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The Risk for Type B Aortic Dissection in Marfan Syndrome

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ABSTRACT

BACKGROUND Aortic dissections involving the descending aorta are a major clinical problem in patients with Marfan syndrome.

OBJECTIVES The purpose of this study was to identify clinical parameters associated with type B aortic dissection and to develop a risk model to predict type B aortic dissection in patients with Marfan syndrome.

METHODS Patients with the diagnosis of Marfan syndrome and magnetic resonance imaging or computed tomographic imaging of the aorta were followed for a median of 6 years for the occurrence of type B dissection or the combined end point of type B aortic dissection, distal aortic surgery, and death. A model using various clinical parameters as well as genotyping was developed to predict the risk for type B dissection in patients with Marfan syndrome.

RESULTS Between 1998 and 2013, 54 type B aortic dissections occurred in 600 patients with Marfan syndrome (mean age 36 ± 14 years, 52% male). Independent variables associated with type B aortic dissection were prior prophylactic aortic surgery (hazard ratio: 2.1; 95% confidence interval: 1.2 to 3.8; p = 0.010) and a proximal descending aorta diameter ≥27 mm (hazard ratio: 2.2; 95% confidence interval: 1.1 to 4.3; p = 0.020). In the risk model, the 10-year occurrence of type B aortic dissection in low-, moderate-, and high-risk patients was 6%, 19%, and 34%, respectively. Angiotensin II receptor blocker therapy was associated with fewer type B aortic dissections (hazard ratio: 0.3; 95% confidence interval: 0.1 to 0.9; p = 0.030).

CONCLUSIONS Patients with Marfan syndrome with prior prophylactic aortic surgery are at substantial risk for type B aortic dissection, even when the descending aorta is only slightly dilated. Angiotensin II receptor blocker therapy may be protective in the prevention of type B aortic dissections. (J Am Coll Cardiol 2015;65:246-54) © 2015 by the American College of Cardiology Foundation.

Life expectancy of patients with Marfan syndrome (MFS) has improved because of a more aggressive surgical approach to ascending aortic disease, such as prophylactic aortic root and ascending aorta replacement (AoRR) (1). However, with the increased longevity of patients with MFS, an increased incidence of complications beyond the ascending aorta (hereafter defined as the "distal aorta") has been identified (2,3). Current surgical guidelines advocate prophylactic surgery of the distal aorta when the diameter exceeds 50 mm (4). However, type B aortic dissection, defined as aortic dissection not involving the ascending aorta, frequently occurs without prior significant aortic dilation in patients with MFS (5). In the present study, we investigated the association of type B aortic dissection in patients

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with MFS with various clinical parameters, including genetic analysis, aortic dimensions, and aortic elastic properties. Furthermore, we established a risk model to predict the occurrence of type B aortic dissection in adult patients with MFS.

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METHODS

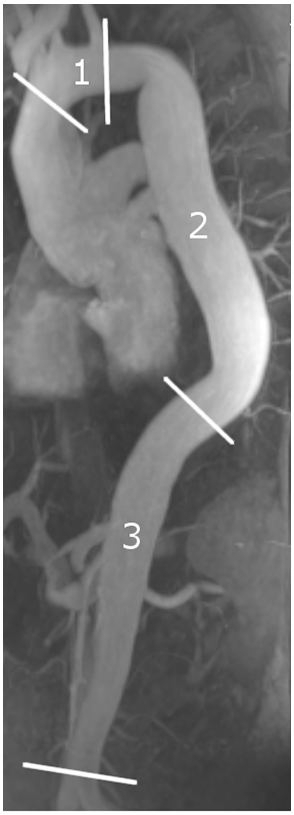
STUDY DESIGN. We included all adult patients who attended 1 of the 4 Dutch university Marfan screening clinics between 1998 and 2013 and were diagnosed with MFS by a multidisciplinary Marfan screening team according to the revised Ghent criteria (6). Included patients had undergone 1 or more scans of the total aorta, acquired either by means of cardiac magnetic resonance (CMR) or computed tomography (CT). Patients with evidence of aortic dissection on the first available magnetic resonance or computed tomographic images were excluded. The starting point of the study was defined as the date of the first available aortic images (CMR or CT). Study end points were the occurrence of type B aortic dissection or a combined end point defined as any of the following events: type B aortic dissection, distal aortic surgery, or death. Type B aortic dissection was defined as a dissection of the descending aorta without involvement of the ascending aorta, as confirmed by CMR or CT (7,8). Patients who had type A aortic dissection occurring during the study were censored. Patients were screened for the *FBN1* mutation, and in those who tested negative, the *TGFBR1*, *TGFBR2*, *TGFB2*, *MYH11*, *MYLK1*, *SMAD3*, and *ACTA2* genes were subsequently screened. Patient demographics, medical treatment, surgical history, date of type B aortic dissection, and family history were obtained from review of the patients' medical charts. Patients with mutations leading to a connective tissue disease other than MFS, such as Loeys-Dietz syndrome, were excluded from analysis. Aortic diameters were measured from the first and last available CMR and/or computed tomographic scan during follow-up, and aortic dilation rates were calculated. The study was conducted in accordance with all human research regulatory guidelines and the institutional conduct code for health-related research.

IMAGE ANALYSIS. Standard, commercially available, non-electrocardiographically gated imaging techniques were used for aortic imaging: 3-dimensional gadolinium-enhanced spoiled-gradient echo for CMR and contrast-enhanced imaging for CT. In a subset of patients, electrocardiographically gated cine CMR was performed perpendicular to the descending aorta at the level of the pulmonary artery, as described by den Hartog et al. (9). Diameter measurements were performed by a single analyst on multiplanar CMR and CT reconstructions from inner edge to inner edge. The largest diameter was measured in the following aortic segments: 1) from the origin of the brachiocephalic trunk to the origin of the subclavian artery (aortic arch); 2) from the origin of the subclavian artery to the diaphragm (descending thoracic aorta); and 3) from the diaphragm to the aortic bifurcation (abdominal aorta) (Figure 1). The frequency of the following aortic characteristics was determined: 1) global dilation of the descending aorta (defined as an aortic diameter in ≥2 segments above the normal mean [10]); 2) aortic diameter above the upper limit of normal (≥27 mm); and 3) the presence of an aortic "hump" (defined as a local

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme
AoRR = aortic root and ascending aorta replacement
ARB = angiotensin II receptor blocker
CI = confidence interval
CMR = cardiac magnetic resonance
CT = computed tomography
HR = hazard ratio
MFS = Marfan syndrome
SE = standard error

FIGURE 1 Three-Dimensional Magnetic Resonance Image of a MFS Aorta



This image shows the aorta in the long-axis view of a patient with Marfan syndrome. The largest aortic diameters of all 3 segments were assessed.

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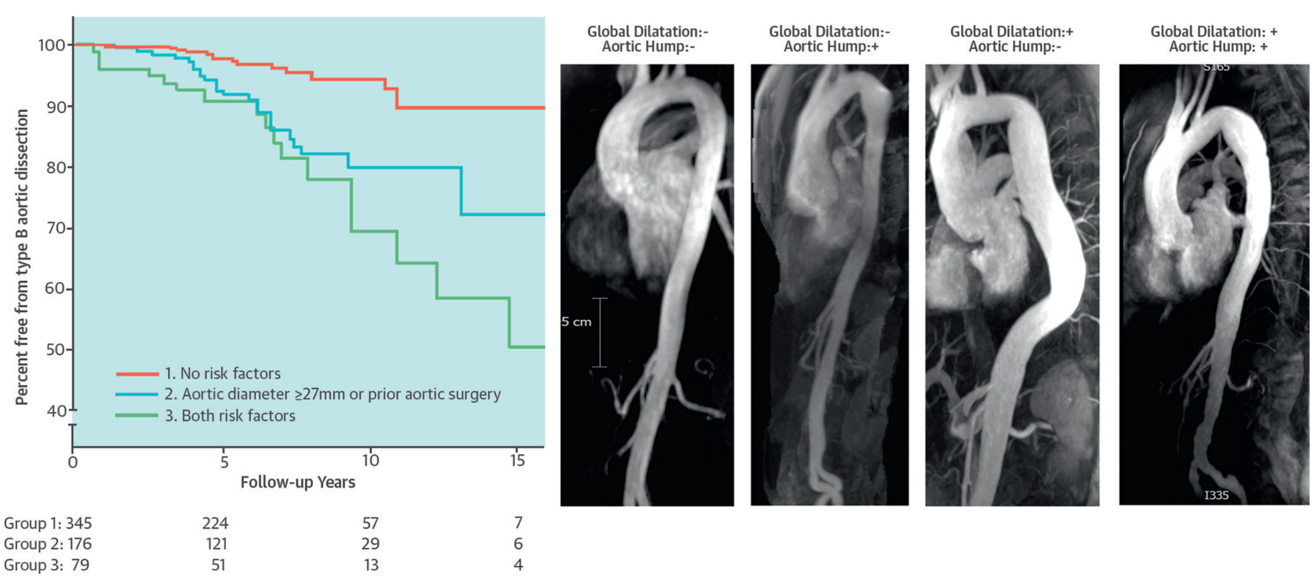
CENTRAL ILLUSTRATION Type B Aortic Dissection in Marfan Syndrome: Kaplan-Meier Curve Based on Risk Model



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Kaplan-Meier curve showing percent freedom of type B aortic dissection in the 3 different patient groups. The starting point of this Kaplan-Meier was defined as the time of first available aortic images. Numbers of patients at risk for type B aortic dissection in the different categories are shown below the figure.

increase of ≥1 mm in aortic diameter within a segment) (Central Illustration). Aortic distensibility was calculated by a single analyst using cine magnetic resonance images and noninvasively measured blood pressure during CMR, as described by Groenink et al. (11).

STATISTICAL ANALYSIS. Data analysis was performed using SPSS version 20.0 for Windows (SPSS, Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are summarized as numbers and percents. Cox proportional hazards analysis was used to identify determinants of type B aortic dissection or the combined outcome. The risks were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Quantitative risk factors were dichotomized. Relevant cutoff values were obtained by plotting a receiver-operating characteristic curve and assessing the area under the curve at fixed time points during follow-up. Aortic diameter, aortic dilation rate, and distensibility were dichotomized using a threshold maximizing the concordance statistic of the Cox regression model.

Two analyses were performed. In the first analysis, patients were followed from the date of the first available CMR or CT images onward until the occurrence of an event or the end of follow-up. In the type B aortic dissection analysis, patients with MFS who died without the occurrence of type B aortic dissection were censored at the date of death. Prophylactic aortic surgery during follow-up and aortic dilation rates were used as time-dependent covariates.

In the second analysis, patients were followed from the date of the last available CMR or CT onward. Prophylactic aortic surgery occurring before the date of the last available CMR or CT images and aortic dilation rate were included as baseline predictor variables.

Variables with p values ≤0.20 in univariate analyses were considered in multivariate models. There were 0% to 30% missing observations per variable in our analysis. Distensibility measurements were assessed in 140 patients. Missing data were imputed 5 times, and the regression parameters were estimated by the mean of the 5 imputation results. The multivariate Cox model on the selected determinants was analyzed with a forward conditional algorithm on each of the 5 imputed datasets. The final model included all predictor variables selected in at least 1 of the imputed datasets.

RISK MODEL. A risk model to predict type B aortic dissection in patients with MFS from the date of the first available aortic images onward was developed. In the risk model, clinical variables that were independently associated with type B aortic dissection were included. We did not consider medical treatment as a prognostic variable in this risk model. To facilitate quick risk stratification, we simplified the regression model by rounding the estimated regression parameters to the nearest integer values. Consequently, the risk score of an individual patient equals the number of risk factors in the patient, weighted with a simple integer value. To assess the discriminatory ability of the risk model, we compared the Kaplan-Meier curves of the cumulative type B aortic dissection risk in the different risk strata (percent with standard error [SE]). We also calculated the C-statistic of the risk model (12).

RESULTS

PATIENTS. A total of 646 adult patients with MFS visited one of the participating centers between 1998 and 2013. Of these 646 patients with MFS, 46 were excluded because of a type A aortic dissection before the first available aortic imaging. No aortic arch dissections occurred. In the remaining 600 patients (mean age 36 ± 14 years, 52% male, mean body surface area 2.0 ± 0.2 m^2), aortic diameters, dilation rate, and distensibility were available in 532 (89%), 423 (71%), and 140 (23%) patients, respectively. Aortic imaging by CMR was available in 500 patients (94%) and by CT in 32 patients (6%). *FBN1* mutation analysis was available in 542 patients (90%), and *FBN1* mutations were found in 448 patients (83%). At baseline, ≥1 prophylactic aortic surgical procedure had been performed in 143 patients with MFS (24%). Surgical procedures included prophylactic AoRR (n = 134) with distal prophylactic aortic surgery (n = 2) and prophylactic AoRR with distal aortic surgery (n = 7). Baseline characteristics are summarized in Table 1.

OUTCOMES. Type B aortic dissection. During a median follow-up period of 6.0 years from the first available images (3,639 person-years), 2 type A aortic dissections (0.05% per year) and 54 type B aortic dissections (1.5% per year) occurred. Sixty-six

TABLE 1 Baseline Characteristics and Associations With Type B Aortic Dissection of 600 Patients With Marfan Syndrome at the Time of the First Available Aortic Images

	Total Cohort	Type B Dissection	No Type B Dissection	Univariate Analysis			Multivariable Analysis		
				HR	95% CI	p Value	HR	95% CI	p Value
n	600	54	546						
Age, yrs	36 ± 14	37 ± 14	36 ± 14	1.0	1.0-1.0	0.317			
Male	312 (52)	30 (57)	282 (52)	1.6	0.8-3.5	0.195			
BSA, m^2	2.0 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	1.3	0.3-5.7	0.766			
FBN1 mutation	448 (83)	36 (86)	411 (82)	1.2	0.4-3.6	0.706			
Aortic surgery†	143 (24)	27 (51)	116 (21)	4.4	2.2-8.9	<0.001	2.1	1.2-3.8	0.010
AoRR	141 (24)	27 (51)	114 (21)	4.4	2.2-9.0	<0.001			
Age at AoRR, yrs	32 ± 14	31 ± 15	33 ± 13	1.0	1.0-1.0	0.958			
Distal aortic surgery	9 (2)	4 (7)	5 (1)	9.6	2.9-31.8	<0.001			
Arch + proximal descending replacement	3 (1)	2 (4)	1 (<1)						
Mid-thoracic replacement	1 (<1)	1 (2)	0						
Bifurcation replacement	5 (1)	1 (2)	4 (1)						
Aortic diameters and characteristics (n = 532)									
Segment I, mm	24 ± 4	26 ± 8	24 ± 4	1.1	1.0-1.2	<0.001			
Segment II, mm	25 ± 5	28 ± 7	24 ± 5	1.1	1.1-1.2	<0.001			
Segment II/BSA, mm/m^2	12 ± 3	14 ± 4	12 ± 3	1.2	1.1-1.3	0.001			
Patients with diameter above normal*	163 (31)	16 (50)	147 (29)	2.5	1.3-4.9	0.009	2.2	1.1-4.3	0.020
Global descending dilation	172 (32)	17 (53)	155 (31)	2.6	1.3-5.2	0.007			
Presence of aortic hump	256 (48)	18 (56)	238 (48)	1.4	0.7-2.9	0.312			
Hump in dilated aorta	226 (42)	21 (66)	205 (41)	2.8	1.0-8.1	0.049			
Segment III, mm	21 ± 5	25 ± 10	20 ± 4	1.0	1.0-1.1	<0.001			
Aortic distensibility (×10^{-3} mm Hg) (n = 140)									
Proximal descending	3.5 ± 1.7	2.1 ± 0.6	3.6 ± 1.7	0.4	0.2-0.8	0.017			
Patients with distensibility <2.5	45 (32)	6 (75)	39 (30)	4.7	1.2-18.8	0.029			
Diaphragm	6.0 ± 2.5	3.6 ± 1.2	6.2 ± 2.4	0.5	0.3-0.7	0.001			
Abdominal	6.3 ± 3.8	4.1 ± 3.1	6.5 ± 3.8	0.9	0.7-1.1	0.199			

Values are mean ± SD or n (%). *Diameter ≥27 mm (13). †At baseline, in 7 patients, distal aortic surgery had been performed after AoRR (not included in 143 patients).
AoRR = aortic root and ascending aorta replacement; BSA = body surface area; CI = confidence interval; HR = hazard ratio.

patients underwent prophylactic aortic surgery (1.8% per year). Fifty-two underwent prophylactic AoRR surgery, 13 underwent prophylactic distal aortic surgery, and 1 underwent combined prophylactic AoRR and distal aortic surgery. Of 9 deaths (0.25% per year), 5 were MFS related. Two patients died as a result of multiple distal aortic surgical procedures after type B aortic dissection, 1 patient died as a result of heart failure after multiple aortic surgical procedures after type A aortic dissection, 1 patient died as a result of heart failure with multiple-organ failure 9 months after reoperation of the AoRR, and 1 patient refused treatment before and after type B aortic dissection. The remaining 4 patients died of intestinal surgery, traumatic brain injury, neurological disorder, or an unknown cause.

In 48 patients (89%), the origin of the type B aortic dissection was the proximal descending aorta, and in 6 patients (11%), the origin was either the distal descending thoracic aorta or the abdominal aorta. In 30 patients with MFS (56%), AoRR had been performed before type B aortic dissection occurred. In the remaining 24 patients with MFS (44%), type B aortic dissection was the first aortic complication.

In univariate Cox analysis, type B aortic dissection was associated with prior prophylactic aortic surgery, greater aortic diameter in all segments, decreased distensibility, and global aortic dilation (Table 1). Faster aortic dilation rate was also associated with type B aortic dissection (Table 2). The optimal cutoff values for aortic diameter to discriminate between high and low risk for type B aortic dissection were 27, 25, 25, and 26 mm for 3, 5, 7, and 10 years of follow-up, respectively. We chose 27 mm as a cutoff value for aortic diameter (area under the curve 0.839) because this corresponded with aortic diameter above the upper limit of normal, as found by Wolak et al. (13). The optimal cutoff value for aortic dilation rate was ≥0.5 mm/year and for aortic distensibility was $<2.5 \times 10^{-3}$ mm Hg^{-1} (areas under the curve 0.694 and 0.747, respectively).

Kaplan-Meier curves (Figure 2A) illustrate the risk for type B aortic dissection in patients with descending thoracic aortic diameters ≥27 or <27 mm. Kaplan-Meier curves for aortic distensibility are shown in Figure 2B. No Kaplan-Meier curves could be constructed for aortic dilation rate because of its time-dependent nature.

In multivariate Cox analysis, prior prophylactic aortic surgery (HR: 2.1; 95% CI: 1.2 to 3.8; p = 0.010) and a descending thoracic aortic diameter ≥27 mm (HR: 2.2; 95% CI: 1.1 to 4.3; p = 0.020) were associated with type B aortic dissection (Table 1). During follow-up, a dilation rate of the descending thoracic aorta ≥0.5 mm/year was also associated with type B aortic dissection (HR: 2.4; 95% CI: 1.2 to 4.7; p = 0.015) (Table 2).

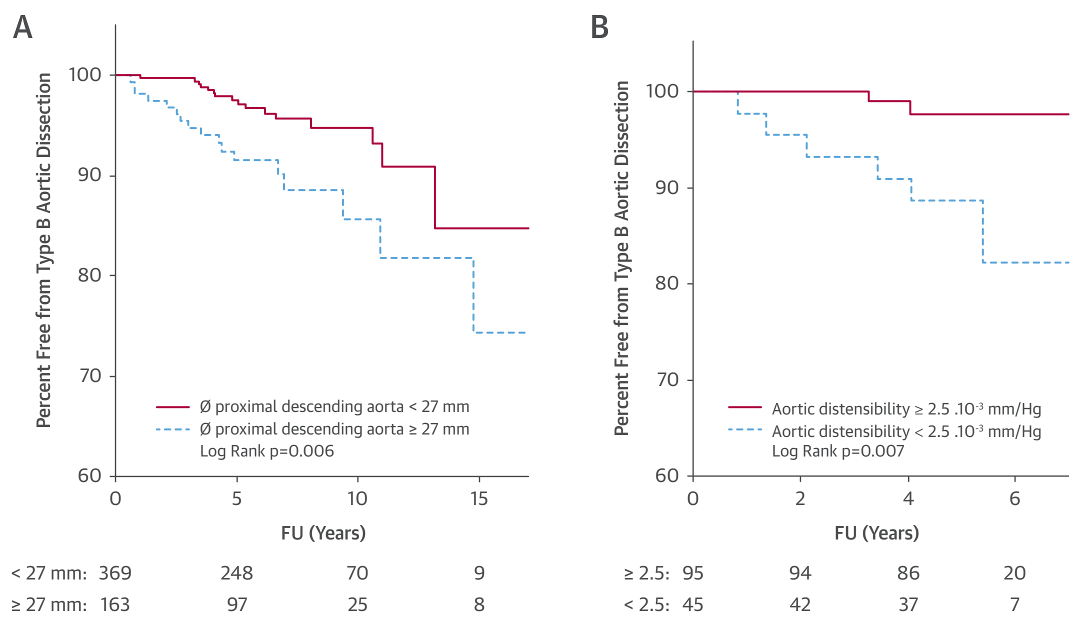
In the second analysis, aortic characteristics of the last available CMR or CT images onward were used. The mean diameter of the descending thoracic aorta of patients with MFS with type B aortic dissections during follow-up was 31 ± 7 mm. The median time from measurement to the event was 1.4 years. In patients without type B aortic dissections during follow-up, the mean diameter of the descending thoracic aorta was 26 ± 5 mm (p < 0.001), and the median time from measurement to the end of the study was 1.9 years. Overall, the second analysis rendered results similar to those of the first analysis. Risk for type B aortic dissection was associated with prior prophylactic aortic surgery (HR: 2.3; 95% CI: 1.3 to 4.2; p = 0.007) and enlarged aortic diameter in all segments (proximal descending aorta diameter ≥ 27 mm) (HR: 3.4; 95% CI: 1.5 to 8.0; p = 0.006) (Table 3). In multivariate Cox analysis, the dilation rate of the aorta was not independently associated with risk for type B aortic dissection. Furthermore, analysis of medical treatment during the last available scan showed that in 146 patients using angiotensin II receptor blockers (ARBs), type B aortic dissection was less frequent compared with 436 patients not on ARB therapy (HR: 0.3; 95% CI: 0.1 to 0.9;

TABLE 2 Aortic Dilation Rate During Follow-Up and Association With Type B Aortic Dissection

				Univariate Analysis			Multivariate Analysis		
	Total Cohort	Type B Dissection	No Type B Dissection	HR	95% CI	p Value	HR	95% CI	p Value
Dilation rate, mm/yr	423	32	391						
Segment I	0.2 ± 0.6	0.2 ± 0.6	0.2 ± 0.6	1.2	1.0–1.3	0.007			
Segment II	0.4 ± 0.6	0.6 ± 0.3	0.3 ± 0.6	1.1	1.1–1.3	<0.001			
Dilation rate ≥ 0.5	135 (32)	11 (50)	124 (31)	5.4	2.5–11.8	<0.001	2.4	1.2–4.7	0.015
Segment III	0.3 ± 0.8	0.5 ± 0.5	0.2 ± 0.8	1.2	1.1–1.2	0.002			

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

FIGURE 2 Kaplan-Meier Curves



(A) Kaplan-Meier curve showing percent freedom from type B aortic dissection in patients with Marfan syndrome with aortic diameters ≥27 mm and in patients with aortic diameters <27 mm at the level of the proximal descending aorta from first available aortic images. Numbers of patients at risk for type B aortic dissection are shown below the figure. **(B)** Kaplan-Meier curve showing percent freedom of type B aortic dissection in patients with Marfan syndrome with aortic distensibility $\geq 2.5 \times 10^{-3}$ mm Hg^{-1} and in patients with aortic distensibility $<2.5 \times 10^{-3}$ mm Hg^{-1} at the level of the proximal descending aorta from first available aortic images. Numbers of patients at risk for type B aortic dissection are shown below the figure. FU = follow-up.

p = 0.030). In univariate analysis, a trend was visible of a potential negative effect of treatment with angiotensin-converting enzyme (ACE) inhibitors (HR: 2.4; p = 0.072). However, in multivariate analysis, this trend was no longer present (HR: 1.7; p = 0.188) (Table 3). No association with blood pressure could be demonstrated (Table 3).

Combined endpoint. Fifty-one type B aortic dissections, 14 distal aortic surgical procedures, and 6 deaths occurred as first events. In multivariate Cox analysis, the following clinical parameters were associated with the combined end point: prior prophylactic aortic surgery (HR: 1.9; 95% CI: 1.1 to 3.1; p = 0.018), a descending thoracic aortic diameter ≥27 mm (HR: 2.1; 95% CI: 1.2 to 3.9; p = 0.015), and dilation rate of the proximal descending thoracic aorta ≥ 0.5 mm/year (HR: 2.4; 95% CI: 1.3 to 4.4; p = 0.004).

Risk score for type B aortic dissection. Three subgroups of patients were created: 1) patients without risk factors for type B aortic dissection; 2) patients with 1 risk factor (either prior prophylactic aortic surgery or descending thoracic aorta diameter ≥27 mm), and 3) patients with both risk factors. Kaplan-Meier curves of the cumulative risk for type B aortic dissection are given in the **Central Illustration**. After 10 years of follow-up, the cumulative risks for type B aortic dissection were 6% (SE = 2%), 19% (SE = 4%), and 34% (SE = 8%), respectively, for low- (n = 345), moderate- (n = 176), and high-risk patients (n = 79) (p < 0.001). The cross-validated C-statistic of this model was 0.53.

Survival after type B aortic dissection. Median follow-up after type B aortic dissection was 7 years. In this period, 25 patients were treated conservatively (41%), 29 patients had ≥1 surgical procedure (53%), and 3 patients died after type B aortic dissection (6%).

DISCUSSION

In this study, we provide a contemporary overview of clinical outcomes in patients with known MFS without prior aortic dissection. This represents one of the largest MFS studies to date using 3-dimensional imaging techniques. We found a type B aortic dissection rate of 9% during a median follow-up period of 6 years. Type B aortic dissections generally occurred in mildly dilated proximal descending aortas, especially

TABLE 3 Patient Characteristics and Clinical Parameters Associated With Type B Aortic Dissection by Using the Last Available Aortic Images

		Univariate Analysis			Multivariate Analysis		
	Mean	HR	95% CI	p Value	HR	95% CI	p Value
n	600						
Age, yrs	40 ± 14	1.0	1.0–1.0	0.697			
Male	312 (52%)	1.9	0.9–4.0	0.074			
BSA, m²	2.0 ± 0.2	1.6	0.4–7.5	0.534			
FBN1 mutation	448 (75%)	1.2	0.4–3.6	0.686			
Blood pressure, mm Hg							
Mean arterial pressure	90 ± 10	1.0	1.0–1.0	0.659			
Systolic blood pressure	123 ± 15	1.0	1.0–1.0	0.891			
Pulse pressure	49 ± 12	1.0	1.0–1.0	0.766			
Medications							
Beta-blocker	426 (73%)	0.7	0.3–1.5	0.428			
ARBs	146 (25%)	0.4	0.2–1.3	0.115	0.3	0.1–0.9	0.030
ACE inhibitors	39 (7%)	2.4	1.0–6.5	0.072			
Calcium-channel blockers	20 (3%)	2.6	0.6–11.0	0.193			
Diuretic agents	33 (6%)	1.5	0.5–4.8	0.531			
Aortic surgery§	198 (33%)	6.3	2.9–13.5	<0.001	2.3	1.3–4.2	0.007
AoRR*	191 (32%)	6.5	3.0–14.0	<0.001			
Age at AoRR, yrs	32 ± 13	1.0	1.0–1.0	0.428			
Distal aortic surgery†	18 (3%)	8.8	3.6–21.5	<0.001			
Aortic diameters and characteristics							
Segment I, mm	25 ± 4	1.1	1.0–1.2	<0.001			
Segment II, mm	26 ± 5	1.1	1.1–1.1	<0.001			
Segment II/BSA, mm/m²	13 ± 3	1.1	1.1–1.2	<0.001			
Patients with diameter above normal‡	220 (41%)	5.2	2.3–11.6	<0.001	3.4	1.5–8.0	0.006
Dilation rate ≥ 0.5 mm/yr	135 (32%)	1.9	0.9–4.4	0.112			
Global descending dilation	382 (72%)	4.5	1.4–14.9	0.013			
Presence of aortic hump	281 (54%)	3.1	1.3–7.0	0.008			
Hump in dilated aorta	242 (46%)	3.5	1.4–7.4	0.003			
Segment III, mm	22 ± 5	1.1	1.0–1.1	<0.001			

Values are mean ± SD or n (%). *In 3 patients with Marfan syndrome, AoRR occurred after last aortic imaging (not included in 191). †Five distal aortic surgical procedures occurred after last aortic imaging (not included in 18). ‡Diameter ≥27 mm (13). §A total of 11 patients underwent distal aortic surgery after AoRR (not included in 198).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; other abbreviations as in Table 1.

in patients with prior prophylactic aortic surgery. From our data, we were able to develop a risk score to predict type B aortic dissection in patients with MFS, on the basis of history of prophylactic aortic root surgery and proximal descending aortic diameter.

The occurrence of type A aortic dissection has become a rare event in patients with known MFS in the era of aggressive prophylactic surgery. Although AoRR has improved life expectancy considerably, distal aortic disease may develop later in patients with MFS (14,15). Replacement of the aortic root or ascending aorta with a stiff vascular prosthesis may result in higher pulsatile forces acting on the native aortic arch and proximal descending aorta, and these forces may become the main constituents of remaining "Windkessel" function. Both factors may play a role in the occurrence of subsequent dissection in the proximal descending aorta (5,9,16). The fact that age at the time of prophylactic aortic root surgery was similar in both groups (mean 31 ± 15 years vs. 33 ± 13 years) seems to underscore the possibility that the surgery itself may be a risk factor for subsequent type B dissection. At the last available aortic images (approximately 1.4 years before the occurrence of type B aortic dissection), the mean diameter of the proximal descending aorta was only 31 ± 7 mm. We showed that a descending thoracic aortic diameter ≥27 mm was associated with type B aortic dissection in patients with a mean age of 36 ± 14 years and a mean body surface area of 2.0 ± 0.2 m². This diameter cutoff value corresponded with the reported upper level of normal of the thoracic descending aorta (13). However, aortic size and dilation pattern alone seem to predict dissection only to a very limited extent. Only 53% of patients with dissections had aortic diameters ≥27 mm at the dissection site. Although aortic dilation rate was significantly associated with type B dissection in our univariate analysis, this was not the case in our multivariate analysis. Aortic dilation rates were low in our study and were probably outweighed by aortic diameter in the multivariate analysis.

Surgical guidelines advocate replacement of an aneurysm of the distal aorta in MFS when the diameter exceeds 50 mm (4). Notably, none of the patients with MFS with a distal aortic dissection were approaching this threshold for distal aortic surgery in our study. Open thoracoabdominal aortic replacement can be achieved relatively safely in experienced centers (17) but can be associated with lung damage, spinal cord injury, and diffuse bleeding requiring surgical revision (18). Therefore, future studies are warranted to assess the risks of elective surgery against the risks for the development and progression of descending thoracic aortic aneurysms and dissections.

TREATMENT EFFECTS. In patients with MFS, rigorous antihypertensive medical treatment aiming at a systolic blood pressure <120 mm Hg is thought to be important in the prevention of type B aortic dissection (4). We could not demonstrate an association of blood pressure with type B aortic dissection, probably because blood pressure was generally well regulated in the cohort. No beneficial effect of beta-blockers on prevention of type B aortic dissection in the cohort could be shown. This may have been due to the design of this study (retrospective, nonrandomized trial), the high percent of patients already using beta-blockers, the large variety in beta-blocking agents used, variations in beta-blocker dosages and treatment duration, and unknown patient adherence. However, we demonstrated that the use of ARBs could be beneficial in the prevention of type B aortic dissection in patients with MFS. Recently, beneficial effects of losartan on aortic dilation rate and aortic arch dilation rate after AoRR were shown in adult patients with MFS (19). However, the effect of losartan on distal aortic dissections could not be determined, because of the low incidence of events and relatively short follow-up period. In addition, ARBs were not superior to atenolol on aortic root dilation rate in a recent trial (20). Meta-analysis of several running trials may serve to address this issue prospectively (20–22).

Interestingly, a possible negative effect of treatment with ACE inhibitors was shown in univariate analysis. Although this trend was no longer present in multivariate analysis, inferiority of treatment with ACE inhibitors compared with losartan has been shown in mouse experiments (23), and in patients with abdominal aneurysms, where the use of enalapril resulted in faster aneurysm growth (24). Therefore, ACE inhibitors seem to be less appropriate in the treatment of aortic disease in patients with MFS.

STUDY LIMITATIONS. The limitations of our study include its retrospective nature, irregular imaging schemes with non-electrocardiographically gated scans, practice variation among centers, and different modalities of aortic imaging. Furthermore, reference values for normal aortic size were derived from measurements including the aortic wall (13), whereas we used measurements from "inner edge to inner edge," thus excluding the aortic wall. Therefore, our cutoff value of 27 mm is actually somewhat larger compared with the reported upper limit of normal. However, aortic diameters measured by various imaging modes have generally been found to correlate well (25,26), and analysis performed with data derived only from CMR rendered similar results in our study. We developed an easily applicable risk-scoring system to predict the probability of a type B aortic dissection. However, the variables used in the scoring system are inherent characteristics of the population to which the model was applied and will need validation in a prospective study or validation cohort. Meanwhile, our risk assessment tool may serve to distinguish patients with at least one risk factor and to intensify monitoring or treatment for these patients.

CONCLUSIONS

Predictors for type B aortic dissection in patients with MFS include prior prophylactic aortic surgery and a slightly enlarged descending thoracic aorta. ARB therapy appears to reduce the incidence of type B aortic dissections. Furthermore, our risk model discriminates patients with MFS with a low risk for type B aortic dissection from patients with MFS at high risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Since the introduction of surgical prophylactic aortic root replacement in patients with MFS, life expectancy has increased, and type B aortic dissections have become a major clinical problem.

COMPETENCY IN PATIENT CARE: Predictors of type B aortic dissection in patients with MFS include prior prophylactic aortic surgery and a slightly enlarged descending thoracic aorta of 27 mm.

TRANSLATIONAL OUTLOOK 1: To prevent type B aortic dissections in patients with MFS, more information is needed on the risks and complications of prophylactic distal aortic surgery at smaller aortic diameters in patients with MFS than recommended in the guidelines. Furthermore, predictors of type B aortic dissections should be prospectively evaluated.

TRANSLATIONAL OUTLOOK 2: Although this was a retrospective study, the use of ARBs appears to reduce the incidence of type B aortic dissections. Large prospective multicenter trials are needed, and currently running, to confirm that losartan reduces the risk for aortic dissection in patients with MFS.

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