Aortic Event Rate in the Marfan Population
A Cohort Study

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Background—Optimal management, including timing of surgery, remains debated in Marfan syndrome because of a lack of data on aortic risk associated with this disease.

Methods and Results—We used our database to evaluate aortic risk associated with standardized care. Patients who fulfilled the international criteria, had not had previous aortic surgery or dissection, and came to our center at least twice were included. Aortic measurements were made with echocardiography (every 2 years); patients were given systematic β-blockade and advice about sports activities. Prophylactic aortic surgery was proposed when the maximal aortic diameter reached 50 mm. Seven hundred thirty-two patients with Marfan syndrome were followed up for a mean of 6.6 years. Five deaths and 2 dissections of the ascending aorta occurred during follow-up. Event rate (death/aortic dissection) was 0.17%/y. Risk rose with increasing aortic diameter measured within 2 years of the event: from 0.09%/y per year (95% confidence interval, 0.00–0.20) when the aortic diameter was <40 mm to 0.3% (95% confidence interval, 0.00–0.71) with diameters of 45 to 49 mm and 1.33% (95% confidence interval, 0.00–3.93) with diameters of 50 to 54 mm. The risk increased 4 times at diameters ≥50 mm. The annual risk dropped below 0.05% when the aortic diameter was <50 mm after exclusion of a neonatal patient, a woman who became pregnant against our recommendation, and a 72-year-old woman with previous myocardial infarction.

Conclusions—Risk of sudden death or aortic dissection remains low in patients with Marfan syndrome and aortic diameter between 45 and 49 mm. Aortic diameter of 50 mm appears to be a reasonable threshold for prophylactic surgery. **(*Circulation*. 2012;125:226-232.)**

Key Words: aorta ■ aortic aneurysm, familial thoracic ■ Marfan syndrome

Marfan syndrome is a genetic disorder associated with a decreased life expectancy related to the risk of aortic dissection and rupture, leading to death.[1] The life expectancy of these individuals has increased tremendously, by 30 years, over the past 30 years.[2] This improvement is due to earlier diagnosis through increased clinical awareness, familial screening in asymptomatic patients, improved presymptomatic diagnosis in family members resulting from greater recognition of genetic mutations, and better evaluation of aortic risk by easy and reproducible aortic imaging with 2-dimensional echocardiography, computed tomography scanning, and magnetic resonance imaging, allowing regular annual follow-up. These improvements have led to scheduled, timely prophylactic aortic surgery, before aortic dissection or rupture. The optimal timing for aortic surgery has been a subject of debate,[3] but 2 recent task forces have proposed 50 mm as a cutoff value for aortic diameter in terms of the timing of aortic root replacement.[4,5] The importance of the aortic diameter at the level of the sinuses of Valsalva as a determinant of risk of an aortic event in patients with ascending aortic aneurysm is well established[6]; it is widely agreed that this is the most accurate variable for assessment of risk of aortic dissection or rupture in this population. However, no such data are available for patients with Marfan syndrome.[7] These data are important because aortic dissection may occur at different diameters in patients with versus without Marfan syndrome.[8]

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Using data from a large population of patients with Marfan syndrome who fulfilled the international criteria and were followed up for >6 years, we calculated the annual aortic

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event rate as a function of aortic root diameter and propose the optimal timing for surgery.

Methods

Patient Population

Our outpatient reference center for patients with Marfan syndrome and related syndromes was established in 1996. The clinic offers complete diagnostic screening and follow-up of patients in France. Over the course of 1 day at the clinic, each patient sees a cardiologist (and has an echocardiogram), a geneticist (and has blood drawn for DNA analysis if appropriate), an ophthalmologist, and a pediatrician or rheumatologist, depending on the patient's age. Patient data are recorded in a database.

Only patients who visited the center at least twice and fulfilled the international Ghent nosology criteria[9] for Marfan syndrome 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 before their first visit to the center.

Follow-Up

The policy is to schedule a follow-up visit at the clinic every 2 years, during which the aortic root diameter is measured with echocardiography. In most cases, follow-up and aortic measurement are carried out in alternate years by a private cardiologist (although some patients are followed up annually in our center). Patients who miss scheduled visits are followed up by telephone to find out the reason.

Medical Care

All patients diagnosed with Marfan syndrome are recommended β-blocker therapy,[10] regardless of their aortic diameter (ie, whether or not it is dilated). In most cases, patients are given atenolol at a target dose of 100 mg, which can be decreased in case of intolerance or changed for another β-blocker (usually bisoprolol or nebivolol at a target dose of 10 mg) or a calcium antagonist (verapamil or diltiazem).

Patients are recommended to limit their levels of exercise and to avoid competitive sports and isometric exercises.[11] Recreational jogging, cycling, and swimming are recommended. These recommendations are for patients with Marfan syndrome who have not had an aortic event.

Surgical Care

Prophylactic aortic surgery is proposed when the patient's maximal aortic diameter reaches $\geq$50 mm. Surgery has, however, been performed earlier in some cases at the patient's request (including prophylactic aortic surgery before scheduled pregnancy), in patients with a family history of early aortic dissection, or because of recommendations of surgeons from other institutions.[3]

Aortic Measurement

Echocardiography was performed by 1 of 5 trained echocardiographers on a Sequoia (Siemens, Mountain View, CA) or Vivid 7 (General Electric, Horten, Norway) ultrasound system. Adequate multifrequency transducers, ranging from 2 to 5 MHz and 3 to 8 MHz, were used. Patients were in lateral decubitus in resting conditions. Aortic root diameters were measured according to the latest 2005 American Society of Echocardiography chamber quantification guidelines,[12] and Roman nomograms were used.[13] 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 sinuses of Valsalva, sinotubular junction, and proximal ascending aorta were measured in diastole perpendicular to the long axis of the aorta with 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, measurement with a different technique (usually computed tomography scanning or magnetic resonance imaging, less frequently transesophageal echocardiography) was performed. This rule was also followed when the aortic diameter changed significantly between 2 measurements (confirmed by another technique).

The echocardiographic measurements were considered the gold standard. Aortic diameter standardized to body surface area (cm/m^2)[3,14] was calculated.

Aortic Events

Aortic events were defined as dissection of the ascending aorta, death, or aortic surgery. Death was classified as death related to aortic dissection, sudden death, noncardiovascular death, or death of unknown cause. Calculation of the aortic event rate was based on the whole population and solely on data from adult patients ($\geq$18 years of age).

Statistical Analysis

Continuous data are presented as mean$\pm$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 (ie, the aortic diameter was considered to be constant over 2 years for the purposes of statistical analysis). 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 annual early aortic event rate was calculated as the ratio of the number of aortic events divided by the number of patient-years for each range of aortic diameter. Only events occurring at most 2 years after the last aortic measurement in our center were used for this calculation. Because of the low values, the results are reported for 100 years (event percent-years); 95% confidence intervals (95% CI) were calculated according to the normal distribution. Statistical analyses were performed with SAS 9.1 (SAS institute Inc, Cary, NC).

Results

Patient Population

A total of 1097 patients who presented to the clinic between 1996 and 2010 fulfilled the international diagnostic criteria for Marfan syndrome. Of these patients, 243 attended only once, 92 had presented aortic dissection of the ascending or descending aorta before their first visit, and 156 had undergone previous aortic surgery; these patients were excluded from the study. Reason for surgery was aortic dissection in 84 (56% male; mean age at first visit, 39.4$\pm$10.9 years; mean age at the time of surgery, 34.4$\pm$11.6 years). In the 72 other patients (59.7% male; age at first visit, 36.1$\pm$12.7 years; mean age at the time of surgery, 30.2 years; mean diameter, 61$\pm$13 mm), the reason given for surgery was aortic diameter $>$50 mm, increase in diameter after pregnancy, and symptomatic mitral or aortic regurgitation. In 3 patients with preoperative aortic diameter $<$50 mm, no clear reason could be obtained.

The population therefore comprised 732 patients, 345 (47.1%) of whom were men. Mean age at first visit was 24.5$\pm$16.4 years (range, 0–80 years; Figure 1); 82.1% received β-blocker therapy during follow-up. The aortic diameter at the level of the sinuses of Valsalva at the first visit ranged from 17 to 67 mm (mean, 37.4$\pm$8.7; median, 38 mm).

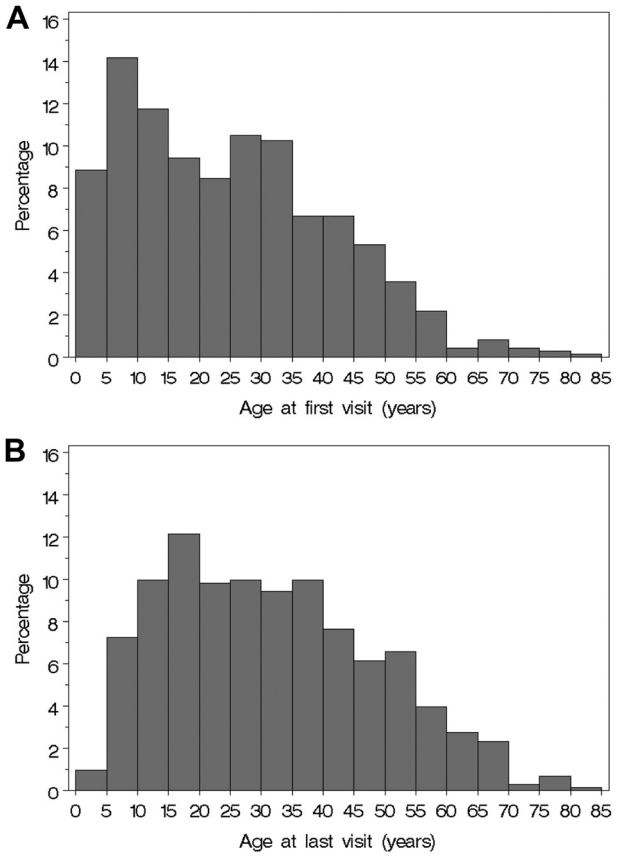

Figure 1. Age of the population at the (**A**) first and (**B**) last visit.

The mean follow-up was 6.6±4.3 years (median, 5.6 years; interquartile range, 2.8 to 10.1 years); the average increase in the sinuses of Valsalva was 0.50±0.89 mm/y.

Follow-up for hospitalization, surgery, or death was obtained for all patients except 15 (2%), including 8 who clearly stated that they did not want to be followed up in our center any more. Only 1 of these 15 patients had an aortic diameter between 45 and 50 mm at the last visit to our center.

Aortic Events During Follow-Up

Over the course of the study, 5 patients died within 2 years of their previous visit:

1. A boy with a severe form of Marfan syndrome (neonatal Marfan syndrome) died at 3 years of age after rapid aortic dilatation and important mitral valve regurgitation with heart failure. His diameter at 1 year of age was measured at 22 mm.
2. An 18-year-old woman who was receiving β-blocker therapy (nadolol 80 mg/d) died suddenly 3 months after her previous visit to our center. Her aortic diameter was stable at 33 mm, ie, 19.3 mm/m^2. No autopsy was performed.
3. A 37-year-old man died suddenly 4 months after his previous visit. His aortic diameter at the level of Valsalva was 48 mm, ie, 23.3 mm/m^2. It was 46 mm 2 years earlier and stable at 45 mm for the 6 preceding years. He was receiving β-blocker therapy. Although an autopsy was performed for police reasons, no precise cause of death was given.
4. A 38-year-old woman died 7 months after her previous visit. She incurred acute aortic dissection during pregnancy (amenorrhea, 25 weeks), and emergency surgery was unsuccessful. Aortic diameter was 45 mm, ie, 22.7 mm/m^2. She had been informed about the risks of pregnancy, which was considered medically contraindicated. She also had a history of phlebitis, and β-blockade was limited to a low dose because of Reynaud phenomenon.
5. A 72-year-old woman died 2 years after her previous visit to our center. She had undergone 2 previous mitral valve replacements, a coronary artery bypass, and percutaneous coronary artery dilatation during an anteroseptal myocardial infarction complicated by acute heart failure necessitating intubation. Aortic measurements was 43 mm, ie, 22.7 mm/m^2.

Two additional patients required emergency aortic surgery (Bentall) because of aortic dissection occurring within 2 years of their previous visit:

1. A 56-year-old man had attended the clinic 1 year before the dissection. He had undergone a previous mitral valve replacement (in 1981). Aortic diameter measurements remained unchanged at 55 mm, ie, 25.4 mm/m^2, for 3 years. Aortic surgery had been proposed but systematically postponed by the patient.
2. A 32-year-old woman had attended the clinic 1 year before the dissection. Her aortic diameter was measured at 53 mm (ie, 31.7 mm/m^2), and aortic regurgitation of 2+ was noted. A computed tomography scan was proposed but rejected by the patient, who did not return to the clinic.

Overall, 7 events occurred during 4110 years of patient follow-up; the mean annual risk of death or aortic dissection was 0.17% in the overall population (0.12% risk of death and 0.05% risk of aortic dissection). This risk dropped below 0.05% when only patients with an aortic diameter <50 mm were considered (excluding data from 2 patients who postponed surgery despite having aortic diameters >50 mm) after the exclusion of a neonatal patient, a woman who became pregnant against medical advice, and a 72-year-old woman with a previous myocardial infarction and multiple cardiac surgery (mitral valve replacement twice and 1 coronary artery bypass).

Additional Events

Three patients (detailed below) who did not undergo surgery and were lost to regular follow-up were reported to have died (ie, who died >2 years after their previous clinic visit). Their deaths were therefore not used to calculate annual aortic risk.

1. A 32-year-man died of an acute aortic dissection, diagnosed at autopsy, 10 years after his last visit to our center. His last aortic measurement was 47 mm, ie, 25.5 mm/m^2. He did not take any medication.
2. A 35-year-old man died of aortic dissection 5 years after his last visit to our center. Last aortic measurement was 43 mm, ie, 21.6 mm/m^2.
3. A 23-year-old man died of aortic rupture 3 years after his last visit. His maximal aortic diameter was measured at 45 mm (28.8 mm/m^2).

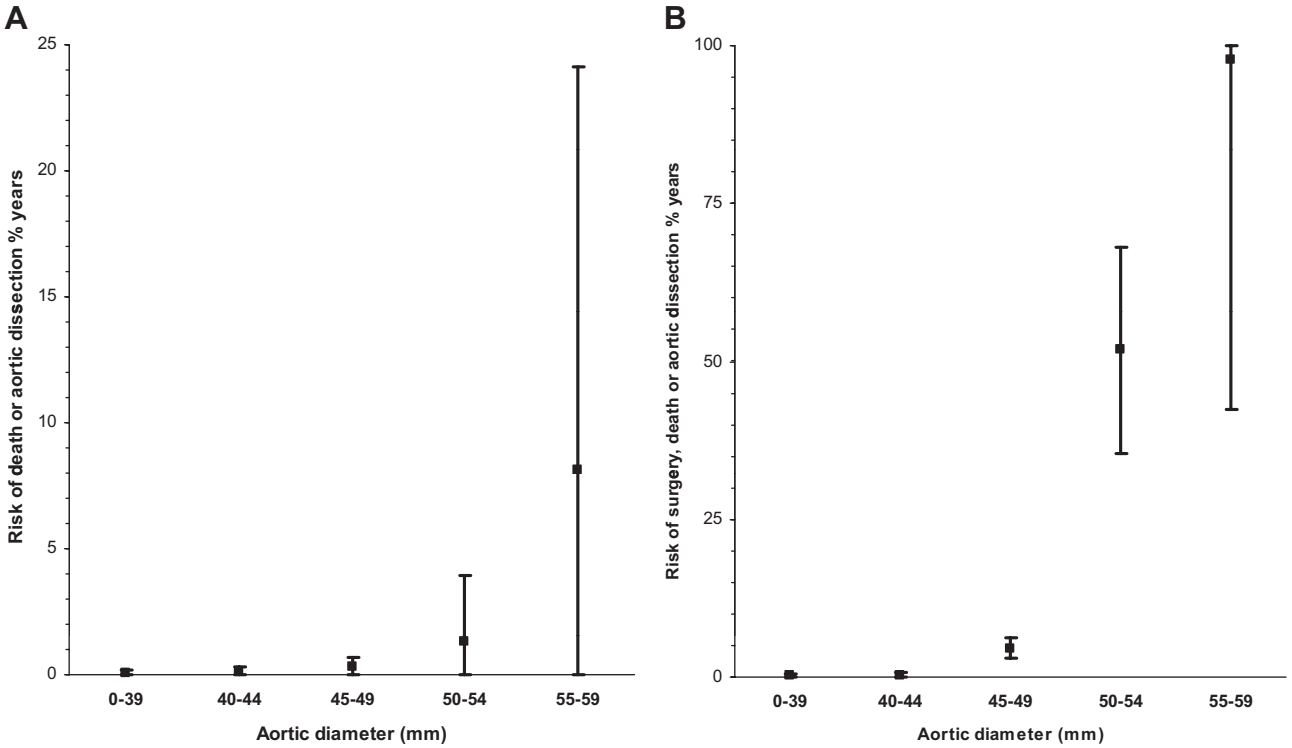

Figure 2. Event rates and 95% confidence interval according to aortic diameter measured at the level of the sinuses of Valsalva: (**A**) death or aortic dissection and (**B**) aortic surgery, death, or aortic dissection. Aortic surgery was performed for aortic dilatation.

4. A 41-year-old man died in a motorcycle accident 3 months after his last visit to the center. At that time, his aortic diameter was 44 mm (20.2 mm/m^2).

Aortic Risk as a Function of Aortic Diameter at the Level of the Sinuses of Valsalva

Annual risk of death or aortic dissection was calculated according to aortic diameter (Figure 2 and the Table). However, because surgery was recommended for diameters ≥50 mm, there remained only a small set of patients who delayed surgery, and the CIs are much wider for diameters ≥50 mm.

Twenty-nine patients underwent aortic surgery at a diameter between 45 and 50 mm as measured with echocardiography. The reasons were a diameter of >50 mm measured with another imaging technique (n=11), planned pregnancy (n=3), history of dissection in the family (n=3), mitral regurgitation (n=2), aortic regurgitation (n=1), important increase in diameter (n=1), planned surgery of the back (n=1), and official recommendations[3] for surgical threshold at 45 mm (n=7).

Because the proposition has been made to use normalized aortic diameter by body surface area (mm/m^2), aortic risk was also calculated according to these values.[3,6] The number obtained should be used with caution because the decision to operate was not based on this variable. Normalized aortic diameter was associated with an aortic risk of 0.10%/y (95% CI, 0.0–0.3) when <20 mm/m^2, 0.14% (95% CI, 0.03–0.27) for 20 to 30 mm/m^2, 0.43% (95% CI, 0.0–1.27) for 30 to 42.5 mm/m^2, and 5.07% (95% CI, 0.0–15.01) for greater diameters. The number of patient-years of follow-up was very low for diameters >42.5 mm/m^2 (19.7 years), rendering the data even more unreliable. One must keep in mind that aortic surgery was performed in this population as a function of absolute aortic diameter (Figure 1B), ie, ≥50 mm.

The same calculations based on only data from adult patients (≥18 years of age) gave similar results; the risk of aortic dissection or death was 0.10%/y (95% CI, 0.00–0.29) for an aortic diameter of 0 to 39 mm, 0.12% (95% CI, 0.00–0.34) for 40 to 44 mm, 0.31% (95% CI, 0.00–0.74) for 45 to 49 mm, 1.37% (95% CI, 0.00–4.07) for 50 to 54 mm, and 8.14% (95% CI, 0.00–24.09) for ≥55 mm.

Discussion

The main finding of our study is the low rate of aortic events in a population diagnosed with Marfan syndrome according to the international criteria (Ghent nosology)[9] when current recommendations are applied, ie, systematic β-blockade, advice about sports and physical activity, regular aortic measurements with echocardiography, and prophylactic aortic root surgery for an absolute aortic diameter of 50 mm.[15] With the use of these rules, 7 aortic events occurred among 732 patients during a follow-up of 6.6±4.3 years, leading to an annual risk of 0.17%. This risk can be stratified according to aortic diameter, as shown in Figure 2. When only patients with aortic diameter <50 mm were considered and excluding 1 neonatal patient with Marfan syndrome, a pregnant woman with an aortic diameter of 45 mm, and a 72-year-old woman who had undergone 2 previous surgeries and had had 1 acute myocardial infarction, the annual risk was <0.05%. Preventing aortic dissection is critical because it is well established that previous aortic dissection alters survival, particularly if

Table. Annual Aortic Risk as a Function of Maximal Aortic Diameter Measured at the Level of the Sinuses of Valsalva With Echocardiography Within 2 Years

	Patients, n	Event, n	Follow-Up, patient-y	Annual Risk, % (95% CI)
Aortic event without surgery				
Aortic diameter (mm)				
0–39	423	2	2353	0.09 (0.00–0.20)
40–44	219	1	995	0.10 (0.00–0.30)
45–49	157	2	675	0.30 (0.00–0.71)
50–54	54	1	75	1.33 (0.00–3.93)
55–59	14	1	12	8.14 (0.00–24.10)
Aortic event with surgery				
Aortic diameter (mm)				
0–39	423	7	2353	0.30 (0.08–0.52)
40–44	219	3	995	0.30 (0.00–0.64)
45–49	157	31	675	4.59 (2.98–6.21)
50–54	54	39	75	51.75 (35.51–68.00)
55–59	14	12	12	97.68 (42.41–100.00)

CI indicates confidence interval. Aortic event without surgery includes death (cardiovascular death, including sudden or of unknown cause) and aortic dissection. Surgery refers to aortic surgery with or without valve replacement.

dissected aorta remains after surgery,[16] and these short- and long-term risks are to be compared with the risk of preventive aortic surgery, which is low in experienced centers.

Very few data are available on the real aortic risk in a population with an aneurysm of the ascending aorta related to Marfan syndrome. From the Duke University database, the event rate was concluded to be low when the maximal diameter was <60 mm in patients with thoracic aortic aneurysm.[6,14] According to the International Registry of Acute Aortic Dissection, limited to patients in whom aortic dissection had occurred, aortic dissection was observed for diameters <50 mm, indicating that this was still a possible event.[8] However, reaching further conclusions from this database is difficult because we do not know how many patients with a similar aortic diameter but without dissection were alive. Estimation of this number is difficult because in most patients the condition can remain unrecognized, which also prevents them from benefiting from preventive care, increasing their risk of aortic dissection or death. Early recognition of affected individuals is possible in most patients with Marfan syndrome because of the genetic nature of the disease and familial screening. It is therefore theoretically easier to evaluate the actual risk of aortic events in this population than in patients with aortic aneurysm from other causes. However, owing to the rarity of the disease and the absence of large series, recommendations have been based on cohorts of patients with aortic aneurysm of unknown cause and on expert opinions, leading to inconsistencies.[3–5] We hope that the data from our present series will help to settle the debate.

In the Marfan population, a greater risk of aortic dissection has been associated with a larger aortic diameter[17]; the extension of dilatation beyond the sino-Valsalva junction[18]; a family history of early aortic dissection[19]; the presence of hypertension; the absence of β-blockade[20]; the practice of intensive sports, including bodybuilding[21,22]; the presence of sleep apnea[23]; and a rapid increase in aortic diameter. We confirm that aortic risk appears to be related to aortic diameter (Figure 1), but we could not evaluate the importance of other factors in this study for 2 reasons. Because the lessons derived from previous studies have been applied to our population, the importance of previously recognized risk factors cannot be derived from the present study; for example, treatment was given for hypertension, participation in intensive sports was discouraged, and aortic surgery was proposed below the usual threshold if the aortic diameter was increasing rapidly (provided that this increase was confirmed by a second imaging technique) or if aortic dissection was documented in a family with an aortic diameter <50 mm. As a result, the low event rate gives us insufficient power to perform a multivariable analysis. On the other hand, our data validate the proposed scheme for medical care of patients with Marfan syndrome. Our data also underscore the importance of precise measurement of aortic diameter in these patients, with differences of a few millimeters being significant, particularly in terms of the indication for surgery.

In the present study, we included only patients who were first seen in our clinic before the occurrence of an aortic event or aortic surgery, indicating that the event rates are those observed in a population with a recognized diagnosis who were prescribed β-blockade or calcium inhibitor when β-blockade was not tolerated, were generally avoiding strenuous exercise, and were being evaluated regularly. The findings may therefore differ from the spontaneous natural history of patients with Marfan syndrome who are not benefiting from such care. However, from a practical perspective, our data reflect the clinical impact of modern care in this population.

The efficiency of modern management of patients with Marfan syndrome underscores the importance of early diagnosis, with the help of systematic familial screening and, when necessary and possible, molecular biology, to give the larger population the chance to benefit from this type of management. The findings also indicate that the end point in studies testing new strategies or therapies should aim at delaying aortic dilatation and therefore surgery and that mortality is probably not a powerful end point in this population.[24–27]

Study Limitations

This study was an observational study in a historical cohort. However, the data were entered prospectively, and the centralized healthcare organization on rare diseases in France—aimed at favoring epidemiological studies—and close collaboration with the French Marfan Association (AFSMA) favor systematic reporting of events in this population to our center, even when patients are not followed up regularly by our center. Besides, only 1 patient with an aortic diameter between 45 and 50 mm was lost to follow-up.

Conclusions

The results of our study suggest that modern medical care and scheduled surgery can prevent aortic dissection in almost all patients with Marfan syndrome, provided that β-blockade is given to all patients, intensive sports activity is avoided, and annual echocardiographic follow-up is provided. In patients with Marfan syndrome, the risk of sudden death or dissection remains low in patients with aortic dilatation between 45 and 49 mm (≈0.3%/y). The risk of sudden death or dissection is even lower (<0.05%/y) when evaluated in a population of Marfan patients following modern care. Therefore, 50 mm appears to be a reasonable threshold for prophylactic surgery in the absence of specific risk factors (eg, family history of dissection with mild dilatation) and underscores the importance of early diagnosis based on familial screening.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Marfan syndrome is a genetic disease usually related to a mutation in the gene coding for *FBN1*. It is transmitted as a dominant autosomal disease. The genetic nature of the disease allows early diagnosis with familial screening. Progressive aortic dilatation leading to aortic dissection and rupture is the main life-threatening complication associated with the syndrome. Medical management includes β-blocker therapy and prohibition of intensive sports. Regular follow-up visits are crucial to evaluate the aortic diameter with echocardiography and the need for prophylactic aortic surgery. In the present study, the management of 732 patients followed these rules, and the value of 50 mm was our threshold for preventive aortic surgery. Using this strategy, we showed that the risk of aortic event (dissection, rupture, or sudden death) was <0.05%/y in the population with an aortic diameter <50 mm in the absence of known risk factors such as pregnancy, familial history of aortic dissection at a low diameter, or rapid increase in diameter. This risk increases with the diameter of the aorta at the level of the sinuses of Valsalva; this increase was >4-fold in the patients whose aorta was 50 to 54 mm compared with 45 to 49 mm. The 50-mm threshold at the level of Valsalva appears to be a reasonable threshold for proposing preventive aortic surgery in patients with Marfan syndrome.