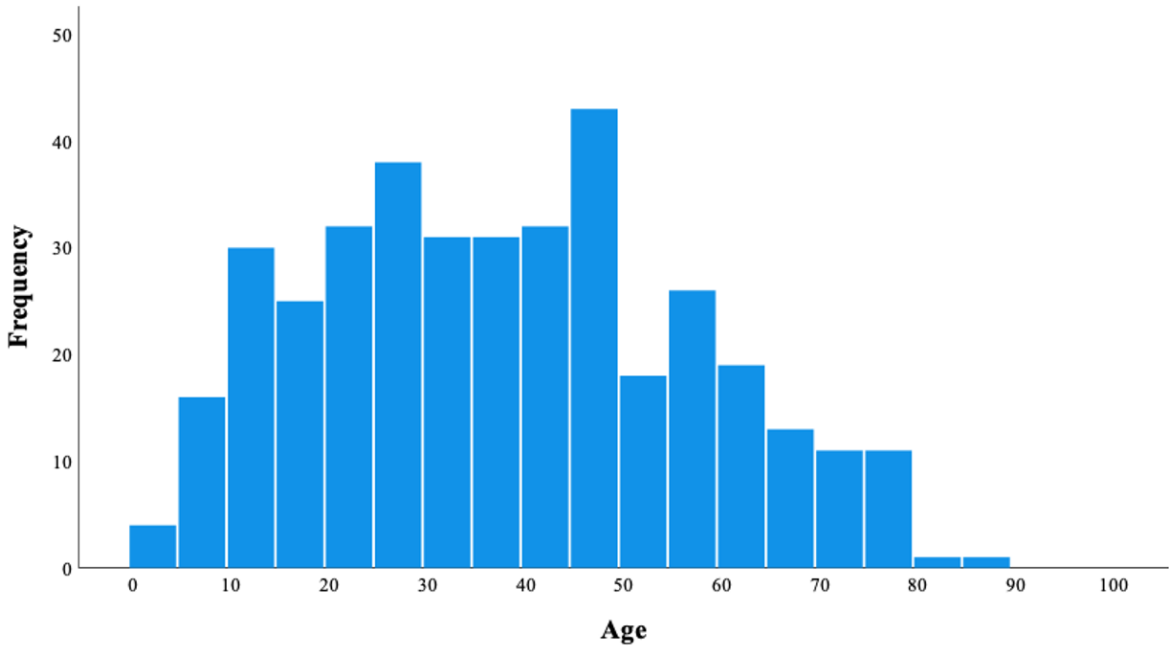

Figure 5: Histogram representing the age distribution of all 384 screened relatives. Mean age was 37,74 (Std. Dev. = 19,046).

When screening was performed, it resulted in a negative yield, defined by a negative family history, normal TTE and no clinical suspicion of developing an aortic aneurysm in every relative, in 56,2% of screened families. In these families, the reason for initial screening of the proband was anxiousness about phenotypic traits of TAD in 58,6%, for a second opinion in 27,4%, 10,8% after referral by the cardiologist or general practitioner because of a positive familial history in earlier generations. Referral by a geneticist accounted for 3,2%. In 43,8% of the screened families, at least one extra affected relative, *i.e.*, relatives with proven aortic aneurysm and/or BAV or high clinical suspicion requiring follow-up within one year was diagnosed. Within the families with at least one extra affected relative, there were on average 1,4237 affected relatives. The trigger for screening of the proband in these families was anxiousness about phenotypic traits of TAD in 42,7%, referral by a cardiologist or a general practitioner because of a positive familial history for TAD in earlier generations in 31,5%, 24,7% was for a second opinion and 1,1% after referral by a geneticist.

In the group of screened relatives, without distinction of the degree of relationship to the proband, 94 of the 384 relatives, *i.e.*, 24,5%, proved to have an aortic diameter above the ULON and 79 of the 384 relatives, *i.e.,* 20,6%, a z-score over two, meaning that the diameter is greater than in the normal population, therefore being at risk for developing an aortic aneurysm. This represents the number of patients that would have gone undetected if no screening was offered. When assuming that non-syndromic familial aortic aneurysms are characterized by an autosomal dominant inheritance pattern and a penetration rate of developing an aneurysm of 100%, 50% of the identified FDRs should have

been diagnosed with a dilated aorta. There were 298 FDRs screened, meaning that, theoretically, 149 FDRs should have been diagnosed with a dilated aorta. However, only 74 FDRs were diagnosed with a dilated aorta, defined as an aortic diameter greater than the ULON, or an aortic aneurysm, defined as an aortic diameter over 40mm, *i.e.,* 24,8% of screened FDRs.

	Probands	**Screened families**	**Screened relatives**	**Relatives +**	**%**
Total	526	121	384	83	21,6
FDR	-	-	298	66	22,1
SDR	-	-	61	11	18,0
TDR	-	-	16	4	25,0
>TDR	-	-	9	2	22,2

Table 1: Table representing the yield of thoracic aortic disease in screened relatives. FDR = first-degree relative, SDR = second-degree relative, TDR = third-degree relative, >TDR = more-than-third-degree relative, relatives + = screened relatives with aortic aneurysm and/or bicuspid aortic valve, % = the percentage of relatives presenting with thoracic aortic disease.

5.1. Influence of familial history

In families with a positive familial history for TAD, *i.e.*, aortic aneurysm, aortic surgery, sudden cardiac death, aortic dissection or BAV, the probability of diagnosing a second family member with an aortic aneurysm is 19,8%. Out of the 172 relatives of a proband with positive familial history at presentation, 34 presented an aortic aneurysm. In 44 relatives, the measured aortic diameter was greater than the calculated ULON, *i.e.*, 25,6%. Of all these relatives from a proband with positive familial history, the aneurysm diameter was in 67,1% between 40 and 44,9mm, in 23,3% between 45 and 49,9mm and in 9,6% a diameter over 50mm. Of these newly diagnosed patients, 84,9% are FDRs, 8,3% SDRs, 4,1% TDRs and 2,7% >TDRs. In 13 of the 172 relatives, a BAV was found. This is 7,6% of screened relatives from probands with positive familial history. In 64,3% it was a FDR, a SDR in 28,6% and a TDR in 7,1%.

In families without familial history of TAD, 40 of 212 relatives, *i.e.*, 18,9%, of relatives presented an aortic aneurysm. These were in 97,6% FDRs, in 2,4% SDRs, in 0% TDRs and in 0% >TDRs. The aortic diameter was between 40 and 44,9mm in 70,7%, between 45 and 49,9mm in 22,0% and over 50mm in 7,3%. In 50 relatives of probands without positive familial history, the measured aortic diameter was greater than the calculated ULON, *i.e.*, in 23,6%. Also, in 15 of the 212 relatives, *i.e.*, 7,1%, a BAV was found. This was in 87,5% a FDR and in 12,5% a SDR.

The difference of relatives with an aortic aneurysm between the groups with versus without positive familial history for TAD in the proband during initial presentation, is not significant (t_{381} = -0,199; p = 0,842). The difference of BAVs found in families with a proband with positive versus negative familial history for TAD is not significant (t_{381} = -0,168; p = 0,867) either.

5.2. Bicuspid aortic valve

After screening of all 384 relatives, a total of 28 relatives with a BAV were identified. This represents 7,3% of all screened relatives. There were 158 probands with a BAV. Of these 158 probands, further screening of relatives occurred in 77 families, this represents the BAV-families. In 25 of these BAV-families, *i.e.*, 28,7%, at least one relative with a BAV was identified. These BAVs were diagnosed for 77,8% in FDRs, 22,2% in SDRs and 0% in TDRs. Also, in 25,4% of BAV-families, screening revealed the presence of at least one relative with an aortic aneurysm.

When the trigger for screening was the presence of an aortic aneurysm in a proband with a tricuspid aortic valve (TAV), screening diagnosed 9 new cases of BAV. This means that a new relative with a BAV is discovered in 7 of 63 aneurysm-families, *i.e.*, in 11,1%.

Specifically, for BAV-initiated screening, a new TAD-relative, defined as a relative presenting an aortic aneurysm and/or a BAV, was discovered in 7 of 17 screened families with a proband with a BAV without an aortic aneurysm, *i.e.*, 41,2%. For aneurysm-initiated screening, a new TAD-relative was discovered in 31 of the 63 screened families, *i.e.*, 49,2%. When the proband presented both a BAV and an aortic aneurysm, TAD in relatives occurred in 15 out of the 42 screened families, *i.e.*, 35,7%. This leads to recategorization of 53 families from a seemingly isolated aortic aneurysm to at least a non-syndromic familial thoracic aortic disease. This represents recategorization of 43,8% of the 121 families where screening by the Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases occurred.

5.3. Influence of Extra-Aortic Identifiers

The present manuscript focuses on two types of XAI. Firstly, clinical signs of generalized connective tissue weakness. Secondly, skeletal involvement, mainly pectus deformities. In 32,9% of screened relatives, at least one XAI was discovered. No distinction between the two types of XAI was made for these analyses. When analyzing aortic diameters in relatives without XAI, the mean diameter was 2,20cm, 3,62cm, 4,41cm and 4,64cm for men and 2,23cm, 3,05cm, 3,79cm and 4,42cm for women

in the age groups under 18, 18 to 39, 40 to 59 and over 60 years, respectively. In contrast, in relatives with the presence of at least one XAI, mean aortic diameters were 2,72cm, 3,71cm, 4,50cm and 4,56cm for men and 2,66cm, 3,25cm, 3,85cm and 4,60cm for women in the age groups under 18, 18 to 39, 40 to 59 and over 60 years old, respectively.

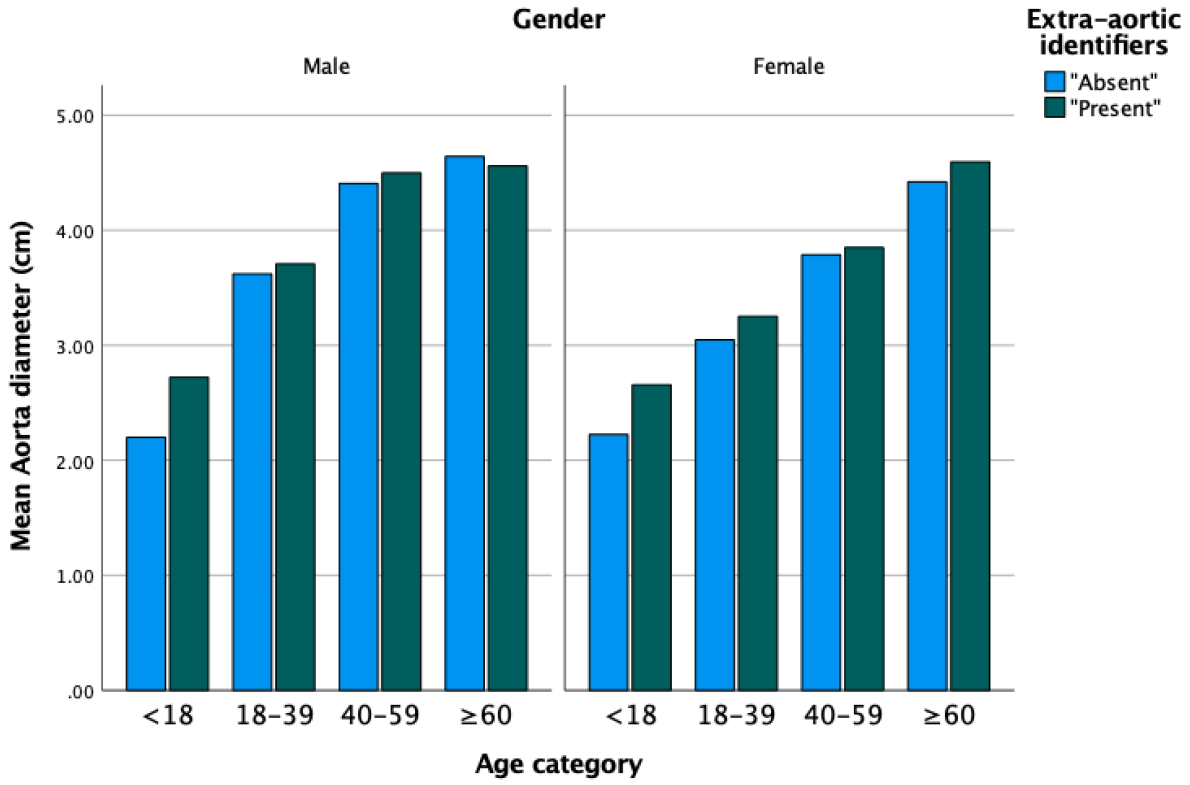

Figure 6: Histogram representing the difference of the mean ascending aortic diameter (in cm) in different gender and age groups according to the presence or absence of extra-aortic identifiers.

The difference of the mean aortic diameter between the groups of positive and absent XAI is significant in men and women under 18 (t_{36} = -3,288; p = 0,002; t_{36} = -3,243; p = 0,003, respectively). It is not significant in all other age groups. In men between 18 and 39 (t_{97} = -0,769; p = 0,444), between 40 and 59 (t_{190} = -1,014; p = 0,312) and over 60 (t_{259} = 1,156; p = 0,249). In women between 18 and 39 (t_{79} = -1,747; p = 0,084), between 40 and 59 (t_{95} = -0,375; p = 0,708) and over 60 (t_{97} = -0,915; p = 0,362). A confidence interval of 95% was used.

The mean z-score of the largest aortic diameter was 0,64, 1,18, 3,27 and 3,57 for men and 0,42, 0,37, 2,46 and 4,10 for women in relatives without the presence of XAI and 1,13, 1,55, 3,48 and 3,28 for men and 0,90, 1,11, 2,66 and 4,55 for women in relatives with the presence of XAI in the age groups under 18, 18 to 39, 40 to 59 and over 60 years old, respectively.

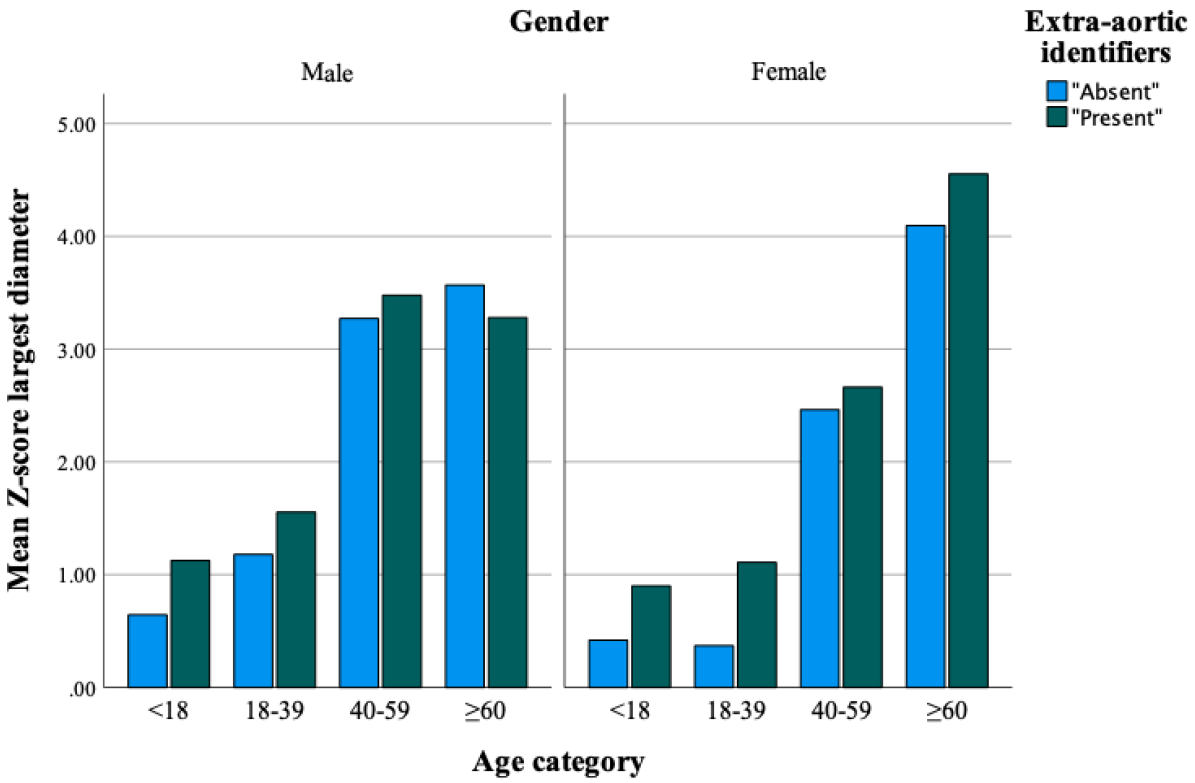

Figure 7: Histogram representing the difference of the mean z-score of the largest ascending aortic diameter in different gender and age groups according to the presence or absence of extra-aortic identifiers.

The difference of the mean z-score of the largest aortic diameter between the groups of positive and absent XAI was not significant. In men under 18 (t_{19} = -1,152; p = 0,263), between 18 and 39 (t_{98} = -0,878; p = 0,382), between 40 and 59 (t_{190} = -0,600; p = 0,549) and over 60 (t_{259} = 1,080; p = 0,281). In women under 18 (t_{36} = -1,010; p = 0,319), between 18 and 39 (t_{80} = -1,838; p = 0,070), between 40 and 59 (t_{95} = -0,308; p = 0,758) and over 60 (t_{97} = -0,628; p = 0,531). A confidence interval of 95% was used.

When the XAI were positive, in men, the aortic diameter was above the ULON in 7,1% when aged under 18, 57,5% when aged 18 to 39, 87,3% when aged 40 to 59 and 80,0% over 60 years old. In women this was the case in 6,3% when aged under 18, 20,7% when aged 18 to 39, 37,5% when aged 40 to 59 and 71,4% over 60 years old. In contrary, when the XAI were absent, in men, the aortic diameter was above the ULON in 0% when aged under 18, 45,8% when aged 18 to 39, 82,5% when aged 40 to 59 and 80,0% over 60 years old. In women this was the case in 0% when aged under 18, 7,7% when aged 18 to 39, 33,8% when aged 40 to 59 and 60,3% over 60 years old.

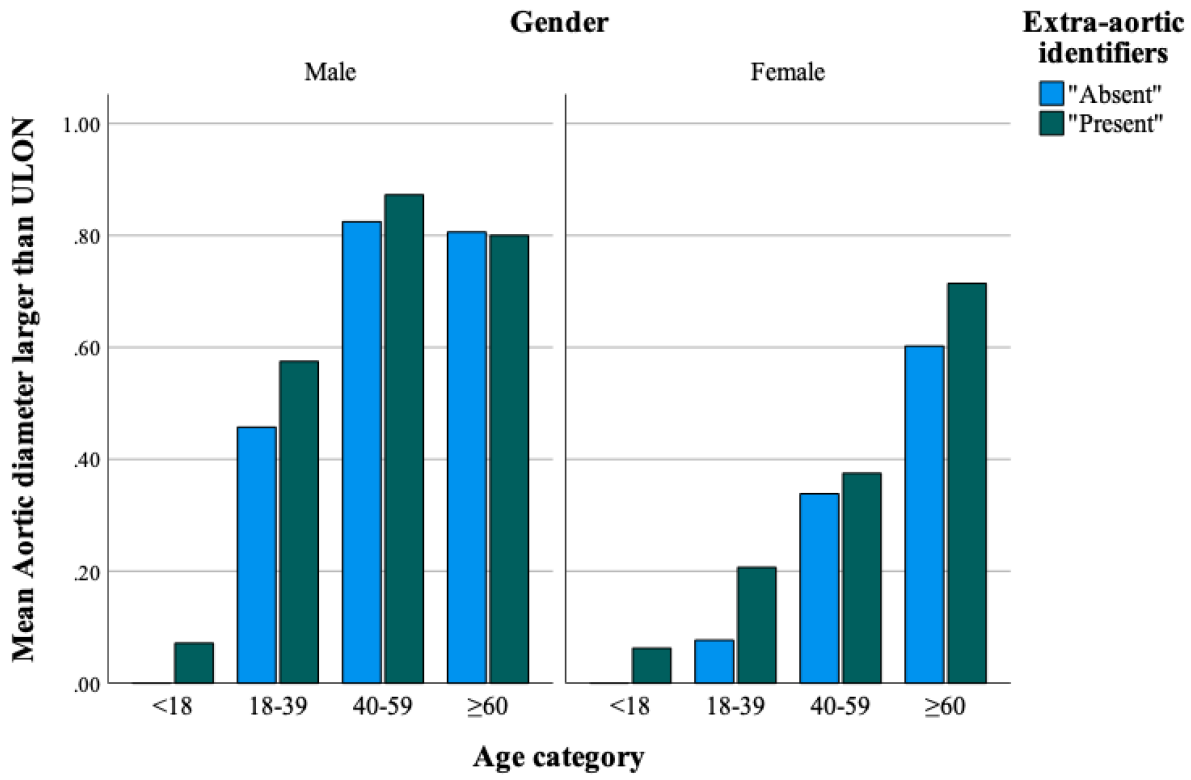

Figure 8: Histogram representing the difference in percentage of the ascending aortic diameter being larger than the upper limit of normal of the ascending aorta in different gender and age groups according to the presence or absence of extra-aortic identifiers.

The difference of the mean aortic diameter being larger than the ULON of the aortic diameter between the groups of positive and absent XAI is significant in men and women under 18 (t_{36} = -3,324; p = 0,002 and t_{36} = -3,022; p = 0,005, respectively). It is not significant in all other age groups. In men between 18 and 39 (t_{97} = -1,081; p = 0,282), between 40 and 59 (t_{54} = -1,103; p = 0,275), over 60 (t_{259} = 1,149; p = 0,252). In women between 18 and 39 (t_{79} = -1,970; p = 0,052), between 40 and 59 (t_{95} = -0,367; p = 0,715) and over 60 (t_{97} = -0,579; p = 0,564). A confidence interval of 95% was used. In women between 18 and 39, the difference would have been significant if a confidence interval of 90% was used.

Relatives were categorized as being suspicious for developing an aortic aneurysm when the aortic diameter was below 40mm but greater than the ULON. This was the case in 11 of 127 relatives with positive XAI, *i.e.*, 8,7%, and in 15 of 257 relatives, *i.e.*, in 5,8%, if XAI were absent. The percentage of relatives that presented an aortic diameter above the ULON but below 40mm did not differ significantly by the presence of XAI as shows a chi-square test of independence, $X^2(1, N = 384)$ = 1,074, p = 0,3.

Analysis of screening results in children shows that there were 66 children under 18 years old screened. Of these 66 children, only one had an aortic diameter greater than the ULON. In this child, XAI were found to be positive. However, nine children had a z-score over two. This is 13,6% of all screened children. Of these nine children, only two did not present XAI.

Of the 384 screened relatives, 290 relatives present with an aortic diameter below the ULON. Of these 290 relatives, 93 are positive for XAI, *i.e.*, 32,1% (37 male and 56 female). In 29,0%, relatives are aged under 18 years old (12 male and 15 female), in 38,7% between 18 and 39 (14 male and 22 female), in 23,7% between 40 and 59 (6 male and 16 female) and in 8,6% over 60 (5 male and 3 female).

Of the 526 families, genetic screening occurred in 64 families. This revealed to be positive in 24 families, *i.e.*, 37,5%. Of these families, 12 had mutations in the *FBN1* gene, two in the *ACTA2*, *PKD1* and *TGFBR1* genes and one in the *MYH11*, *SMAD3*, *TBX3*, *TGFB2*, *TGFBR2* and *LDB3* genes.

5.4. Illustrative case report

In one family, the proband presented with an aortic aneurysm of 4,7cm and a positive familial history. Screening of his relatives led to diagnosing two FDRs with an aortic aneurysm of 4,8cm and 4,7cm. The other five screened relatives (3 FDRs and 2 SDRs) had seemingly normal aortic sizes. However, one FDR (FDR-3, aged 28) presented an aortic diameter greater than the ULON and a z-score over two. Another FDR (FDR-4, aged 59) presented a z-score over two with an aortic diameter below the ULON. In this family, screening led to two newly diagnosed affected relatives and two relatives suspicious for developing an aortic aneurysm. The other 11 known relatives were not screened yet. Genetic screening took place and a *FBN1* gene mutation was discovered in the proband. Further screening happened in the two affected relatives. Only in one an *FBN1* gene mutation was found. When analyzing both aneurysms, the FDR without genetic mutation presented an aneurysm in the ascending aorta whereas the other affected FDR and the proband presented an aneurysm of the aortic root. Genetic screening for a *FBN1* gene mutation also occurred in the two SDRs and the FDR-4. All three relatives presented the mutation. No genetic screening in the other relatives happened.

6. Discussion

The distinct categorization of ascending aortic aneurysms into syndromic, non-syndromic familial and isolated aneurysms is challenged in recent years. Several factors are responsible for this. Syndromic aneurysms often present with incomplete penetrance of extra-aortic manifestations. As such, they are often classified as isolated aneurysms. On the other hand, most presumed isolated ascending aortic aneurysms are diagnosed, followed and treated without considering the possibility of having a familial occurrence. In many cases, no familial history is taken and no pedigree analysis is performed. The strongest recommendation in the literature is echocardiographic screening of FDRs of patients with a BAV (Class I recommendation). Screening of relatives of patients with ascending aortic aneurysms in the setting of a TAV is less strongly recommended and mainly addresses genetic screening.(7) Imaging of FDRs of patients with thoracic aortic aneurysms receives a Class I, LOE B recommendation in the 2010 ACC/AHA Guidelines addressing TAD.(13) These recommendations are unfortunately not widely applied. Consequently, many of the ascending aortic aneurysms are being missed as being familial thoracic aortic aneurysm and dissection (FTAAD) disease. On the other hand, when looking carefully, patients with presumed isolated ascending aortic aneurysms share some clinical characteristics with patients with syndromic aneurysms, albeit often subtle. These clinical signs, together with pedigree analysis, might draw attention to the possibility of a familial or even syndromic TAAD. Above that, an increasing number of genetic mutations responsible for ascending aortic aneurysms is found. Whenever genetic testing is performed, despite often incomplete penetrance of syndromic features, this results in the return of an increasing number of patients reallocated as being syndromic. When screening of relatives does take place, it often concerns offspring of a younger age in which the TTE returns as being normal. However, when one calculates the expected diameter, z-scores and the ULON, many of these normal TTEs prove to be not as normal as communicated. These presumed but incorrect normal TTE findings result in reassurance of the patients, which is mostly permanent for the rest of their life. In case they do develop an aneurysm later in life and present with an aortic emergency, this historical reassurance might mislead the rapid diagnosis of aortic dissection.

The familial pattern of non-syndromic ascending aortic aneurysms is known since the late 1990s. However, standardized systematic screening of relatives is not uniformly executed. The Brussels Center for Aortic and Cardiovascular Connective Tissue Diseases gradually implemented a pro-active proband-initiated screening, offered to FDRs and SDRs of patients with an ascending aortic aneurysm and patients with a BAV. Often, relatives located further away in the pedigree (TDRs and more) present themselves for screening, often triggered by anxiety regarding their familial history. The

patient is thoroughly questioned for a positive familial history. Subsequently, clinical testing for joint hypermobility and pectus deformities are “borrowed” from syndromic aortic aneurysm patients. Finally, a dedicated TTE is performed measuring aortic diameters, assessing valve cuspidity and excluding any other congenital or acquired cardiac structured abnormalities.

The present manuscript uses the combination of familial history, joint hypermobility and pectus deformities and TTE to analyze whether, firstly, this results in identification of new diagnoses of ascending aortic aneurysms and/or BAVs in relatives of patients with an ascending aortic aneurysm and, secondly, relatives at risk for aneurysm development are identified and brought on the radar for longitudinal follow-up. Consequently, this study also identifies the number of patients reallocated from isolated ascending aortic aneurysm to FTAAD or even syndromic aneurysms. Analyzing the yield of screening of relatives of patients with an ascending aortic aneurysm and/or a BAV, highlights the clinical relevance of structured screening. Important for the interpretation of this interim analysis is the fact that screening is an ongoing process, which means that many relatives of the probands analyzed still need to be screened. Often the diagnosis in the proband is recent with attention temporarily centered on the proband before screening of their relatives is addressed. Also, probands are often not ready yet to share their diagnosis fully with their relatives or hesitate to involve them.

In 2016, Elefteriades *et al.*(23) reported several clinical features being *associates* of TAD. Among them are a positive familial history, a positive thumb-palm sign, renal cysts, intracranial aneurysms, aortic arch anomalies, temporal arteritis, *etc*. Identification of these might trigger suspicion for an ascending aortic aneurysm. He introduced the concept of *guilt by association*. Already in the late nineties it was recognized many TAAD are in fact FTAAD. Gonzalo Albornoz *et al.*(29) identified an inheritance pattern in 21,5% of non-Marfan pedigrees being familial. Coady *et al*.(30) from Yale identified 19,3% of 135 probands belonging to multiplex pedigrees, this being defined as a risk factor for aneurysm development. Robertson *et al*.(17) identified 37% of 997 FDRs at risk as having a dilated aorta. A systematic review of literature covering screening for dilated ascending aortas by Mariscalco *et al.*(31) from the Elefteriades group identified newly affected individuals in 33% of FDRs, 24% of SDRs and 15% of TDRs using imaging and/or genetic screening. Jakob Raunsø *et al*.(32) screened 68.939 Danish individuals for a dilated aorta and concluded that FDRs of a patient with a dilated aorta have a tenfold higher risk of developing an aortic aneurysm themselves. In the Framingham Heart Study, offspring (n=235) whose parent(s) had a sex- and age-standardized aortic size in the upper quartile had a multivariable-adjusted two- to threefold increased odds ratio of belonging to the upper quartile themselves.(32) Biddinger *et al*.(33) screened 843 FDRs of 158 probands with non-syndromic ascending aortic aneurysms and used 547 FDRs from their spouses as

control. They conclude that the relative risk of a dilated aorta was 1,8 in fathers, 10,9 in brothers and 1,8 in sisters. Specifically for BAVs, Cozijnsen *et al*.(34) analyzed the yield of screening. New BAVs were diagnosed in 6% of FDRs. Others found this yield to be 17%. They diagnosed an ascending aortic aneurysm with a normal TAV in 7,5% of FDRs of BAV-patients. Cripe *et al.*(35) found ascending aortic aneurysms in 27% of FDRs with a BAV. However, Cripe did use an indexed diameter of the aorta. Cozijnsen diagnosed two new positive cases per proband, compared to 5,2 (37%) new BAVs per proband by Huntington *et al*.(36) and 6,3 BAVs per proband (32%) by Cripe *et al*. They conclude that the more FDRs you screen, the more new diagnoses of BAVs and/or aortic aneurysms will be made.

In 2015 Hannuksela *et al*.(37) stated that the outcome of screening programs is largely unknown, despite the present recommendations. They echocardiographically screened seven families (FDRs and SDRs) with FTAAD who genetically tested negative for underlying syndromes. There were 19 of 106 relatives diagnosed with a dilated aorta. Only one of 20 relatives younger than 40 years of age proved to have a dilated aorta, while, in case of an autosomal dominant inheritance pattern, this should have been 10. They conclude that, based on aortic diameters alone, not all potential carriers of the disease are identified.

In the present study, out of 526 probands with an ascending aortic aneurysm or a BAV identified, pedigree analysis revealed 1689 relatives. The relatives of 121 probands were invited for screening. This resulted in 384 patients effectively screened: 298 FDRs, 61 SDRs, 16 TDRs, 9 >TDRs. This accounted for 3,14 FDRs and 1,28 SDRs per proband.

In 43,8% of the families at least one new diagnosis of TAD or BAV was made (mean 1,42 per family). When considering their aortic diameter as being above the ULON or at least two z-scores above the expected diameter, patients at risk for developing an aortic aneurysm were identified in 24,5% and 20,6% of the families, respectively.

Importantly and in contrast to the literature, the presence or absence of a positive familial history does not influence the yield of screening in a statistically significant way. Respectively in 19,8% and 18,9% of the families a new affected relative is identified. However, this yield is comparable to the literature. Importantly is the diagnosis of respectively 25,6% and 23,6% of relatives with an aortic diameter above the ULON. These mainly represent individuals in the age range younger than 45. As such, they are diagnosed with an abnormally high diameter of the ascending aorta and are at risk of developing a frank aneurysm in the future. Of note is the constatation that, especially in the group of

patients with a positive familial history, SDRs, TDRs and even >TDRs are identified with an aortic diameter above the ULON. A new diagnosis of BAV in a relative is not influenced statistically significant by the presence of a familial history. Of note, these newly diagnosed BAVs occur also in SDRs and TDRs.

In 7,3% of all screened relatives, a new BAV diagnosis is made. If one only considers the 77 families with a BAV proband, a new BAV is diagnosed in 28,7% of which 77,8% are FDR and in 25,4% a new aneurysm was detected. If the trigger for screening was BAV minus aneurysm, a new diagnosis of TAD in at least one relative was present in 41,2%. In case the trigger was the presence of a BAV and aortic aneurysm, 35,7% of the screened families led to a new TAD diagnosis. When screening was initiated because of an aneurysm with a TAV, a new relative was diagnosed in 49,2%. In this group, a first BAV was diagnosed in 11,1%. As a result, in 53 of the 121 families screened, *i.e.,* 43,8%, this screening led to a recategorization of the family from an isolated case towards at least a familial occurrence of the disease.

Considering XAI, 32,9 % of the relatives screened expressed XAI. A statistically significant correlation was present between the presence of XAI and the maximal diameter of the aorta and an aortic diameter larger than the ULON for individuals aged under 18 years, regardless their gender. A z-score over two was found in 13,6% of the 66 screened children of whom 77,7% presented XAI. For all other age groups, the presence or absence of XAI was not statistically significant in predicting the presence of an abnormally dilated aorta. This finding might be representative for the presence of a generalized weakness of connective tissues before the presence of a frank aneurysm. In either way, the presence of XAI in minors needs to raise suspicion regarding the presence of an aortic diameter larger than the ULON and warrants longitudinal follow-up of these patients. XAI, however, are not pathognomonic, since 32,1% of individuals with an aortic diameter below the ULON also present with XAI.

7. Study limitations

There were 526 probands with an ascending aortic aneurysm and/or a BAV identified. Only 121 of these underwent familial screening. However, we think a group of 384 screened relatives is an important population. Within the families screened, not all relatives attended a screening visit. Firstly, because the screening program is an ongoing process and, secondly, some individuals will never attend a screening visit for which the reasons are depicted in the analysis above. As a result, the yield

of the screening program is surely underestimated as shown by the detection of 24,8% new diagnoses in FDR while, in case of autosomal dominant inheritance, this would have been 50%. However incomplete penetrance of aortic dilatation and possible screening at an age before onset of the disease might also play a role.

Furthermore, only a minor part of our patient cohort has been genetically tested. Consequently, some probands might have had a syndromic aneurysm that was not diagnosed as such. As genetic testing becomes more easily accessible, this will help to recategorize patients in the future.

8. Conclusion

Systematic screening of patients with an ascending aortic aneurysm and/or a BAV has a substantial yield in terms of detecting newly affected relatives and relatives at risk for development of an aortic aneurysm later in life.

Screening further down the lane horizontally and vertically in the pedigree increases the yield compared to screening FDRs only. Consequently, individuals are diagnosed who would have gone undetected when following most of the current guidelines. This constatation underscores the usefulness and interest of screening beyond FDRs.

Calculating z-scores and ULON identifies relatives at risk for future development of an aortic aneurysm. XAI were “borrowed” from syndromic aneurysm assessment and applied to all relatives screened in this population of originally isolated ascending aortic aneurysms. This proved to be worthwhile in almost all age and gender subgroups, except for the male-over-60 subgroup. Indeed, greater aortic diameters and z-scores when XAI were present were noted, however, they were only significant in the youngest age-group. Therefore, especially in individuals aged under 18 years, the presence of XAI should raise the index of suspicion of aneurysmatic growth of the ascending aorta in the future, regardless the gender of the relative screened. A one-stop screening in these cases needs to be avoided. Instead, a longitudinal follow-up with TTE should be offered to these relatives at intervals of five to 10 years until an age far enough beyond that of the proband or until they arrive at an age at which the probability of developing an ascending aortic aneurysm becomes unlikely. During this follow-up, risk factors need to be assessed and treated when present.

Dedicated screening programs for ascending aortic dilatation and BAV in the setting of dedicated Aortic Centers should be encouraged. Screening efforts from the physician's perspective need to be increased in order to reach more relatives and increase detection of potential carriers of the disease in order to avoid aortic catastrophes. From the relatives point-of-view, obstructions to accept screening invitations should be overcome by getting offered correct information about the usefulness and possible consequences of screening and efforts need to be undertaken to avoid fear of getting diagnosed with psychological, insurance and mortgage consequences.

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