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Aortic Event Rate in the Marfan Population: A Cohort Study

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Journal Subject Codes: [109] Clinical genetics; [35] CV surgery: aortic and vascular disease
Abstract:

Background - Optimal management, including timing of surgery, remains debated in Marfan syndrome (MFS), due to lack of data on aortic risk associated with this disease.

Methods and Results - We used our database to evaluate aortic risk associated with standardised care. Patients who fulfilled the international criteria, had not had previous aortic surgery or dissection and who came to our centre at least twice were included. Aortic measurements were made using echocardiography (every 2 years); patients were given systematic beta-blockade and advice about sports activities. Prophylactic aortic surgery was proposed when the maximal aortic diameter reached 50 mm.

732 patients with MFS were followed up for a mean of 6.6 years. Five deaths and two dissections of the ascending aorta occurred during follow-up. Event rate (death/aortic dissection) was 0.17% per year. Risk rose with increasing aortic diameter measured within 2 years of the event: from 0.09% per year (95% confidence interval 0.00–0.20) when the aortic diameter was <40 mm, to 0.3% (0.00–0.71) with diameters of 45–49 mm, and 1.33% (0.00–3.93) with diameters of 50-54 mm: the risk increased 4-times above 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 MFS and aortic diameter between 45 and 49 mm. 50 mm appears to be a reasonable threshold for prophylactic surgery.

Key words: Marfan Syndrome, Aorta, Aortic Dissection, Aortic Surgery
Introduction

Marfan syndrome is a genetic disorder associated with a decreased life expectancy related to the risk of aortic dissection and rupture leading to death.\textsuperscript{1} The life expectancy of these individuals has increased tremendously, by 30 years, over the past 30 years.\textsuperscript{2} This improvement is due to earlier diagnosis through increased clinical awareness, familial screening in asymptomatic patients, improved pre-symptomatic diagnosis in family members due to greater recognition of genetic mutations, and better evaluation of aortic risk by easy and reproducible aortic imaging using two-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 the subject of debate \textsuperscript{3}, but the 2 more recent task forces have proposed 50 mm as a cut-off value for aortic diameter in terms of the timing of aortic root replacement \textsuperscript{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\textsuperscript{6}; it is widely agreed that this is the more 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.\textsuperscript{7} These data are important because aortic dissection may occur at different diameters in patients with versus those without Marfan syndrome.\textsuperscript{8}

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

Patient population

Our outpatient reference centre 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 blood is drawn for DNA analysis, if appropriate), an ophthalmologist, and a paediatrician or rheumatologist, depending upon the patient’s age. Patient data are recorded in a database.

Only patients who visited the centre at least twice and fulfilled the international Ghent nosology criteria for Marfan syndrome were considered for this study. Patients were excluded from the study if they had undergone aortic root surgery or presented a history of aortic dissection before their first visit to the centre.

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 using 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 centre). 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 beta-blocker therapy, irrespective 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 beta-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 avoid competitive sports and isometric exercises. 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 patients 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.

Aortic measurement

Echocardiography was performed by one of five trained echocardiographists on a Sequoia (Siemens, Mountain View, CA, USA) or Vivid 7 (General Electrics, Horten, Norway) ultrasound system. Adequate multifrequency transducers, ranging from 2–5 and 3–8 MHz, were used. Patients were in lateral decubitus, in resting conditions. Aortic root diameters were measured according to the latest 2005 American Society of Echography chamber quantification guidelines, and Roman nomograms were used. The best parasternal great axis view was used, in two-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, sino-tubular 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
four defined levels was recorded in the database. Measurements were done on-line and off-line, using appropriate blown-up views for higher precision. Diameters were given in millimetres (mm).

When the aortic-diameter measurement was thought to be unreliable by the cardiologist, measurement using a different technique (usually computed tomography scanning or magnetic resonance imaging, and less frequently transoesophageal echocardiography) was performed. This rule was also followed when the aortic diameter changed significantly between two measurements (confirmed by another technique). The echocardiographic measurements were considered as the gold standard. Aortic diameter standardised to body surface area \( \frac{\text{cm/m}^2}{3,14} \) 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, non-cardiovascular death, or death of unknown cause. Calculation of the aortic event rate was based and on the whole population and solely on data from adult patients (aged \( \geq 18 \) years).

**Statistical analysis**

Continuous data are presented as mean ± standard deviation 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 centre were used for this calculation. Because of the low values, the results are reported for 100 years (event%years); 95CI intervals were calculated according to the normal distribution. Statistical analyses were performed using SAS 9.1 (SAS institute Inc, Cary, NC, USA)

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 only attended 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% males, mean age at first visit 39.4 ± 10.9 years, mean age at the time of surgery 34.4 ± 11.6 years). In the 72 other patients (59.7% males, age at first visit 36.1 ± 12.7 years, mean age at the time of surgery 30.2 years, mean diameter 61 ± 13 mm), the reason given for surgery was aortic diameter above 50 mm, increase in diameter after pregnancy, symptomatic mitral or aortic regurgitation. In 3 patients with preoperative aortic diameter below 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 ± 16·4 years (range 0–80) (Figure 1); 82·1% received beta-blocker therapy during follow-up. The aortic diameter at the level of the sinuses of Valsalva at the first visit ranged from 17–67 mm (mean 37·4 ± 8·7, median 38 mm). The mean follow-up was 6·6 ±
4·3 years, median 5·6 years, IQR [2·8-10·1]; average increase in the sinuses of Valsalva was 0·50 ± 0·89 mm/year.

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

**Aortic events during follow-up**

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

- 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.

- An 18-year-old woman, who was receiving beta-blocker therapy (nadolol 80 mg/d), presented sudden death 3 months after her previous visit to our centre. Her aortic diameter was stable at 33 mm, ie, 19·3 mm/m². No autopsy was performed.

- 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/m². It was 46 mm 2 years earlier, and stable at 45 mm for the 6 preceding years. He was receiving beta-blocker therapy. Although an autopsy was performed for police reasons, no precise cause of death was given.

- A 38-year-old woman died 7 months after her previous visit. She incurred acute aortic dissection during pregnancy (amenorrhoea 25 weeks) and emergency surgery was unsuccessful. Aortic diameter was 45 mm, ie, 22·7 mm/m². She had been informed about the risks of pregnancy, which was considered as medically contraindicated. She also had a history of phlebitis, and beta-blockade was limited to a low dose due to Raynaud’s
phenomenon.

- A 72-year-old woman died 2 years after her previous visit to our centre. She had undergone two 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/m².

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

- 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/m² for 3 years. Aortic surgery had been proposed, but systematically postponed by the patient.

- 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/m²) and aortic regurgitation 2+ was noted. A computed tomography scan was proposed but rejected by the patient, who did not return subsequently to the clinic.

Overall, seven 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 two 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 by-
pass).

**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 not therefore used for the calculation of annual aortic risk.

- A 32-year-man died because of an acute aortic dissection, diagnosed at autopsy, 10 years after his last visit to our centre. Last aortic measurement was 47 mm, ie, 25·5 mm/m². He did not take any medication.
- A 35-year-old man died from aortic dissection 5 years after his last visit to our centre. Last aortic measurement was 43 mm, ie, 21·6 mm/m².
- A 23-year-old man died from aortic rupture 3 years after his last visit. His maximal aortic diameter was measured at 45 mm (28.8 mm/m²).
- A 41-year-old man died in a motorcycle accident 3 months after his last visit to the centre. At that time the aortic diameter was 44 mm (20.2 mm/m²).

**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 **Table 1**. However, as surgery was recommended for diameters of 50 mm or more, there remained only a small set of patients who delayed surgery and the confidence intervals are much wider for diameters >50 mm.

Twenty nine patients underwent aortic surgery at a diameter measured between 45 and 50 mm with echocardiography. This was because a diameter exceeding 50 mm was measured using 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
planned surgery of the back (n=1), and official recommendations\textsuperscript{3} for surgical threshold at 45 mm (n=7).

As the proposition has been made to use normalised aortic diameter by body surface area (mm/m\textsuperscript{2}), aortic risk was also calculated according to these values.\textsuperscript{3,6} The figures obtained should be used with caution, as the decision to operate was not based upon this variable. Normalised aortic diameter was associated with an aortic risk of 0·10% per year (95% confidence interval 0.0–0·3) when <20 mm/m\textsuperscript{2}; 0·14% (0·03–0·27) for 20–30 mm/m\textsuperscript{2}, 0·43% (0.0–1·27) for 30–42·5 mm/m\textsuperscript{2}, and 5·07% (0.0–15·01) for diameters above. The number of patient-years of follow-up was very low above 42·5 mm/m\textsuperscript{2} (19·7 years), rendering the data even more unreliable. One has to keep in mind that aortic surgery was performed in this population as a function of absolute aortic diameter (\textbf{Figure 1B}), i.e. >50 mm.

The same calculations based on data from adult patients (age ≥18 years) only gave similar results: the risk of aortic dissection or death was 0·10% per year (95% confidence interval 0·00–0·29) for an aortic diameter of 0–39 mm; 0·12% (0·00–0·34) for a diameter of 40–44 mm; 0·31% (0·00–0·74) for 45–49 mm; 1·37% (0·00–4·07) for 50–54 mm; and 8·14% (0·00–24·09) for ≥55 mm.

\textbf{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),\textsuperscript{9} when current recommendations are applied, i.e., systematic beta-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.\textsuperscript{15} Using these rules, seven 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 one neonatal patient with Marfan
syndrome, a pregnant woman with an aortic diameter of 45 mm, and a 72-year-old woman who
had undergone two previous surgeries and had had one acute myocardial infarction, the annual
risk was <0.05%. Preventing aortic dissection is critical as it is well established that previous
aortic dissection alters survival, particularly if dissected aorta remains after surgery\(^\text{16}\), and this
short and long-term risk is to be compared with the risk of preventive aortic surgery which is low
in experienced centres.

Very few data are available about 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.\(^\text{6,14}\) 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.\(^\text{8}\) However, reaching further conclusions
from this database is difficult, as one does 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 unrecognised, 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 due to the genetic nature of the
disease and the 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 from expert opinions, leading to inconsistencies.\textsuperscript{3-5} We hope that the data from our current 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,\textsuperscript{17} the extension of dilatation beyond the sino-valsalva junction,\textsuperscript{18} a family history of early aortic dissection,\textsuperscript{19} the presence of hypertension, the absence of beta-blockade,\textsuperscript{20} the practice of intensive sports including body-building,\textsuperscript{21-22} the presence of sleep apnoea,\textsuperscript{23} and a rapid increase in aortic diameter. We confirm that aortic risk appears related to aortic diameter (Figure 1), but we could not evaluate the importance of other factors in this study for two reasons. As the lessons derived from previous studies have been applied to our population, the importance of previously recognised 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 below the range of 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 few mm being significant, particularly regarding 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 recognised diagnosis, who were prescribed beta-blockade or calcium...
inhibitor when not tolerated, were generally avoiding strenuous exercise, and were regularly being evaluated. 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 endpoint in this population.24-27

**Study limitations**

This study was an observational study in a historical cohort. However, the data were entered prospectively, and centralised healthcare organisation on rare diseases in France – aimed at favouring epidemiological studies – as well as close collaboration with the French Marfan Association (AFSMA), favour systematic reporting of events in this population to our centre, even when patients are not followed-up regularly by our centre. Besides, only one 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: beta-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%/year). The risk of sudden death or dissection is even lower (<0.05%/year) 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 (e.g. family history of dissection with mild dilatation) and underscores the importance of early diagnosis, based on familial screening.

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Conflict of Interest Disclosures: None

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**Table 1.** Annual aortic risk as a function of maximal aortic diameter measured at the level of the sinuses of Valsalva using echocardiography within 2 years. Aortic event without surgery includes death (cardiovascular death, including sudden or of unknown cause) or aortic dissection. Surgery refers to aortic surgery with or without valve replacement.

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<th>Patient-years of follow-up</th>
<th>Annual risk (%) [CI 95%]</th>
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<th>Patients (n)</th>
<th>Event number</th>
<th>Patient-years of follow-up</th>
<th>Annual risk (%) [CI 95%]</th>
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Figure Legends:

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

**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.