Pathogenic FBN1 Genetic Variation and Aortic Dissection in Patients With Marfan Syndrome

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Aortic Dissection in Patients with Marfan Syndrome and Underlying Pathogenic Variant in the *FBN1* Gene

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Funding: Fondation Cœur et Recherche, Paris France, Fédération Française de Cardiologie, Paris France, ANR-14-CE15-0012, Paris France, CRCBD18119, Paris France. No relationships with industry or financial disclosure to report
Tweet: Risk for aortic dissection is low below 50 mm in Marfan patients with a *FBN1* pathogenic variant
Acknowledgements: We are indebted to the patients and their families for agreeing to use their clinical data. We are also indebted to the referring physicians. We wish to thank Natasha Barr for the expert language review of this article.

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Abstract
Background: Aortic risk has not been evaluated in patients with Marfan Syndrome and documented pathogenic variants in the *FBN1* gene.
Objectives: We sought to describe the aortic risk in a population with Marfan syndrome with pathogenic variants in the *FBN1* gene as a function of aortic root diameter.
Methods: Patients carrying a *FBN1* pathogenic variant who came to our reference center at least twice were included, provided they had not undergone aortic surgery or had an aortic dissection prior to their first visit. Aortic events (aortic surgery or aortic dissection) and deaths were evaluated during the 2 years following each patient visit. The risk was calculated as the number of events divided by the number of years of follow-up (FU).
Results: 954 patients were included (54% women, mean age 23 years). During FU (9.1 years), 142 patients underwent prophylactic aortic root surgery, 5 experienced type A aortic dissection, and 12 died (non-cardiovascular causes in 3, unknown etiology in 3, postoperative in 6).
When aortic root diameter was <50 mm, risk for proven type A dissection (0.4 events/1000 pt-years) and risk for possible aortic dissection (proven aortic dissection plus death of unknown cause, 0.7 events/1000 pt-years) remained low in this population treated according to guidelines. Three type A aortic dissections occurred in this population during the 8594 years of follow-up including one in a patient with a tubular aortic diameter of 50 mm, but none in patients with family history of aortic dissection. The risk for type B aortic dissection in the same population was 0.5 events/1000 pt-years.
Conclusion: In patients with *FBN1* pathogenic variants, receiving beta-blocker therapy and limiting strenuous exercise, aortic risk remains low when maximal aortic diameter is below 50 mm. The risk of type B aortic dissection is close to the remaining risk of type A aortic dissection in this population underlining the global aortic risk.

Keywords: Aorta; Marfan; *FBN1*; dissection; diameter

Condensed abstract: Aortic risk was calculated in 954 patients carrying a *FBN1* pathogenic variant, who came at least twice to the reference center, during a 9.1-year follow-up period. Care included beta-blocker therapy and avoidance of strenuous exercise. Risk remained low when aortic maximal diameter was below 50 mm (type A dissection: 0.4/1000 pt-years, type A dissection or death of unknown cause, possibly cardiovascular: 0.7/1000 pt-years, type B dissection: 0.5/1000 pt-years). The risk of type B dissection was close to the remaining risk of type A dissection, underlining the global aortic risk in this population.

Abbreviations
FBN1: Fibrillin 1 gene
MFS: Marfan Syndrome
CT: computed tomography

Introduction

Marfan syndrome is a genetic disease with multisystem features involving the aorta, mitral valve, skeleton, eyes, skin, and muscles. The aortopathy may be responsible for thoracic aortic aneurysm, dissection and death, and is the main cause of death when undiagnosed. Prevention of aortic dissection in this population is based on the early recognition of the disease through familial screening, enhanced by genetic screening when a *FBN1* pathogenic variant has been found in a patient (1, 2). This allows for early recognition of the syndrome and application of preventive measures, which include avoidance of competitive sports (that produce a brisk rise in blood pressure), beta-blocker therapy, and prophylactic surgery when the risk of aortic dissection /rupture is thought to outweigh the risk of surgery (1, 2). However, aortic risk as a function of aortic root diameter, which is the site of maximal dilatation in Marfan patients and the parameter used to recommend prophylactic surgery, has not been evaluated in a population with *FBN1* gene pathogenic variants: in the previous series on clinical Marfan syndrome evaluating risk as a function of aortic diameter, the presence of a *FBN1* pathogenic variant was not required, and Marfan syndrome was only clinically defined (3). It is now recognised that clinical Marfan syndrome may be seen in patients with a pathogenic variant in other genes (4), and that the aortic risk may vary according to the pathogenic variant causing the aortopathy (5,6). Besides, in recent years, numerous new genes have been reported, with specific natural histories (7) and the use of genetic testing has increased. As a consequence, the mutated gene responsible for the aortopathy is now also used to evaluate the aortic risk, in addition to the aortic diameter (8,9). Although differences between *FBN1* pathogenic variants causing haploinsufficiency (HI) and variants with dominant negative (DN) effect have been reported

(10–12), with a greater aortic risk associated with HI, this has not yet translated into different recommendations in these 2 populations.

We extracted the data of patients with a *FBN1* pathogenic variant, who came at least twice to the French center of reference for Marfan syndrome and related disorders. This is a well-documented population, including probands and family members, thanks to the use of systematic familial screening and the provision of treatment that adheres to the current guidelines. The selection of patients who visited the center twice was chosen in order to evaluate the prognosis in a population in whom diagnosis was recognised and care given according to recommendations.

Methods

Patient Population

The French reference Center for Marfan syndrome and related disorders opened in 1995. This was the only reference center in France until 2016, meaning that patients were referred from all over France for screening or care. Familial screening was systematic when Marfan syndrome was confirmed, i.e. all the affected members of the family were seen in the center. The familial screening was initially based on the clinical evaluation of the relatives, followed by the search for the familial pathogenic variant in relatives when familial pathogenic variant was known. The population seen is therefore representative of all *FBN1* patients, and not of a selected subgroup. Upon the first visit to the center, each patient is seen, within the same day, by a cardiologist after having an echocardiogram, a geneticist for pedigree information and prescription for DNA analysis when appropriate, an ophthalmologist for slit lamp examination, and a paediatrician or a rheumatologist, according to the patient's age. Afterwards, visits are scheduled every other year

in the Reference center, alternating with their private local doctors. During the visits, the patient's data are recorded in the online database.

Patients carrying a *FBN1* pathogenic variant (class 4 or 5) who came to our reference center at least twice between 1995 and March 2015 were considered for this study. Sequence variant reporting was performed according to Human Genome Variant Society nomenclature (13). Only variants of classes 4 and 5 according to ACMG-AMP recommendation were considered for this study.

Patients were excluded from the study if they had undergone aortic root surgery or presented with a history of aortic dissection prior to their first visit to the center.

Medical Care

Beta-blocker therapy is proposed to all patients with a definite Marfan diagnosis, whether or not the aorta is dilated. Bisoprolol at a dose of 10 mg is the most prescribed beta-blocker, or atenolol at a target dose of 100 mg, which can be decreased in case of intolerance or changed for another beta-blocker (usually nebivolol at a target dose of 10 mg, or nadolol at a target dose of 80 mg). In children, treatment is usually started with bisoprolol 1.25 mg/day and increased until the resting heart rate is below 60 bpm unless side effects occur. The type of beta-blocker is the decision of the prescribing physician. Sartans are rarely given to the patients except when specifically requested by the patients.

Isometric exercises or competitive sports are discouraged, but recreational jogging, cycling, and swimming are recommended.

Surgical Care

In Marfan patients with pathogenic variants in the *FBN1* gene, we follow the international recommendations and perform prophylactic aortic root surgery when the patient's maximal

aortic diameter reaches 50 mm, a threshold lowered to 45 mm in case of a desire for pregnancy, and when the aortic diameter growth rate is greater than 3 mm/year in adulthood (2, 8). However, some patients have been operated on outside the Reference center, with surgery sometimes performed at an earlier stage.

Aortic Measurement

Echocardiography was performed by 1 of 5 trained echocardiographers on a Sequoia (Siemens, Mountain View, CA) or Vivid 7 then Vivid 9 (General Electric, Horten, Norway) ultrasound system. Adequate multi-frequency transducers, ranging from 2 to 5 MHz and 3 to 8 MHz, were used. Patients were in lateral decubitus position, in resting conditions. Aortic root diameters were measured according to the 2005 American Society of Echocardiography Chamber Quantification Guidelines (14). The best parasternal great-axis view was used in the 2-dimensional mode.

Great care was taken to align the echocardiographic plane with the aortic root and to obtain the largest aortic diameters. The aortic annulus was measured in systole at the hinge point of the aortic leaflets. The diameters at the sinus of Valsalva, sinotubular junction, and proximal ascending aorta were measured in diastole perpendicular to the long axis of the aorta using the leading-edge-to-leading-edge technique.

Thus, the measurements included the anterior wall of the aorta and not the posterior wall. The largest of several measurements at each of the 4 defined levels was recorded in the database. Measurements were done online and offline with the use of appropriate blown-up views for higher precision. Diameters were given in millimeters. When the aortic diameter measurement was thought to be unreliable by the cardiologist, the measurement was made using a different technique (usually computed tomography scanning, less often magnetic resonance imaging, and

rarely transoesophageal echocardiography). This rule was also followed when the aortic diameter changed significantly between 2 measurements, i.e. the change had to be confirmed by another technique (or at least the last diameter, when only one reference diameter was available).

The echocardiographic measurements were considered the gold standard. Because it has been suggested that normalised aortic diameters should be used to define optimal prophylactic aortic surgery, aortic diameters were also standardized to body surface area (mm/m2) and to height (cm/m), and the ratio of surface area/height (cm2/m) was calculated (15–17).

Clinical events

Deaths were classified as cardiovascular, non-cardiovascular or deaths of unknown cause; Aortic dissections were classified as type A or type B aortic dissections. Calculation of the clinical event rate was made both on the whole population and solely on data from adult patients (>18 years of age).

Statistical Analysis

Continuous data are presented as mean±SD and qualitative variables as frequency and percentage. The validity of an aortic diameter measurement was considered to last for 2 years unless another measurement was performed in the meantime (i.e., the aortic diameter was considered to be constant over 2 years for the purpose of statistical analysis). In order to assess the impact of aortic size on the incidence of events, the patients were classified by their successive aortic diameters, and their total individual follow-up times split according to the periods of time they belonged to a particular size category. Thus, a patient with a stable 43 mm diameter at the aortic sinus for 4 years and dilating to 46 mm over the subsequent 6 years would contribute 4 years to the cumulative follow-up sum of the 40-44 mm category and 6 years to the 45-49 mm category. The number of patient-years for a defined range of aortic diameters was

calculated as the sum of the number of years during which every patient was within the defined range. Follow-up was censored after the first event (aortic dissection, death, or surgery). The clinical event rate was calculated as the ratio of the number clinical events divided by the number of patient-years (linearized incidence rate). The results are expressed as events/ 1000 pt-years. Exact central 95% Poisson confidence intervals (95% CI) were calculated using `exactci` R package.Statistical analyses were performed with R software (18).

RESULTS

Patient Population (figure 1)

A *FBN1* pathogenic variant (class 4 or 5) was discovered in a total of 1402 patients. 718 of these patients were women (51%). 294 visited the clinic only once and were therefore excluded. Of the remaining patients, 143 had undergone aortic surgery prior to their first visit. Reason for surgery was aortic dissection in 46 [34 (74%) male; mean age at first visit, 36.7 years]. In the 97 other patients [59 (61%) male; mean age at first visit, 38 years; mean age at the time of surgery, 32.4 years], the reason given for surgery was aortic root diameter reaching or exceeding 50 mm, increase in diameter with pregnancy, and symptomatic mitral or aortic regurgitation. Of the 965 remaining, 11 had presented type B aortic dissection before their first visit and were excluded from the study.

The population therefore comprised 954 patients including 372 (39%) with a haploinsufficiency pathogenic variant, who came for 4482 outpatient visits. 516 (54%) of patients were women, with the mean age at first visit being 22.6 y.o. (SD 16.1, median 19.1, range 0 – 83 years); 73% received beta-blocker therapy during follow-up. The aortic diameter at the level of the sinuses of Valsalva at the first visit ranged from 16 to 67 mm (**Figure 1**). Normalized aortic diameters ranged from : 10 to 76 mm/m2, mean 22.9 mm/m2, median 22.2

mm/m2 (by body surface area); 0.71 to 4.2 cm/m, mean 2.17 cm/m, median 2.15 cm/m (by height), and 1.3 to 20 cm²/m, mean 6.5cm²/m, median 6.3cm²/m (aortic surface normalised by height).

In this population, mean blood pressure was 103/60, mean heart rate was 60bpm, ectopia lentis was present in 63%; pectus excavatum or recurvatum was present in 74%, arachnodactyly in 59%, flat feet in 28%, and scoliosis in 36%.

The mean follow-up was 9.1 years (time from first visit to clinical event or last visit), and ranged from 2 to 19.8 years. Follow-up for hospitalization, surgery, or death was obtained on the date of March 2015 for all but 15 patients, among whom 5 moved without providing their new contact information, and 10 who were lost to follow-up. Vital status at the end of the study was known for all patients but one (no death reported). In the last patient vital status was unknown at the end of the study. Aortic root diameter at last visit was below 30 mm in 2 patients, 30 -34 mm in 3, 35-39 mm in 5 (including the patient with unknown vital status), 40-45 mm in 3, and 45-50 mm in 2.

Events During Follow-Up

Death

12 patients died within 2 years after their last visit. Death was from a non-cardiovascular cause in 3 patients (suicide, motorbike accident, cancer), and from an unknown cause in 3 patients. These last 3 deaths were included in the calculation of the aortic risk. Six additional deaths occurred during or after aortic surgery (see below).

- Non cardiovascular cause of death (2 men 1 woman):
    - A suicide in a 33-year-old man with a DN variant, with an aortic root diameter of 47 mm (normalised 22.1 mm/m², 2.5 cm/m, 9.3 cm²/m) 6 months earlier

- 1 motorbike accident in a 41-year-old man with a HI pathogenic variant with an aortic root diameter measured at 44 mm (normalised 19.9 mm/m², 2.4 cm/m, 8.2 cm²/m) 4 months earlier
- 1 death in an 80-year-old woman with a DN variant with advanced angiosarcoma, with an aortic root diameter measured at 33 mm (normalised 18.4 mm/m², 2.1 cm/m, 5.4 cm²/m) 445 days earlier.

- Unknown cause of death (and therefore possibly cardiovascular, as no autopsy was performed):
  - 1 sudden death occurred in an 18-year-old woman with a DN pathogenic variant, after her visit with an aortic root diameter measured at 33 mm (normalised 19.9 mm/m², 1.9 cm/m, 4.8 cm²/m) 4.5 months earlier. She was known as having long QT syndrome.
  - 1 sudden death in a 33-year-old man with a HI pathogenic variant and an aortic root diameter measured at 46 mm (normalised 23.4 mm/m²,2.4 cm/m, 8.6 cm²/m) 2.7 months earlier.
  - A death in a 37-year-old man with a HI pathogenic variant after fainting at work, the aortic root had been measured at 48 mm (normalised 24.4 mm/m², 2.4 cm/m, 9.1 cm²/m) 4 months earlier.

  Of note, none of the normalised aortic diameters calculated in these patients were in the higher quartile of the population before the event.

Aortic surgery

During the course of the study, prophylactic surgery of the ascending aorta was performed in 142 patients (52 women, i.e. 10% of all women, and 90 men, i.e. 21% of all men), including 66

patients with a haploinsufficiency *FBN1* variant (46% of patients undergoing surgery). Surgery was performed outside the Reference center in 55 patients, at a mean diameter of 50.9 mm. Of note, 6 patients died after surgery within 2 years of their last aortic measurement [in-hospital death related to surgery in 5 patients (3.5% in-hospital mortality) and 1 subsequent death after heart transplantation].

- A 29-year-old woman with a DN pathogenic variant, following prophylactic surgery (valve sparing), with an aortic root diameter of 45 mm measured 15 months earlier.
- A 62-year-old woman with a DN pathogenic variant, following prophylactic Bentall procedure performed 2 months after a diameter was measured at 48 mm with echocardiography, and at 51 mm using CT scanner.
- A 32--year-old man with a HI pathogenic variant following aortic valve and root and mitral valve replacements, with aortic root measuring 48 mm 5 months earlier.
- A 29-year-old man with a HI pathogenic variant following aortic and mitral valve surgery with an aortic root diameter measured at 55 mm, 2 months earlier.
- A post-operative death in a 69-year-old woman with a DN pathogenic variant following Bentall procedure with an aortic root diameter of 60 mm, 4 months earlier.
- A late post-operative death after heart transplantation in a 30-year-old man with a HI pathogenic variant. Heart transplantation was directly following a complicated prophylactic aortic root surgery for aortic root diameter of 51 mm.

Type A aortic dissection (figure 2)

Dissection of the ascending aorta occurred in 5 patients (3 women, 2 men):

- 8 months after an aortic root measurement of at 38 mm (normalised 23.5 mm/m², 2.2cm/m, 6.6cm²/m, unchanged during the previous year) in a 40-year-old woman with a DN pathogenic variant.
- 1 month after an aortic root measurement of 47 mm (normalised 23.4 mm/m², 2.3 cm/m, 8.5cm²/m, increased by 2 mm during the previous year) in a 16-year-old man with a DN pathogenic variant.
- 5 months after an aortic root measurement of 47 mm (normalised 28.4 mm/m², 2.8 cm/m, 10.3cm²/m, unchanged during the previous year) in a 32-year-old woman with a DN pathogenic variant. Of note, the aortic tubular aorta was measured at 50 mm at this time
- 2 months after an aortic root measurement of 50 mm (normalised 22.2 mm/m², 2.7 cm/m, 10.7cm²/m) in a 50-year-old man with a HI pathogenic variant. Of note, the tubular aorta was measured at 52 mm.
- 5 months after an aortic root measurement of 59 mm (normalised 32.9 mm/m², 3.23 cm/m, 15.2cm²/m) in a 32-year-old woman with a HI pathogenic variant who delayed surgery.

Type B aortic dissection

Type B aortic dissection occurred in 6 patients (5 women, 1 man):

- 22 months after an aortic root diameter measurement of 42 mm in a 35-year-old woman with a HI pathogenic variant.
- 4 months after an aortic root measurement of 38 mm in a 61-year-old woman with a HI pathogenic variant.

- 4 months after an aortic root measurement of 50 mm in a 46-year-old woman with a DN pathogenic variant. This dissection occurred 14 days after prophylactic ascending aorta surgery.
- 4 months after an aortic root measurement of 57 mm in a 34-year-old woman with a HI pathogenic variant, 3 months after prophylactic ascending aorta surgery.
- 22 months after an aortic root measurement of 46 mm in a 24-year-old man with a DN pathogenic variant.
- 1 month after an aortic root measurement of 38 mm in a 35-year-old woman with a HI pathogenic variant.

The number of clinical events and the linearized incidence rate are reported in table 1 in the complete population, and in table 2 in adults only. The risk in the complete population was 0.6 type A aortic dissection / 1000 pt-years, 0.7 type B aortic dissection / 1000 pt-years, 1.4 death of any cause / 1000 pt-years, and 16 surgery were performed / 1000 pt-years.

To evaluate the relevance of present guidelines, the risk for the population with aortic root diameter below 50 mm was calculated: the risk for type A aortic dissection was 0.4 events/ 1000 pt-years, meaning that one type A aortic dissection is observed for a mean follow-up of 2865 years. When only adults are considered, risk for type A aortic dissection was 0.38 events/ 1000 pt-years. When risk for deaths of unknown cause (which could be unrecognised aortic dissection) and risk for aortic dissection are added, this figure increases to 0.7 events/1000 pt-years (0.95 events/1000 pt-years in adults only). The risk for type A aortic dissection increases with increasing aortic root diameter (**Central Illustration**).

These results are equivalent to those obtained in patients with Marfan syndrome in which diagnosis was based on clinical features only (7); in this population, the risk for aortic dissection

or death of unknown cause was 0.9 events/ 1000 pt-years (0-39 mm), 1 event/ 1000 pt-years (40-44 mm), 3 events/ 1000 pt-years (45-49 mm), 13 events/ 1000 pt-years (50-55 mm) and 81 events/ 1000 pt-years (55-59 mm).

Discussion

Evaluating the risk of aortic dissection or rupture in the Marfan population remains a challenge, but it is crucial in order to propose timely prophylactic aortic root surgery. Up until now, only the aortic root diameter has emerged as a strong risk factor and it is used for the purpose of recommending prophylactic aortic root replacement (1, 8). However, studies evaluating the aortic risk as a function of aortic diameter are scarce, due to the fact that this is a rare disease and diagnosis is demanding, rendering selection bias difficult to avoid. In addition, the criteria used for diagnosing Marfan syndrome are usually mainly clinical, as genetic studies are not systematically performed in all medical centers (19). The population followed by the French reference center for Marfan syndrome and related disorders, which systematically screens parents and proposes systematic follow-up, and genetic testing when a minimum of features is present (20), keeps this bias to a minimum.

In this population with a *FBN1* pathogenic variant treated according to the guidelines, including more than 7400 years of follow up in almost 1000 patients, one can regret the occurrence of 5 identified dissections of the ascending aorta, and at most 8 patients with a possible aortic dissection (either diagnosed aortic dissection or death of unknown cause). This provides a risk for dissection of the ascending aorta of 0.57 or 0.9 events/1000 pt-years.

When only patients with an aortic root diameter below 50 mm are included, 3 type A dissections and 3 deaths of unknown cause are observed during 8594 years of follow-up, including one type A dissection in a patient with a tubular aortic diameter of 50 mm. This

indicates that the risk of proven or possible dissection in this population is 0.7 events/ 1000 pt-years when aortic root is considered, and 0.6 when maximal aortic diameter is considered, equivalent to the occurrence of one proven or possible aortic dissection after a mean of 1432 or 1718 years of follow-up. When only the patients with maximal aortic diameter between 45 and 50 mm are considered, the risk for proven type A aortic dissection is 1.7 events/ 1000 pt-years and the risk of possible type A aortic dissection and death of unknown aetiology is 3.5 events/ 1000 pt-years, equivalent to occurrence of an event after a mean follow-up of 579 years or 289 years respectively.

These figures are to be compared with the rate of aortic surgery which was 14% in the population followed with the rate sharply increasing with aortic diameter, as expected. The post-operative mortality rate of 4% is in keeping with published studies (21, 22). Besides, it is known that late complications and an alteration in quality of life may occur after surgery related notably to the presence of a mechanical valve (23). These later drawbacks are probably lower after valve sparing operations (21, 24).

One may wonder if aortic diameter should be modulated according to the height of the patient, e.g. through normalisation by body surface area, or height, or if we should use aortic area normalised by height (15, 17, 25, 26). This study does not support such a proposition, as the normalised aortic root diameter of patients experiencing an aortic dissection below 50 mm were not in the upper range of the normalised values, except for one patient whose aortic maximal diameter (tubular aorta) reached 50 mm. Other indicators of aortic fragility are therefore still necessary to improve the care of these patients. New indicators are being examined such as arterial tortuosity (27) and aortic distensibility (28), among others. No familial aortic dissection, nor hypertension were present in patients who presented with type A aortic dissection with a

maximal diameter below 50 mm, and the predictive value of these clinical parameters is therefore not reinforced by our study.

Factors that are increasingly recognised as being associated with increased aortic risk are male gender and the HI nature of the *FBN1* gene mutation. Male gender was associated with a higher rate of aortic surgery, but it is difficult to make a conclusion about the role of these factors on the risk of aortic dissection, as the numbers are limited. Type A aortic dissections occurred in both men (n=2) and women (n=3), but type B aortic dissections were more frequent in women (4 of the 6 type B dissections). Surgery was slightly more frequent in patients with HI rather than DN pathogenic variants (18% vs 15%), but all type A dissections occurring at an aortic root diameter below 50 mm were DN and not HI pathogenic variants. However, 4 of the 6 type B aortic dissections occurred in a patient with HI mutation, which is in keeping with the findings of Franken (11). More data has to be collected before these new factors can be included in the decision making process.

It is not unexpected that the progress achieved in preventing type A aortic dissections may allow for new problems, previously considered as rare events, to come to the frontline. In this study, the occurrence of a proven type B dissection was more frequent than the occurrence of a proven type A dissection. Interestingly, in 2 patients, the type B dissection occurred after prophylactic surgery of the aortic root. As of today, we are not yet able to recognise which patient will present with a dissection of the descending aorta, although aortic tortuosity (29) and dilatation of the descending aorta are known risk factors(30).

It should be stressed that the figures reported in this paper may not be representative of the whole Marfan population:

1) The population has been selected on the identification of a pathogenic variant in the *FBN1* gene, which is more selective than a clinical diagnosis alone (31). The aortic risk in Marfan-like syndrome, such as those observed in patients carrying a *TGFBR2* pathogenic variant, may be different. Indeed, a recent report suggested that there is a great variability in the aortic risk in this population, and that the risk can also be evaluated by the presence/absence of clinical features (5); the consensus is now to propose surgery earlier in this population.

2) The diagnosis was made prior to any aortic event, which may differ from the overall population of Marfan patients who, in part, are diagnosed at the moment of a catastrophic event (4).

3) The population is followed-up regularly in an expert center recognised as such by national and European institutions (www.vascern.eu). All patients are instructed to take beta-blocker therapy, to avoid strenuous exercise, and are educated about the clinical features that lead to the suspicion of aortic dissection (1).

4) Only the patients who came twice to the reference center were included in this study: this indicates compliance with therapy and the global care proposed, which is a recognised prognostic factor in medicine(32). Hence, our population should be seen as a selected population.

5) Our population is relatively young and the observation of a dilated aortic root at a young age is suggestive of rapid aortic dilatation or more rapid that in an older population with similar aortic root dilatation. Because rapid aortic dilatation is considered a risk factor for aortic dissection, the risk in this relatively young population is probably greater than the aortic risk in an older population with a similar aortic root diameter.

Aortic diameter was evaluated using echocardiography, and it is now more and more frequently measured with CT scans in our practice. The translation of aortic root diameter into

diameter obtained using CT scans may be difficult, as many different diameters may be calculated using this imaging technique (32). In our experience, the diameter obtained from sinus to sinus on a transverse image of the aortic root is equivalent to the echocardiographic aortic root diameter used in this study (33).

Limitations

The major limitation of this report is the limited number of events encountered, so that the occurrence by chance of one additional event or one event less may substantially modify the figures. It remains nevertheless the only objective evaluation of aortic risk in a population with *FBN1* pathogenic variants available in such a large group of Marfan patients.

Conclusion

The rules proposed by international guidelines for managing patients with Marfan syndrome seem to be well adapted to the population of Marfan syndrome associated with a pathogenic variant in the *FBN1* gene. Normalised aortic root diameter does not appear to help in identifying patients with aortic dissection occurring at an unexpectedly low absolute aortic maximal diameter.

Clinical Perspectives:

Competency in Medical Knowledge: Recommended care (beta blocker therapy and avoidance of strenuous sports) of patients with Marfan syndrome related to a *FBN1* pathogenic variant is associated with a very low risk for aortic dissection provided the aortic maximal diameter remains below 50 mm.

Translational Outlook: Similar studies in related disorders associated with other pathogenic gene variants are needed in order to evaluate whether similar thresholds should be used in these related conditions.

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Figure Legends

Figure 1: Flow chart for the population included in the study. 1402 patients with a Marfan syndrome related to *FBN1* pathogenic variants were seen, and 954 who came to the reference center twice and had not undergone aortic surgery or dissection prior to the first visit were included in the study. During follow up, surgery, aortic dissection and deaths occurred is some patients.

Figure 2: Age and aortic root diameter of the population. Scattergram of aortic root diameter (mm) as a function of age (year) in the population. Red dots are patients who presented with type A aortic dissection within 2 years of measurement.

Central Illustration: Risk as a function of aortic root diameter. Risk for aortic dissection (type A and type B), all deaths, and combined risk of aortic dissection and death of unknown cause in the total population, as a function of aortic root diameter measured in diastole using echocardiography.

Table 1: Clinical events as a function of aortic root diameter in the complete patient cohort

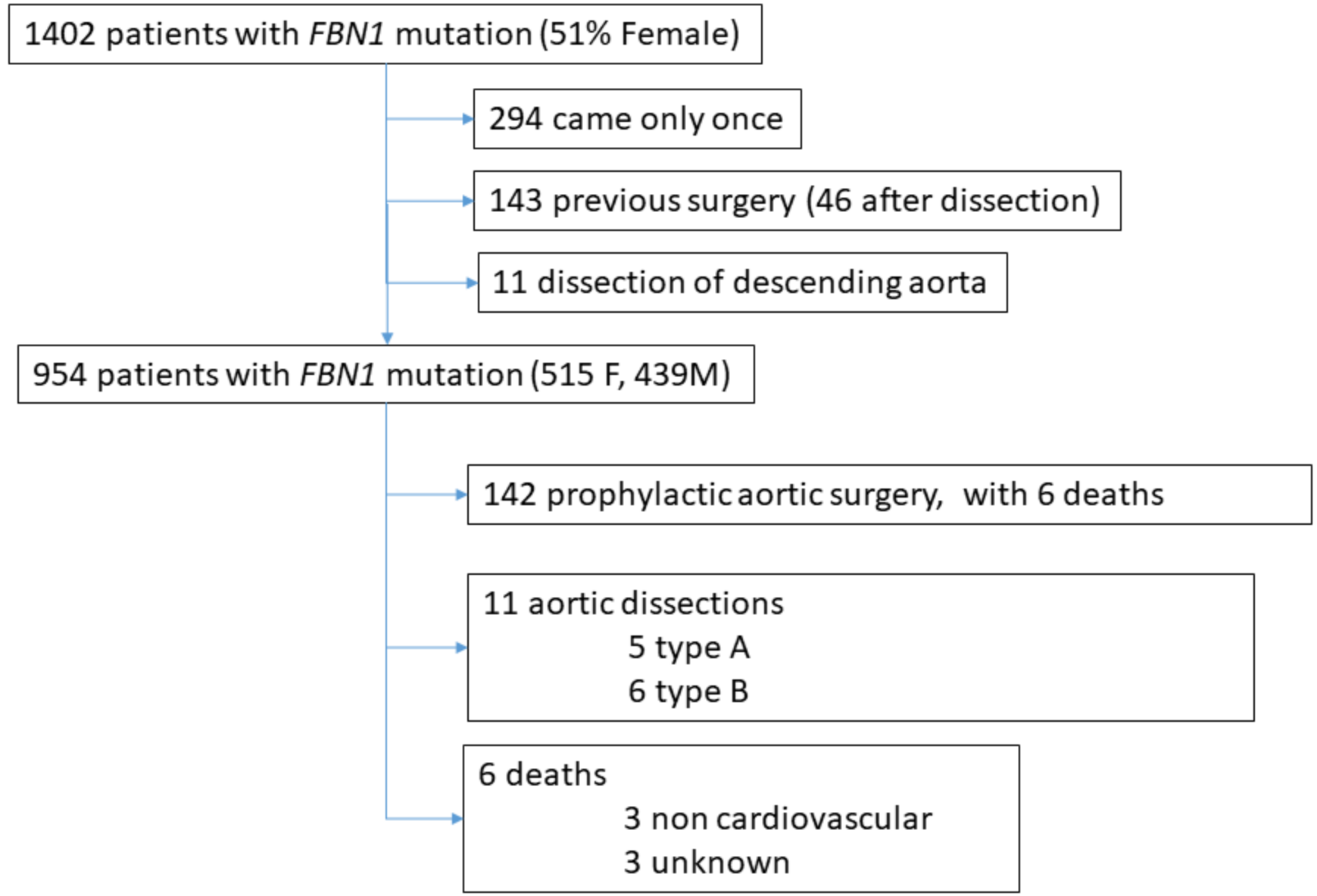
Aortic root diameter (mm)	**0-39**	**40-44**	**45-49**	**50-54**	**55-67**	**<50**	**Total**
Visit (n)	2663	1065	618	112	24	4346	4482
Total Follow Up (pt- years)	5317.0	2119.9	1157.2	118.9	9.0	8594.1	8721.9
Clinical events (n)							
Type A dissection	1	0	2	1	1	3	5
Type B dissection	2	1	1	1	1	4	6
All deaths	2	1	6	1	2	9	12
Death of unknown cause	1	0	2	0	0	3	3
Prophylactic Aortic surgery	2	5	51	65	19	58	142
Events/ 1000 pt-years [95% CI]							
Type A dissection	0.19 [0; 1.05]	0.00 [0; 1.74]	1.7 [0.2; 6.2]	8.41 [0.21; 46.9]	111 [2.8; 619]	0.4 [0.07; 1.0]	0.57 [0.19; 1.34]
Type B dissection	0.38 [0.05; 1.4]	0.47 [0.01; 2.63]	0.86 [0.02; 4.8]	8.41 [0.21; 46.9]	111 [2.8; 619]	0.47 [0.13; 1.2]	0.69 [0.25; 1.5]
All deaths	0.38 [0.05; 1.4]	0.47 [0.01; 2.63]	5.18 [1.9; 11.3]	8.41 [0.21; 46.9]	222 [27; 802]	1.1 [0.5; 2]	1.4 [0.71; 2.4]
Type A dissection or death of unknown cause	0.38 [0.05; 1.4]	0.00 [0; 1.74]	3.5 [0.9; 8.9]	8.41 [0.21; 46.9]	111 [2.8; 619]	0.7 [0.3; 1.5]	0.9 [0.4; 1.8]
Prophylactic aortic surgery	0.38 [0.05; 1.4]	2.36 [0.77; 5.5]	44 [32.8; 58.0]	547 [422; 697]	2111 [1271; 3297]	6.8 [5.1; 8.7]	16.28 [13.7; 19.2]

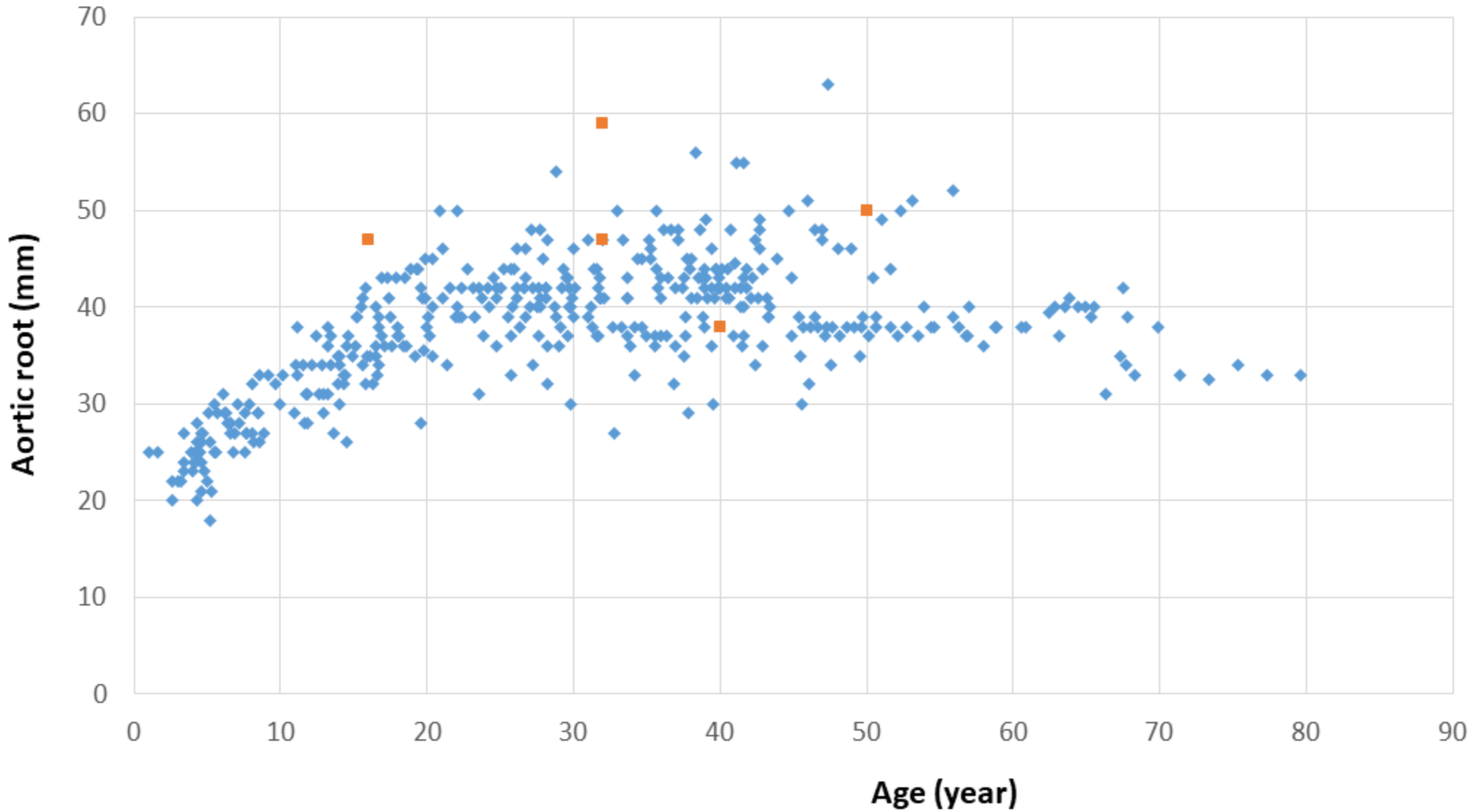
Aortic root diameter. clinical event. linearized incidence rate in the total population

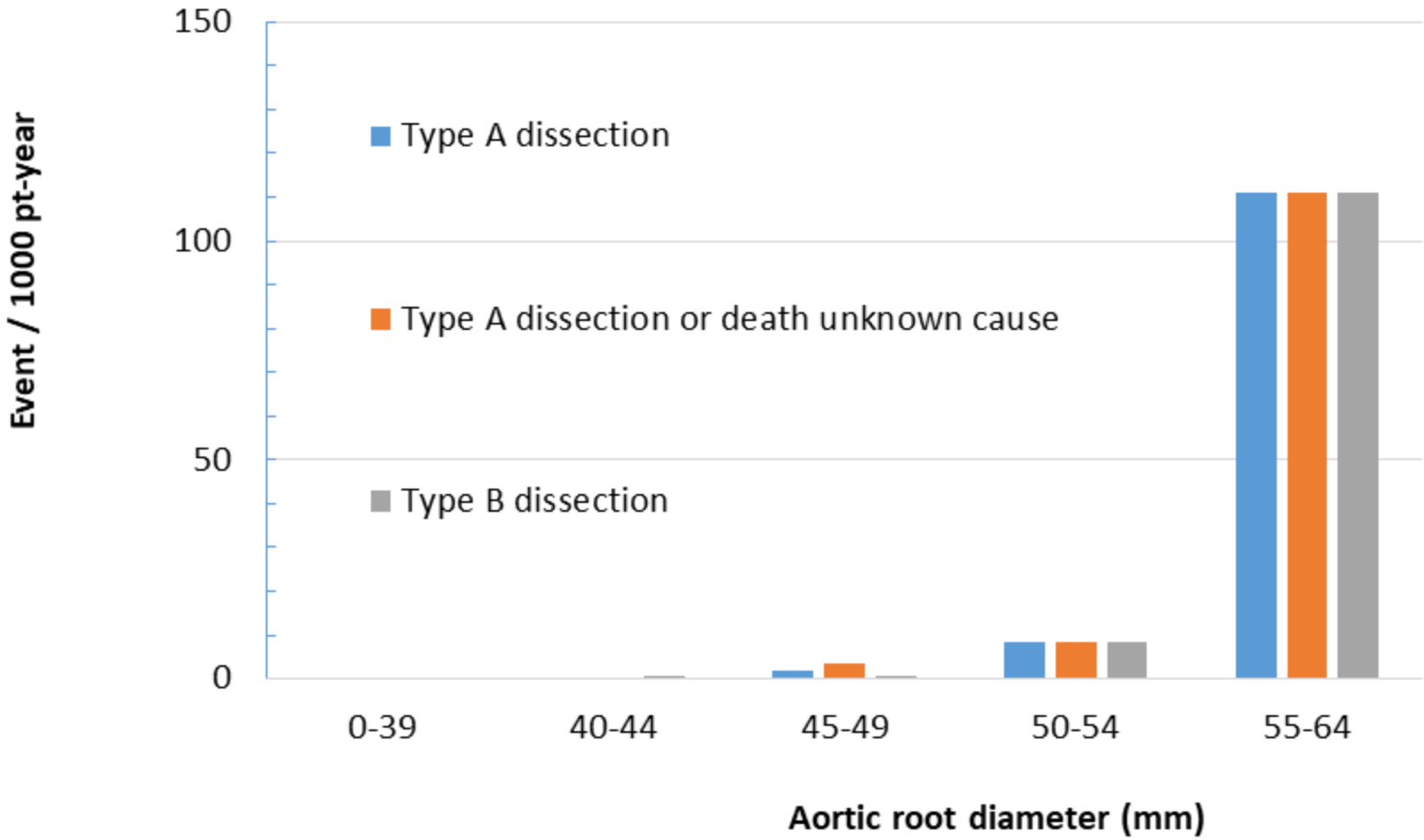
Table 2: Complications as a function of aortic root diameter in patients >18 years

Aortic root diameter (mm)	**0-39**	**40-44**	**45-49**	**50-54**	**55-64**	**<50**	**total**
Visit (n)	1162	942	571	106	23	2675	2804
Total Follow Up (pt- years)	2316.5	1875.5	1072.5	117.8	9.0	5264.5	5391.3
Clinical events (n)							
Type A dissection	1	0	1	1	1	2	4
Type B dissection	2	1	1	1	1	4	6
All deaths	2	1	6	1	2	9	12
Death of unknown cause	1	0	2	0	0	3	3
Prophylactic Aortic surgery	1	4	46	59	18	51	128
Events/ 1000 pt-years [95% CI]							
Type A dissection	0.43 [0.01 ; 2 .41]	0.00 [0.00 ; 1.97]	0.93 [0.02 5.20]	8.49 [0.21 ; 47.3]	111 [2.8 ;619.1]	0.38 [0.05 ; 1.37]	0.74 [0.20 ; 1.90]
Type B dissection	0.86 [0.10 ; 3.12]	0.53 [0.01 ; 2.97]	0.93 [0.02 5.20]	8.49 [0.21 ; 47.3]	111 [2.8 ;619]	0.76 [0.21 ; 1.95]	1.11 [0.41 ; 2.42]
All deaths	0.86 [0.10 ; 3.12]	0.53 [0.01 ; 2.97]	5.6 [2.0 12.2]	8.49 [0.21 ; 47.3]	222 [26.9 ; 802.7]	1.71 [0.78 ; 3.25]	2.23 [1.15 ; 3.89]
Type A or death of unknown cause	0.86 [0.10 ; 3.12]	0.00 [0.00 ; 1.97]	2.8 [0.58 8.17]	8.49 [0.21 ; 47.3]	111 [2.8 ;619.1]	0.95 [0.31 ; 2.22]	1.30 [0.52 ; 2.68]
Prophylactic aortic surgery	0.43 [0.01 ; 2.41]	2.13 [0.58 ; 5.46]	42.9 [31.4 57.2]	501 [382 ; 646]	2000 [1185 ; 3161]	9.69 [7.21 ; 12.74]	23.74 [19.81 ; 28.23]

Aortic root diameter. clinical event. linearized incidence rate in the adult population.


1402 patients with *FBN1* mutation (51% Female)
294 came only once
143 previous surgery (46 after dissection)
11 dissection of descending aorta
954 patients with *FBN1* mutation (515 F, 439M)
142 prophylactic aortic surgery, with 6 deaths
11 aortic dissections
5 type A
6 type B
6 deaths
3 non cardiovascular
3 unknown


Aortic root (mm)
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Age (year)


150
100
50
0
Event / 1000 pt-year
Type A dissection
Type A dissection or death unknown cause
Type B dissection
0-39
40-44
45-49
50-54
55-64
Aortic root diameter (mm)