# Marfan syndrome and related connective tissue disorders

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CHAPTER 8

# Prophylactic aortic root surgery in patients with Marfan syndrome: 10 years' experience with a protocol based on body surface area

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**ABSTRACT**

***Background***

Current guidelines recommending prophylactic aortic root replacement in Marfan syndrome are based on absolute diameters of the aortic root. However, aortic root diameter is a function of body surface area (BSA). Here, we report our experience with a protocol for prophylactic aortic root replacement based on BSA.

***Methods***

Patients with established Marfan syndrome (Ghent criteria) and without prior aortic surgery were eligible for our study. Aortic root ratio was defined as the ratio between the observed aortic root diameter (as measured during annual echocardiography) and the maximum predicted aortic root diameter as calculated according to age and BSA. Replacement surgery was performed if dilatation of the aortic root during follow up resulted in an aortic root ratio $\geq$1.3.

***Results***

Fifty-three patients fulfilled the entry criteria (24 men/29 women, median age at baseline 27 years, range 18-59 years). During follow up between 1997 and 2007 (mean 4.7 ±3.2 years) four patients underwent uncomplicated aortic root replacement; two had an aortic root ratio $\geq$1.3 (aortic root diameters were 4.9 and 5.2 cm, respectively), one had aortic root dilatation of 0.4 cm/year and a positive family history for aortic dissection and one had an aneurysm of the ascending aorta as the primary indication. None of the patients in the whole group suffered from type A aortic dissection and there was no mortality.

***Conclusions***

Although numbers are small, our protocol for prophylactic aortic root replacement in patients with Marfan syndrome based on BSA, was effective in terms of preventing aortic dissection and mortality.

## INTRODUCTION

Marfan syndrome is an autosomal dominantly inherited disorder of connective tissue involving the ocular, skeletal and cardiovascular systems.[1] From a management point of view, aortic root dilatation is the most important cardiovascular manifestation, predisposing to aortic dissection and rupture. [2] Prophylactic aortic root replacement is being applied to prevent these potentially catastrophic aortic complications but there is still some debate about the diameter at which the aortic root should be replaced. The current international guideline states that the aortic root should be replaced when the diameter is >5.0-5.5 cm.[3] The Dutch guideline[4] provides a further specification and states that the following situations warrant surgical intervention: 1) an aortic root diameter >5.5 cm, 2) an aortic root diameter >5.0 cm in patients with a family history of aortic dissection, aortic root dilatation >0.2 cm/year, or severe aortic or mitral valve regurgitation that necessitates surgery, or 3) progressive dilatation or a diameter of approximately 5.0 cm in other parts of the aorta. However, several studies have shown that below these respective thresholds, aortic dissection and rupture can still occur.[5,6] Interestingly, in a retrospective analysis, Legget et al. demonstrated that when body surface area (BSA) is taken into account, Marfan syndrome patients are particularly at risk for dissection, rupture or cardiovascular death when the aortic root ratio (measured diameter/predicted diameter) is $\geq$1.3 (relative risk 2.7).[7] From 1997 onwards, we have applied Legget et al.'s threshold in a protocol for prophylactic aortic root replacement (with a slight modification). This study aims to describe our ten years of experience with this protocol based on BSA.

## PATIENTS AND METHODS

The study was performed in compliance with the principles outlined in the declaration of Helsinki and consistent with the regulations of the institutional ethics committee. Only patients who fulfilled the Ghent criteria for Marfan syndrome, as judged by the clinical geneticist (JPvT), were eligible for this study.[8] Part of our routine follow-up is to have every Marfan syndrome patient visit our outpatient clinic annually, and echocardiographic imaging is performed during this visit. If deemed necessary by the attending cardiologist (MPvdB), and particularly in the case of rapid dilatation of the aortic root, echocardiograms are done more often. Echocardiograms are performed according to a standard protocol, which includes measuring the aortic diameter at the level of the sinuses of Valsalva (aortic root). To account for possible inaccuracies in case of poor image quality is poor, an MRI- or CT-scan is performed. Only patients $\geq$18 years and for whom at least two echocardiograms were available, were included in this study. Patients who had prior aortic surgery were excluded. All Marfan syndrome patients in our institution receive treatment with a beta-blocker, unless contra-indicated or not tolerated. Alternative treatments consist of an angiotensin converting enzyme (ACE)-inhibitor or an angiotensin-2 (AT) receptor blocker.

The aortic root diameter was used to calculate the "aortic root ratio". This ratio was defined as:

$$\text{aortic root ratio} = \frac{\text{observed aortic root diameter (cm)}}{\text{maximum predicted aortic root diameter (cm)}}$$

The maximum predicted aortic root diameter based on body surface area (BSA) and age was established by inspecting the graphs as provided by Roman et al. which display in different age groups of healthy subjects the relation between BSA and aortic root diameter, including the upper limit of normal (figure 1a and 1b).[9] Body surface area was calculated using the following formula:[10]
BSA ($m^2$) = weight $(kg)^{0.5378}$ x length $(cm)^{0.3964}$ x 0.024265

Note: we used the *maximum* instead of the *mean* predicted aortic root diameter to calculate the aortic root ratio, by adding two standard deviations to the mean predicted aortic root diameter.

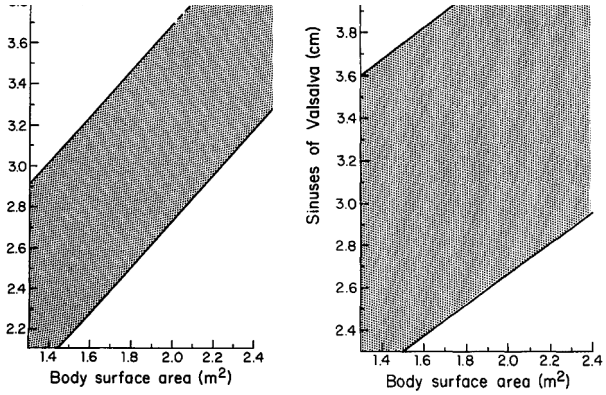


**Figure 1a.** 95% normal confidence limits for aortic root diameter at the sinuses of Valsalva in relation to body surface area in adults younger than 40 years of age (reprinted with permission).[9]
**Figure 1b.** 95% normal confidence limits for aortic root diameter at the sinuses of Valsalva in relation to body surface area in adults 40 years of age and older (reprinted with permission).[9]

According to the devised protocol, patients with an aortic root ratio ≥1.3 underwent prophylactic aortic root replacement within 3 months. In addition, prophylactic aortic root replacement was performed if aortic root dilatation was >0.2 cm/year, irrespective of the aortic root diameter, and especially in the case of a positive family history of aortic dissection. When echocardiographic assessment showed that patients met the criteria for prophylactic aortic root replacement, additional imaging studies were performed (CT- or MRI scan) to confirm echocardiographic measurements.

Finally, in order to get a global impression of the potential impact of our protocol on clinical practice, we also reviewed our surgical database to retrieve all the cases of surgically treated, acute type A aortic dissection in our institution between 1990 and 2006.

**Data analysis**

Continuous data are reported as mean (± SD) and categorical data as percentages unless stated otherwise. Median values (with range) are given in the case of non-normal distributions. Differences between groups were tested using parametric or non-parametric tests, as appropriate. A Multilevel

Model for Change was used to assess aortic root dilatation as a function of time and a p-value <0.05 was considered to indicate statistical significance. The analyses were carried out using STATA, version 10.0.

## RESULTS

### Clinical characteristics

Between January 1997 and April 2007, 53 patients fulfilled the inclusion criteria of this study. Their clinical characteristics are summarized in Table 1. Median age at baseline was 27 years (range 18-59 years). BSA varied considerably, ranging from 1.80 to 2.20 $m^2$. Accordingly, the threshold diameter for aortic root replacement (1.3 x maximum predicted aortic root diameter) varied considerably, ranging from 4.2 to 5.6 cm. Note: not only the absolute diameter at the first measurement but also the aortic root ratio was significantly larger in men compared to women, as well as the threshold for aortic root replacement. Beta-blocking agents were used by 33 patients (62%), ACE-inhibitors were used by 3 patients and an AT-receptor blocker was used by 1 patient. Mean follow-up was 4.7 years (±3.2), ranging from 0.1 to 10.3 years and total follow-up for the group was 251 years. The median number of repeated echocardiographic measurements was 4, ranging from 2 to 12.

**Table 1.** Clinical characteristics of the 53 patients with Marfan syndrome included in the study

| Characteristic | Men<br>n = 24 | Women<br>n = 29 | p-value |
|---|---|---|---|
| Age at first measurement (range in years) | 24 (18-59) | 29 (30-55) | 0.661 |
| Aortic root diameter at first measurement (cm) | 4.1 (±0.44) | 3.5 (±0.53) | <0.001 |
| Body surface area (BSA) ($m^2$) | 2.12 (±0.17) | 1.89 (±0.14) | <0.001 |
| Aortic root ratio at first calculation | 1.05 (±0.12) | 0.95 (±0.13) | 0.011 |
| Threshold diameter for aortic root replacement (cm) | 5.1 (±0.33) | 4.7 (±0.27) | <0.001 |

### Aortic root dilatation

The diameter of the aortic root as a function of time (aging) is given in Figure 2. Despite individual differences, there was a modest but statistically significant progression of the aortic root dilatation over time with an average of 0.132 cm/year (95% confidence interval: 0.0145 - 0.249, p=0.028). The aortic root ratio as a function of time is given in Figure 3. Likewise, on average, there was a modest but statistically significant increase of the aortic root ratio over time with 0.005/year (95% confidence interval: 0.0006016 - 0.0101333, p=0.027). There was no difference in the aortic root dilatation rate between men and women.

### Type A aortic dissection

During the follow-up (251 patient-years), none of the patients suffered from type A aortic dissection. Furthermore, no mortality was observed, and particularly no cardiovascular mortality.

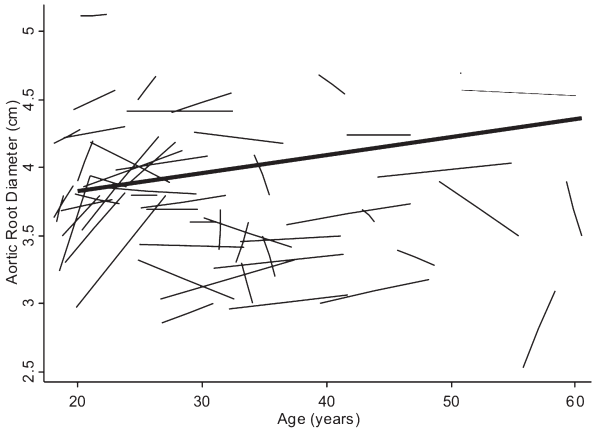


**Figure 2.** Diameter of the aortic root as a function of time (aging) measured in the group of 53 Marfan syndrome patients. Every thin line represents an individual patient (fitted function); the thick line represents the calculated average function.

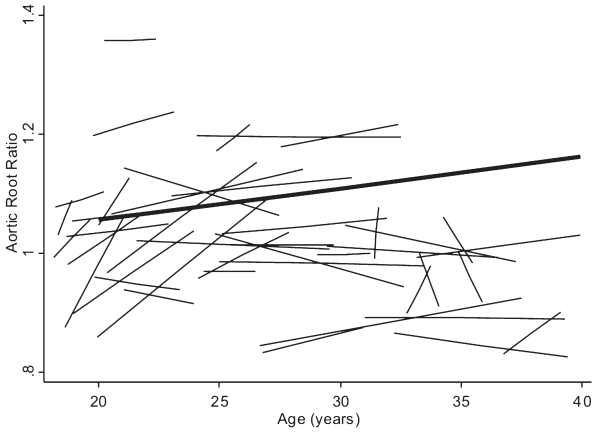


**Figure 3.** Aortic root ratio as a function of time (aging) measured in the group of 53 Marfan syndrome patients. Every thin line represents an individual patient (fitted function); the thick line represents the calculated average function.

**Prophylactic aortic root replacement**

During follow-up, 4 patients underwent prophylactic aortic root replacement; their clinical characteristics are summarized in Table 2. An aortic root ratio ≥1.3 was the reason for prophylactic aortic root replacement in patients A and B. Progressive dilatation (0.4 cm/year) of the aortic root diameter, in combination with a positive family history for aortic dissection, was the reason for replacement in patient C. Concomitantly with surgery for an aneurysm of the ascending aorta, patient D also underwent prophylactic aortic root replacement. In all 4 patients, the operation was uncomplicated.

**Table 2.** Clinical characteristics of the 4 patients who underwent aortic root replacement

| Patient | Gender | Age (years) | Aortic root diameter cm | Aortic root ratio | Indication for surgery | Operative procedure |
|---|---|---|---|---|---|---|
| A | male | 33 | 4.9 | 1.31 | ratio >1.3 | David I |
| B | male | 22 | 5.2 | 1.38 | ratio >1.3 | Bentall (bioprosthetic valve) |
| C | female | 50 | 4.7 | 1.15 | 0.4 cm dilatation/ year | Yacoub |
| D | male | 42 | 4.6 | 1.15 | aneurysm ascending aorta (5.0 cm) | Bentall + arch replacement |

During follow-up patient B required re-operation on the biological aortic valve because of rapid degeneration. The valve was replaced by a mechanical aortic valve 5 years after the initial operation. Patient C developed severe aortic regurgitation due to dilatation of the aortic annulus, necessitating replacement of the native valve by a mechanical aortic valve 9 years after the first operation.

**Other consequences**

During follow-up in our institution, 1 patient developed an uncomplicated type B aortic dissection, which was treated medically. However, she developed a post-dissection aneurysm of her abdominal aorta requiring surgical treatment 2 years after the dissection. Another patient also developed an abdominal aneurysm, which was also treated surgically. Outcome in both patients after surgery was uncomplicated.

During the follow-up period, 9 patients moved to other regions in the Netherlands. All of them were followed in other cardiologic centers and thus were not necessarily treated according to our protocol. Obtained correspondence indicated that the clinical course was uneventful in 7 patients and that 1 patient underwent an uncomplicated Bentall procedure. However, one patient, a 23-year-old female, died in 2006 from a fatal acute type A aortic dissection. The final measurement of the aortic root in our institution in 2004 prior to her transfer was 3.8 cm and the final measurement prior to the aortic dissection in 2006 was 4.3 cm, corresponding with an aortic root ratio of 1.19, but the yearly dilatation was thus greater than 0.2 cm. Her mother had died shortly before due to aortic dissection.

**Surgically treated acute type A aortic dissections**

During the period 1990-2006, a total of 105 patients were surgically treated for an acute type A aortic dissection. Marfan syndrome was diagnosed in four of these patients, either before or after the operation. The dissection in these four patients occurred in the period 1990-1997, i.e. before our protocol for prophylactic aortic root replacement was implemented. Thereafter no patients with Marfan syndrome were surgically treated for type A aortic dissection.

## DISCUSSION

Medical and surgical treatment has greatly improved life expectancy in patients with Marfan syndrome.[11,12] Beta-blockade therapy is being applied to slow down aortic root dilatation and prophylactic aortic root replacement can prevent aortic dissection. However, there is still debate about the diameter at which the aortic root should be replaced. Since the normal aortic root diameter is dependent on BSA (figure 1a and 1b)[9] and Legget et al. discovered that patients with Marfan syndrome are particularly at risk for aortic dissection or cardiovascular mortality with an aortic root ratio $\geq$1.3 (relative risk 2.7),[7] we decided to apply this finding in a protocol for prophylactic aortic root replacement. However, we used the *maximum* predicted aortic diameter (i.e. upper limit of normal) to determine the aortic root ratio instead of the *mean* predicted aortic root diameter, because we felt that many patients would otherwise undergo aortic root replacement "too early". The results show that our modified protocol has so far been effective; only four patients underwent prophylactic aortic root replacement, none of the patients suffered from acute type A aortic dissection and there was also no cardiovascular mortality. Importantly, according to the international guideline[3] at least three of the four patients (A, C and D) would not have been candidates for surgery, and even according to the current Dutch guideline[4] at least two patients (patient A and B) would have not been considered candidates. Of course, it remains uncertain whether aortic dissection would have occurred in any of the four patients operated, and perhaps their aortic root could have grown safely to a diameter of 5.5 cm. However, based on the literature, they would thus have been at considerable risk for aortic dissection and cardiovascular mortality.[5-7] Support (albeit circumstantial evidence) for our approach is also provided by the finding that there were four cases of surgery for acute type A aortic dissection in Marfan patients from 1990 to 1997 before the implementation of our protocol, whereas no such cases were observed thereafter.

Notwithstanding our findings, one could wonder why BSA should be taken into account at all when considering the risk of an event (dissection or rupture) in the aorta, since Laplace's law states that aortic wall tension is merely defined by pressure, radius and wall thickness (P (pressure) x R (radius) / wall thickness). However, it is rather likely that patients with larger BSA's in principle also have a thicker aortic wall, which would keep aortic wall tension within normal limits. Moreover, our approach is supported by a recent study in patients with thoracic aneurysms (mainly due to hypertension and atherosclerosis) which found that relative aortic size (i.e. corrected for BSA) was more important than absolute size in predicting complications.[13] Having said that, as patients with Marfan syndrome often have large BSA's (due to their tall stature), their threshold for aortic root replacement, when applying our protocol, can exceed 5.5 cm. However, in our opinion patients with Marfan syndrome should probably not be allowed to have an aortic root diameter >5.5 cm, irrespective of their BSA*. Our protocol is based on a previous study where subjects with (very) large BSA's were relatively underrepresented,[9] so it is not sure whether it is safe to allow Marfan patients to have aortic root diameters >5.5 cm.

* See also Chapter 9

The patient with a fatal acute type A aortic dissection, who moved to another region in the Netherlands and was not treated according to our protocol, showed a progression of aortic root dilatation of 0.5 cm in the last two years before the dissection (3.8 cm → 4.3 cm). This would have qualified her for prophylactic aortic root replacement according to our protocol (dilatation >0.2 cm/year) and also according to the current Dutch guideline. This case exemplifies that rapid dilatation of the aortic root is a dangerous scenario, requiring careful management.

Aortic root replacement in Marfan syndrome patients has been shown to be safe in an elective setting, in-hospital mortality ranging from 0-2.6%[5,14,15] whereas in-hospital mortality of surgical treated acute type A aortic dissections is 20-25%.[16,17] This means elective aortic root replacement is highly preferred compared to an acute operation. Indeed, aortic root replacement has also been performed uneventfully in our (albeit small) population. Two patients did require re-operation, including one patient (B) who had rapid degeneration of a bioprosthetic aortic valve. Perhaps it is more important to mention the re-operation in patient C, who initially underwent a valve sparing aortic root replacement according to Yacoub.[18] Good results have been described with this technique but others have mentioned that it might not be appropriate in patients with Marfan syndrome.[19,20] Dilatation of the aortic annulus can still occur in these patients, creating aortic regurgitation that might require re-operation in the future.[21,22] In the currently preferred valve-sparing technique according to David, annular dilatation is prevented as the entire aortic valve is secured inside a tubular vascular graft.[20] Finally, the results of our study confirm the common fact that patients with Marfan syndrome are also at risk for pathology in the distal aorta (one patient with type B aortic dissection followed by aneurysm of the abdominal aorta and one patient with an abdominal aortic aneurysm).[21]

Coincidentally, we observed a smaller aortic ratio in women compared to men. In fact, at first measurement the aortic ratio in the female patients was still, on average, below the upper limit of normal, unlike the aortic ratio in the male patients (0.95 and 1.05, respectively). A gender-difference was not observed by Roman et al. whose regression formulas we used to calculate the predicted aortic root diameter; in their study, aortic root diameters in a healthy population were only dependent on BSA and not on gender.[9] In contrast, Vasan et al. reported a smaller aortic root diameter in women compared to men even when taking BSA into account.[22] To our knowledge, our study is the first to report a gender difference in Marfan patients; on average the female patients appeared to have a smaller aortic root than the male patients, even after correcting for their smaller BSA. The clinical implication of this finding is as yet uncertain. In our study we did not observe a difference in outcome between men and women. Meijboom et al. reported more type A aortic dissections in women (n=9) than men (n=4) (not significant).[5] In addition, more men than women underwent prophylactic aortic root replacement in their patient group, but the investigators did not correct for BSA. It is possible that men reached the threshold (not specified) for prophylactic aortic root replacement earlier.[5] Future research is needed to establish if gender differences have to be taken into account in guidelines for prophylactic aortic root replacement in Marfan syndrome patients.

**Methodologic considerations**

Our study was limited by the fact that it was not a randomized comparison between two treatment strategies. Moreover, our small number of patients and the relatively short follow-up period obviously limited the possibility to test our protocol thoroughly. A strength of our study was the dedicated management of the patients in terms of consistency in diagnosis, follow-up and treatment (Ghent criteria, echocardiography, operation) executed by an experienced team.

## CONCLUSIONS

In this study we describe the results of a protocol for prophylactic aortic root replacement in Marfan syndrome patients based on body surface area. We feel our findings, warrant reconsideration of the current guidelines for prophylactic aortic root replacement and that body surface area should be taken into account. In addition, rapid dilatation of the aortic root and a family history of aortic dissection should play a larger role when considering the option of aortic root replacement. This would enable a better risk assessment and a more individually tailored treatment of patients with Marfan syndrome.

## ACKNOWLEDGEMENTS

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