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ORIGINAL ARTICLE

Predictors of Rapid Aortic Root Dilation and Referral for Aortic Surgery in Marfan Syndrome

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Abstract

Few data exist regarding predictors of rapid aortic root dilation and referral for aortic surgery in Marfan syndrome (MFS). To identify independent predictors of the rate of aortic root (AoR) dilation and referral for aortic surgery, we investigated the data from the Pediatric Heart Network randomized trial of atenolol versus losartan in young patients with MFS. Data were analyzed from the echocardiograms at 0, 12, 24, and 36 months read in the core laboratory of 608 trial subjects, aged 6 months to 25 years, who met original Ghent criteria and had an AoR z-score (AoRz) > 3. Repeated measures linear and logistic regressions were used to determine multivariable predictors of AoR dilation. Receiver operator characteristic curves were used to determine cut-points in AoR dilation predicting referral for aortic surgery. Multivariable analysis showed rapid AoR dilation as defined by change in AoRz/year > 90th percentile was associated with older age, higher sinotubular junction z-score, and atenolol use ($R^2 = 0.01$) or by change in AoR diameter (AoRd)/year > 90th percentile with higher sinotubular junction z-score and non-white race ($R^2 = 0.02$). Referral for aortic root surgery was associated with higher AoRd, higher ascending aorta z-score, and higher sinotubular junction diameter:ascending aorta diameter ratio ($R^2 = 0.17$). Change in AoRz of 0.72 SD units/year had 42% sensitivity and 92% specificity and change in AoRd of 0.34 cm/year had 38% sensitivity and 95% specificity for predicting referral for aortic surgery. In this cohort of young patients with MFS, no new robust predictors of rapid AoR dilation or referral for aortic root surgery were identified. Further investigation may determine whether generalized proximal aortic dilation and effacement of the sinotubular junction will allow for better risk stratification. Rate of AoR dilation cut-points had high specificity, but low sensitivity for predicting referral for aortic surgery, limiting their clinical use. *Clinical Trial Number* ClinicalTrials.gov number, NCT00429364.

Keywords Marfan syndrome · Predictors · Aortic root dilation · Referral for aortic surgery

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder affecting approximately 1 in 5000 people [1]. Progressive aortic root (AoR) dilation leading to aortic dissection and rupture has long been recognized as the leading cause of death in MFS [2, 3]. Although the majority (60–80%) of patients with MFS have some degree of AoR dilation [4], there is lack of large multicenter studies evaluating the factors that predict the rate of aortic dilation and the need for aortic surgery among individual patients.

In healthy children and adults, AoR diameter correlates with age, height, weight, and body surface area [5–8]. In children and adults with MFS, larger baseline AoR diameter has been shown to predict progressive AoR dilation [9, 10]. Older age, increased height, higher systolic blood pressure, larger baseline AoR diameter, more rapid AoR dilation, and a pattern of generalized proximal aortic dilation have been shown to predict aortic complications such as aortic

A complete list of investigators who participated in the Pediatric Heart Network Marfan Trial is provided in the Acknowledgement section.

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regurgitation, aortic dissection and rupture, and death [4, 11–15]. Previous studies have been limited by retrospective design, single-center enrollment, small sample size, and/or short follow-up times. Identification of more robust risk factors associated with rapid AoR dilation and need for aortic surgery would allow for better risk stratification to determine those who would most benefit from more frequent follow-up and initiation of earlier medical therapy and/or surgical intervention.

The Pediatric Heart Network (PHN) Marfan trial enrolled 608 subjects to compare the effects of beta blocker therapy (atenolol) versus angiotensin II receptor blocker therapy (losartan) on aortic dilation in individuals with MFS [16]. This trial provides one of the largest and most robust international databases for children and young adults with MFS who have significant aortic root involvement [17]. The primary aim of this study was to analyze data arising from the trial to identify independent clinical and echocardiographic predictors of the rate of AoR dilation, including annual rate of change in AoR z-score (AoRz)/year and in AoR diameter (AoRd)/year. The secondary aims were to determine independent clinical and echocardiographic predictors of rapid AoR dilation (change in AoRz/year and AoRd/year > 90th percentile) and referral for aortic surgery.

Methods

Study Design

We performed a post hoc analysis of data from the PHN randomized clinical trial of atenolol versus losartan in children and young adults with MFS. The trial design and main results have been previously reported [16, 17]. The main trial protocol was approved by the institutional review board or ethics committee at each participating study center, and informed consent and assent were obtained. The clinical data and the echocardiograms were collected from 21 participating centers. The echocardiograms were read in a core laboratory and the data used for this analysis were the measures at baseline, 12, 24, and 36 months after randomization.

Participants

The PHN MFS trial enrolled 608 subjects aged 6 months to 25 years who met the original Ghent diagnostic criteria for MFS [18], with an AoRz > 3 and AoRd < 5 cm. Patients who had previous aortic surgery, planned aortic surgery within 6 months of enrollment, or a history of aortic dissection were excluded from the trial. Data from all participants were analyzed except for 6 subjects with change in AoR z-score ≤ − 3 or ≥ 3 SD units/year, which were considered clinically implausible and attributed to measurement error.

Predictors

The baseline clinical characteristics, echocardiographic measures, and the maintenance doses of study drugs by treatment arm, which were considered as predictors, are included in Table 1. Seven outlier values among the predictors were identified and excluded from analysis to avoid undue influence on the results.

Outcomes

The outcomes for this analysis were (1) annual rate of change in AoR dilation (AoRz/year and AoRd/year); (2) rapid aortic dilation defined as change in AoRz/year and AoRd/year > 90th percentile; and (3) referral for aortic surgery.

Statistical Analysis

All analyses were conducted using SAS v9.3 (SAS Institute Inc., Cary, NC).

Rate of Aortic Dilation/Year and Rapid Aortic Root Dilation

Repeated measures multivariable linear and logistic regressions with compound symmetric variance structure were used to assess variables associated with rate of AoR dilation and rapid AoR dilation, as defined above. A confirmatory analysis with multiple imputation showed similar results (data not shown).

Referral for Aortic Root Surgery

Multivariable logistic regression was used to assess variables associated with referral for aortic surgery. C-statistics were performed to generate receiver operator characteristic (ROC) curves to determine cut-points in AoR dilation predicting referral for aortic surgery. The cut-point was chosen as the point on the ROC curve that maximizes Youden's Index.

Multivariable Modeling Procedures

Predictors significant at level 0.20 in binary analysis were entered into a multivariate model with backwards elimination. A P value < 0.05 was accepted for statistical significance. The amount of variance explained by the models (R^2) was examined. Since many of the predictors were derived from echocardiographic measurement of aortic dimensions, cluster analysis and correlations were examined to evaluate the collinearity. For highly collinear variables (correlations ≥ 0.8), only the predictor considered most clinically relevant from each group was chosen to include in the models.

Table 1 Predictors

Predictors	*N*	Mean ± SD or *n* (%)
Baseline clinical characteristics		
Age (years)	606	11.2 ± 6.3
Male gender	608	366 (60%)
Hispanic	607	82 (14%)
Race	608	
White		526 (87%)
Black or African American		46 (8%)
Asian		16 (3%)
Other		20 (3%)
Family history (any relative with Marfan syndrome)	585	361 (62%)
Prior cardiac surgery (non-aortic)	608	12 (2%)
Prior medication use		
Beta blocker	608	344 (57%)
Angiotensin converting enzyme inhibitors	608	34 (6%)
Calcium channel blocker	608	8 (1%)
Angiotensin receptor blocker	608	18 (3%)
Other anti-hypertensive	608	2 (< 1%)
Any endocrine history	608	7 (1%)
Any neurodevelopmental history	608	117 (19%)
Any psychiatric history	608	39 (6%)
Height-for-age z-score[a]	541	1.97 ± 1.14
Weight-for-age z-score[a]	548	0.31 ± 1.14
BMI-for-age z-score	513	− 1.21 ± 1.66
Systolic BP-for-age z-score	606	− 0.64 ± 0.98
Diastolic BP-for-age z-score	606	0.32 ± 0.94
Mean BP-for-age z-score	595	− 0.24 ± 0.96
Pulse pressure (mmHg)	606	39 ± 9
Resting heart rate-for-age z-score	604	− 0.01 ± 0.92
Average 24-h heart rate-for-age z-score	608	0.63 ± 0.67
Baseline echocardiographic measures		
Aortic annulus z-score (SD units)	589	1.76 ± 1.30
Aortic annulus diameter (cm)	589	2.01 ± 0.42
Aortic root z-score (SD units)	607	4.32 ± 1.35
Aortic root diameter (cm)	607	3.36 ± 0.61
Sinotubular junction z-score (SD units)	552	2.12 ± 1.27
Sinotubular junction diameter (cm)	552	2.41 ± 0.53
Ascending aortic z-score (SD units)	543	1.00 ± 1.00
Ascending aortic diameter (cm)	543	2.29 ± 0.49
Aortic root diameter:aortic annulus diameter ratio	589	1.68 ± 0.17
Sinotubular junction diameter:aortic annulus diameter ratio	543	1.22 ± 0.15
Sinotubular junction diameter:aortic root diameter ratio	552	0.73 ± 0.06
Sinotubular junction diameter:ascending aortic diameter ratio	506	1.06 ± 0.10
Ascending aortic diameter:aortic annulus diameter ratio	531	1.16 ± 0.14
Ascending aortic diameter:aortic root diameter ratio	543	0.69 ± 0.08
Aortic root diameter:height ratio	540	0.023 ± 0.0025
Ascending aortic diameter:height ratio	527	0.016 ± 0.0019
Aortic root elastic modulus	598	101 ± 71
Aortic root stiffness index	598	9.9 ± 6.5
Ascending aortic elastic modulus	492	50 ± 28
Ascending aortic stiffness index	492	5.0 ± 2.8

Table 1 (continued)

Predictors	*N*	Mean ± SD or *n* (%)
Study drug by treatment arm		
Atenolol maintenance dose (mg/kg/day)	303	2.7 ± 1.1
Losartan maintenance dose (mg/kg/day)	305	1.3 ± 0.2

[a]Only available age ≤ 20 years

Consequently, only AoRd was included and aortic annulus, sinotubular junction, and ascending aortic dimensions were not, and only the stiffness index for AoR and ascending aorta were included, and the elastic modulus for both were not. A confirmatory analysis including or excluding these collinear predictors showed similar results (data not shown).

Since the effect of age on AoR dilation is not linear, age was plotted against outcomes, with a Loess (non-parametric) curve overlaid to assess the shape of the relationship between age and outcomes (Fig. 1a, b). The Loess (non-parametric) curves suggested a non-linear, but age group-dependent, effect of age on AoR dilation. On the basis of these curves, we used age cut-points for AoRz of 11 and 15 years for girls and 11 and 16 years for boys. For AoRd, we used cut-points of 8 and 14 for both genders. For referral for aortic surgery, a quadratic effect of age was chosen.

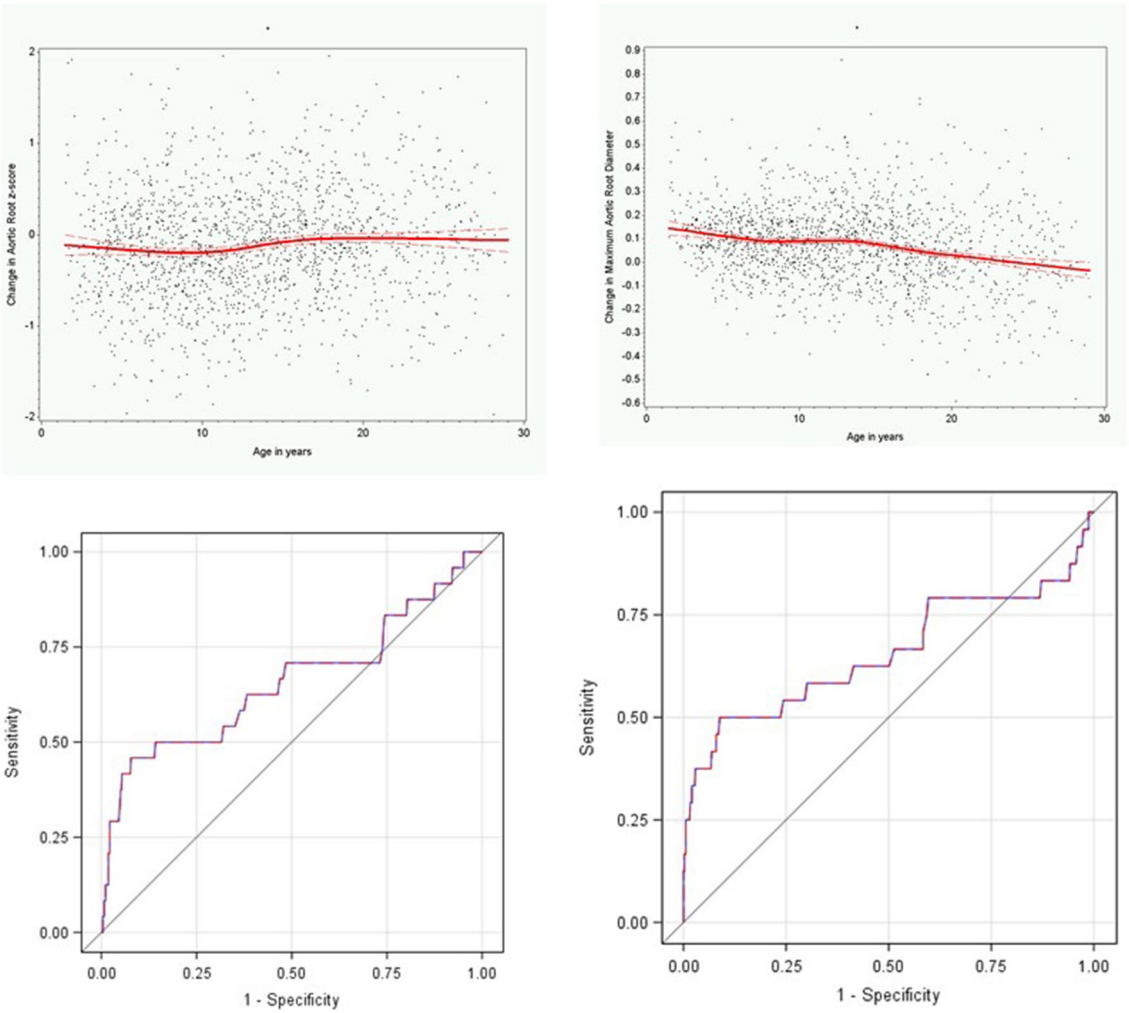

Fig. 1 **a, b** The Loess (non-parametric) curves, that were used to assess the relationship of the annual changes in AoRz and AoRd with age, as solid red lines with the dotted red lines representing the 95% confidence intervals. **c, d** The ROC curves that were used to determine the AoR dilation cut-points in annual changes in AoRz and AoRd, that maximized the sensitivity and specificity for referral for aortic surgery

Results

The mean age of the analytic cohort was 11.2 ± 6.3 years with the majority being male (60%) and white (87%) (Table 1). The mean baseline AoRz was 4.32 ± 1.35 SD units and AoRd was 3.36 ± 0.61 cm.

Independent of study arm, on medical treatment with atenolol or losartan, the mean annual change in AoRz was a decrease of − 0.13 ± 0.70 SD units/year, and the mean annual change in AoRd was an increase of 0.07 ± 0.18 cm/year (Table 2). In this study cohort, the cut-off for rapid AoR root dilation > 90th percentile was > 0.64 SD units/year for AoRz and > 0.26 cm/year for AoRd. During the study period, 28 subjects (5%) were referred for aortic root surgery including 2 (0.33%) subjects who underwent aortic root surgery for aortic dissection. There was one death due to congestive heart failure; this subject had neither aortic dissection nor aortic root surgery.

In the multivariable analysis (Table 3), an increased change in AoRz/year was associated with older age, a higher sinotubular junction diameter:AoR diameter ratio, and male gender ($R^2 = 0.02$). An increased change in AoRd/year was associated with younger age, higher sinotubular junction z-score, male gender, and the absence of any psychiatric history ($R^2 = 0.07$). Rapid AoR dilation, as defined by change in AoRz/year > 90th percentile, was associated with older age, higher sinotubular junction z-score, and atenolol as the study drug ($R^2 = 0.02$). Rapid AoR dilation, as defined by change in AoRd/year > 90th percentile, was associated with higher sinotubular junction z-score and non-white race ($R^2 = 0.01$).

Table 2 Outcomes

Outcomes	*N*	Mean ± SD or *n* (%)
AoR dilation		
Annual change in AoRz/year (SD units/year)	1659[a]	− 0.13 ± 0.70
Annual change in AoRd/year (cm/year)	1661[a]	0.07 ± 0.18
Referral for aortic surgery	608	28 (5%)

AoR aortic root, *AoRz* AoR z-score, *AoRd* AoR diameter

[a]Of 1824 potential measures (3 annual changes per each of 608 subjects)

Table 3 Results of multivariable analysis

Outcomes	Predictors	Slope	SE	*P*	R^2
AoR dilation					
Annual change in AoRz/year	Created age variable: increase from child to young adult, with linear increase from age 11 to 15 for girls or 16 for boys	0.16	0.035	< 0.001	0.02
	STJ diameter:AoR diameter ratio	0.62	0.26	0.02	
	Female gender	− 0.076	0.032	0.02	
Annual change in AoRd/year	Created age variable: number of years younger than 8 (negative, or 0 if ≥ 8)	− 0.011	0.0030	< 0.001	0.07
	Created age variable: number of years older than 14 (or 0 if ≤ 14)	− 0.0077	0.0013	< 0.001	
	STJ z-score (SD)	0.012	0.0036	< 0.001	
	Female gender	− 0.030	0.0084	< 0.001	
	Psychiatric history	− 0.035	0.017	0.03	
Outcomes	Predictors	OR	CL	*P*	R^2
Rapid AoR dilation					
Annual change in AoRz/year > 90th percentile	Created age variable: increase from child to young adult, with linear increase from age 11 to 15 for girls or 16 for boys	1.71	1.17–2.49	0.005	0.02
	STJ z-score (SD)	1.24	1.05–1.45	0.009	
	Study drug losartan vs. atenolol	0.72	0.52–1.00	0.05	
Annual change in AoRd/year > 90th percentile	STJ z-score (SD)	1.31	1.12–1.52	< 0.001	0.01
	Race other vs. white	5.48	1.15–26.18	0.03	
Referral for aortic surgery	AoR diameter (cm)	172	23 to > 999	< 0.001	0.17
	AAo z-score (SD)	2.57	1.37–4.81	0.003	
	STJ diameter:AAo diameter ratio	811	4 to > 999	0.01	

AAo ascending aorta, *AoR* aortic root, *AoRz* AoR z-score, *AoRd* AoR diameter, *CL* confidence limits, *OR* odds ratio, *SE* standard error, *STJ* sinotubular junction

Referral for aortic root surgery was associated with higher AoRd, higher ascending aorta z-score, and higher sinotubular junction diameter:ascending aorta diameter ratio ($R^2 = 0.17$). Although statistically significant, the associations were weak, and none of the above-described clinical or echocardiographic factors were found to be robust predictors of AoR dilation or referral for aortic surgery.

ROC curves for change in AoRz and AoRd are shown (Fig. 1c, d). A change of AoRz of 0.72 SD units/year had 42% sensitivity and 92% specificity for predicting referral for aortic surgery, and a change in AoRD of 0.34 cm/year had 38% sensitivity and 95% specificity for predicting referral for aortic surgery.

Discussion

In this post hoc analysis of the data from the PHN Marfan trial, we did not find any robust clinical or echocardiographic predictors of rapid AoR dilation or referral for aortic surgery in children and young adults with MFS monitored over 3 years. Although some associations were statistically significant, these associations were only weakly predictive and explained little of the variation in outcomes. In this study cohort, AoR dilation cut-points had high specificity, but low sensitivity for predicting referral for aortic surgery.

Previous studies have shown larger baseline AoR dimensions to predict progressive AoR dilation in MFS. In 19 children with MFS (aged 1–18 years) followed by echocardiography for up to 8 years, those with AoRz > 2 at baseline showed more rapid AoR dilation [9]. In 78 adults with MFS (aged 18–50 years) with a median echocardiography follow-up of 71 months, baseline AoRd was the major predictor for progressive aortic root dilation (OR 1.37, 95% CI 1.16–1.62) [10].

We found progressive AoR dilation as measured by an increased change in AoRz/year was associated with older age, a higher sinotubular junction diameter:AoR diameter ratio, and male gender, whereas AoR dilation as measured by increased change in AoRd/year was associated with younger age, higher sinotubular junction z-score, male gender, and absence of any psychiatric history. We postulate that the differential effect of age here is due to somatic growth in childhood. Younger individuals with MFS tend to maintain a similar AoRz throughout childhood, as their AoR grows in parallel to their more advanced somatic growth. Older individuals with MFS tend to have increasing AoRz, as their AoR continues to grow in adulthood, but their body surface area becomes fixed once somatic growth is complete. In contrast, AoRd in all age groups with MFS tends to increase. We also found that more rapid AoR dilation as defined by change in AoRz/year > 90th percentile was associated with older age, higher sinotubular junction z-score, and atenolol, whereas more rapid AoR dilation as defined by change in AoRd/year > 90th percentile was associated with higher sinotubular junction z-score, and non-white race. Although these associations were only weakly predictive, a common theme in these models was an increased sinotubular junction z-score and an increase in the sinotubular junction dimension relative to the AoR or ascending aortic dimension, or the so-called effacement of the sinotubular junction. This may suggest that monitoring the sinotubular junction dimensions by echocardiography could be an additional useful marker of more rapid AoR dilation, both clinically and in future studies. However, data reported previously from this trial suggested that the maximum sinotubular junction diameter was one of the least consistently measured of the proximal aortic dimensions with the highest interobserver variability [19]. Therefore, simply recognizing effacement of the sinotubular junction by echocardiography might prove more useful than actually monitoring the sinotubular junction dimensions.

Similarly, aortic complications in MFS have previously been shown to be consistently associated with larger baseline AoR dimensions [4, 11–15]. In 113 patients with MFS (aged 6 months to 66 years), with a mean follow-up of 49 ± 24 months, aortic complications (dissection, marked dilation requiring surgery, or progressive moderate-to-severe aortic regurgitation) were associated with larger baseline AoRd, older age, increased height, higher systolic blood pressure, and AoR growth rate, but the only independent predictor was baseline AoRd [4]. Interestingly, when AoRd, one of the indications for surgical referral, was excluded from their analyses, the only independent predictor of aortic complications was generalized proximal aortic dilation involving the AoR, sinotubular junction, and ascending aorta, which was present in 51% of their study participants. AoR growth rate has also been shown previously to be associated with aortic complications in MFS in other studies. In 62 patients with MFS (aged 1 months to 54 years) with echocardiography follow-up for up to 16 years, aortic complications were again associated with larger baseline AoRd and older age, along with AoR growth rate > 5% per year [11]. In 57 children with MFS (aged 1–16 years) with echocardiography follow-up for up to 14 years, AoR growth rate was also shown to be of prognostic value for occurrence of aortic complications [12]. In 43 patients with MFS (aged 22 ± 14 years) with a mean echocardiography follow-up of 5 ± 3 years, aortic dissection both in the ascending and descending aorta only occurred in the group with more rapid AoR growth rate > 3% per year [13].

We found that referral for aortic root surgery was associated with higher AoRd, higher ascending aorta z-score, and higher sinotubular junction diameter:ascending aorta diameter ratio. The higher sinotubular junction diameter:ascending aorta diameter ratio again suggests effacement of the

sinotubular junction. Along with the higher ascending aorta z-score, this suggests that generalized proximal aortic dilation as has previously been shown [4] is associated with referral for aortic root surgery. As above, this may suggest that recognizing effacement of the sinotubular junction and generalized proximal aortic dilation could be useful clinical markers in determining the need for referral for aortic root surgery.

The main limitation of this study cohort is the short follow-up duration of only 3 years. The selection of only patients with moderate AoR disease, with AoRz > 3 and AoRd < 5 cm, and no potential for aortic surgery within 6 months of enrollment, also limited the numbers of referrals for aortic surgery during the study period. There was also likely variation in institutional criteria for referral for aortic surgery, as this was not prescribed within the main trial protocol. Including specific details about any family history of early dissection or need for aortic surgery may have added to our analysis. Genetic screening for the presence of an *FBN1* mutation was only available in just over half of study participants, so was also not included in this analysis. Future planned genotype-specific and pharmacogenetics studies may provide additional information.

In conclusion, our analysis of data from a large randomized study of children and young adults with MFS did not identify any new clinical or echocardiographic predictors of aortic root dilation or referral for aortic root surgery. Further work may determine whether other risk factors, beyond baseline AoR dimensions (AoRz and AoRd) and AoR growth rate, such as generalized proximal aortic dilation and effacement of the sinotubular junction, may allow for better risk stratification. Rate of AoR dilation cut-points had high specificity, but low sensitivity for predicting referral for aortic surgery, limiting their clinical use. Establishment of registries monitoring patients with MFS longer term would allow us to determine whether such factors and family- and/or genotype-specific predictors, may aid in identifying those patients who would most benefit from more frequent follow-up and initiation of earlier medical therapy and/or surgical intervention.

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Compliance with Ethical Standards

Conflict of interest/Relation to Industry The authors do not have any conflict of interest. The views expressed in this article are those of the authors and do not represent the official views of the National Heart, Lung, and Blood Institute (NHLBI) or the National Institutes of Health.

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