

# Effect of Perindopril on Large Artery Stiffness and Aortic Root Diameter in Patients With Marfan Syndrome

## A Randomized Controlled Trial

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**M**ARFAN SYNDROME (MFS) is an autosomal dominant connective tissue disorder caused by mutations in *FBNI*, the gene encoding fibrillin 1. Fibrillin 1 is a key component of extracellular matrix elastic fibers and also a negative regulator of the cytokine transforming growth factor  $\beta$  (TGF- $\beta$ ), which contributes to matrix metalloproteinase (MMP) activation and extracellular matrix degeneration.<sup>1</sup> The main clinical manifestations of MFS involve the skeletal, ocular, and cardiovascular systems. Progressive aortic stiffening, dilatation, and rupture are the most serious complications and the most common cause of premature death. Based on a single trial<sup>2</sup> of propranolol in 32 patients with MFS and 38 controls,  $\beta$ -blockers are currently the standard treatment for MFS. The rationale for the use of  $\beta$ -blockers includes reduction in the rate of pressure change in the aortic root (ie, left ventricular ejection) and heart rate, and therefore aortic wall stress. However,  $\beta$ -blockers may not directly address the underlying pathobi-

**Context** Aortic stiffness is increased in Marfan syndrome contributing to aortic dilatation and rupture, the major cause of premature death in this population. Angiotensin-converting enzyme inhibitors have been shown to reduce arterial stiffness.

**Objective** To determine whether perindopril therapy reduces aortic stiffness and attenuates aortic dilatation in patients with Marfan syndrome.

**Design, Setting, and Participants** A randomized, double-blind, placebo-controlled trial of 17 patients with Marfan syndrome (mean [SD], 33 [6] years) taking standard  $\beta$ -blocker therapy, initiated in January 2004 and completed in September 2006, at Alfred Hospital Marfan Syndrome Clinic, Melbourne, Australia.

**Intervention** Patients were administered 8 mg/d of perindopril (n=10) or placebo (n=7) for 24 weeks.

**Main Outcome Measures** Indices of arterial stiffness were assessed via systemic arterial compliance, and central and peripheral pulse wave velocities. Aortic root diameters were assessed at 4 sites via transthoracic echocardiography.

**Results** Perindopril reduced arterial stiffness as indicated by increased systemic arterial compliance (mean [SEM], 0.33 [0.01] mL/mm Hg at baseline to 0.54 [0.04] mL/mm Hg at 24 weeks in perindopril group vs 0.30 [0.01] mL/mm Hg to 0.29 [0.01] mL/mm Hg in placebo group,  $P=.004$ ), and reduced central (7.6 [0.4] m/s to 5.9 [0.3] m/s in perindopril group,  $P<.001$  vs placebo) and peripheral (10.9 [0.4] m/s to 8.7 [0.4] m/s in perindopril group,  $P<.001$  vs placebo) pulse wave velocities. In addition, perindopril significantly reduced aortic root diameters relative to placebo in both end-systole and end-diastole ( $P<.01$  to  $P<.001$  for all comparisons between groups). Although perindopril marginally reduced mean arterial pressure (from 81 [2] mm Hg to 80 [1] mm Hg in perindopril group vs 83 [2] mm Hg to 84 [3] mm Hg in placebo group,  $P=.004$ ), the observed changes in both stiffness and left ventricular outflow tract diameter remained significant when mean arterial pressure was included as a covariate. Transforming growth factor  $\beta$  (TGF- $\beta$ ), which contributes to aortic degeneration in Marfan syndrome, was reduced by perindopril compared with placebo in both latent (59 [6] ng/mL to 45 [3] ng/mL in perindopril group,  $P=.01$  vs placebo) and active (46 [2] ng/mL to 42 [1] ng/mL in perindopril group,  $P=.02$  vs placebo) forms.

**Conclusions** Perindopril reduced both aortic stiffness and aortic root diameter in patients with Marfan syndrome taking standard  $\beta$ -blocker therapy, possibly through attenuation of TGF- $\beta$  signaling. Large clinical trials are needed to assess the clinical benefit of angiotensin II blockade in Marfan syndrome.

**Trial Registration** clinicaltrials.gov Identifier: NCT00485368

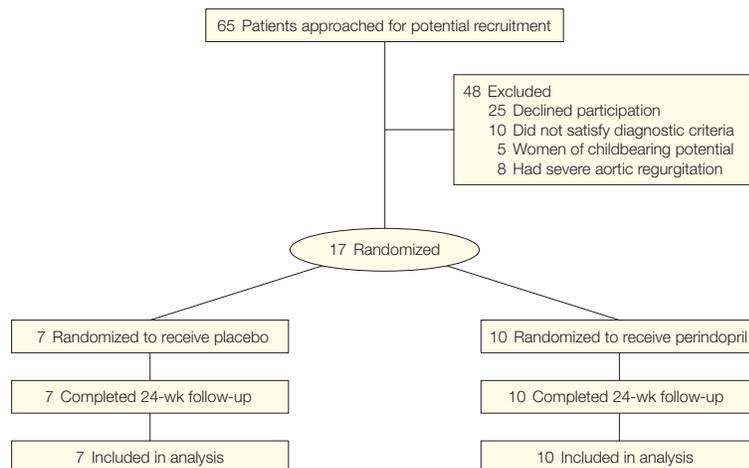
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**Figure 1.** Flow of Patients Through the Study

ology of aortic wall degeneration<sup>3-5</sup> as effectively as other agents.<sup>6-9</sup>

A number of recent studies have implicated the renin-angiotensin system in development of aortic stiffening, dilatation, and rupture in MFS through multiple mechanisms involving both the angiotensin II type 1 (AT<sub>1</sub>) and angiotensin II type 2 (AT<sub>2</sub>) receptors. In fibrillin 1-deficient mice, enhanced activation of and signaling by TGF- $\beta$  can be blocked by the AT<sub>1</sub> antagonist losartan preventing aortic aneurysm.<sup>10</sup> On the other hand, both angiotensin II and AT<sub>2</sub> receptor expression are increased in MFS aortas and associated with cystic medial degeneration, which contributes to aortic rupture.<sup>11</sup> Angiotensin-converting enzyme (ACE) inhibition and AT<sub>2</sub> receptor antagonism also significantly inhibit vascular smooth muscle cell apoptosis in cultured aortic cells from patients with MFS.<sup>11</sup> ACE inhibitors are known to reduce large artery stiffness<sup>6</sup> and a small nonrandomized clinical study has also reported that ACE inhibitors increase aortic distensibility compared with  $\beta$ -blocker therapy in children and adolescents with MFS.<sup>12</sup>

Given the efficacy of ACE inhibitors to inhibit the actions of angiotensin II through both the AT<sub>1</sub> and AT<sub>2</sub> receptors, we hypothesized that such

therapy would reduce arterial stiffness and aortic dilatation relative to placebo in adult patients with MFS taking standard  $\beta$ -blocker therapy. We also hypothesized that these aortic changes would be associated with reduction in TGF- $\beta$  and MMP plasma levels, particularly MMP-2 and MMP-3, which are up-regulated by TGF- $\beta$  in MFS.<sup>13,14</sup>

## METHODS

Seventeen patients (mean [SD], 33 [6] years; range, 27-40 years) were recruited from the Alfred Hospital Marfan Syndrome Clinic, Melbourne, Australia, and completed the trial, which was initiated in January 2004 and completed in September 2006 (FIGURE 1). All patients gave written informed consent to participate in the study, which was approved by the Alfred Hospital Ethics Committee. Inclusion criteria included (1) positive strict diagnosis of MFS using Ghent criteria,<sup>15</sup> (2) age 18 to 40 years, (3) serum creatinine level of less than 1.2 mg/dL (to convert to micromoles per liter, multiply by 88.4), (4) systolic blood pressure of 140/90 mm Hg or less (when measured on  $\beta$ -blocker therapy), and (5) no history of previous aortic surgery. Homocysteinuria was excluded as an alternative diagnosis. All patients were

receiving long-term treatment with a  $\beta$ -blocker.

Computer-generated numbers specified the drug allocation sequence. A tamper-proof randomization process generated by the hospital research center randomly assigned participants to receive either perindopril (2 mg/d for 1 week, 4 mg/d for 2 weeks, and thereafter 8 mg/d for 21 weeks; Coversyl, Servier Laboratories Ltd Pty, Hawthorn Victoria, Australia) or placebo (2 mg/d equivalent for 1 week, 4 mg/d equivalent for 2 weeks, and thereafter 8 mg/d equivalent for 21 weeks) in a parallel-group, double-blind design. All patients reached the 8 mg/d dosage. Both investigators and patients were blinded to drug assignment. Furthermore, investigators did not have access to baseline data when they performed follow-up measurements and patients were not asked which treatment they thought they were receiving. No patient assigned to placebo crossed over to perindopril during the trial or vice versa. The study had 80% power to detect a 10% change in arterial stiffness parameters and a 5% change in aortic diameters with an  $\alpha=.05$ .

## Resting Blood Pressure

On the morning of testing and 10 hours following the last medication dose, supine resting brachial arterial blood pressure and heart rate were measured 3 times at 3-minute intervals using an automated oscillometric blood pressure monitor (Dinamap Vital Signs Monitor 18465X, Criticon, Florida) following 15 minutes of quiet rest in a temperature-controlled room.

## Arterial Stiffness

Arterial stiffness was assessed globally via systemic arterial compliance (carotid tonometry and Doppler velocimetry) and regionally via pulse wave velocity. Systemic arterial compliance was determined noninvasively using calculations based on the area method of Liu et al<sup>16</sup> and a 2-element Windkessel model of the arterial system as described previously.<sup>16,17</sup> This method

has been validated to primarily assess the properties of the large vessels, including the aorta and carotid arteries.<sup>18</sup> Pulse wave velocity is related directly to aortic stiffness and was measured centrally between the right carotid and right femoral arteries and peripherally between the right femoral and dorsalis pedis arteries, by simultaneous applanation tonometry (SPT-301; Miller Instruments, Houston, Texas).<sup>19</sup> The experienced analyst performing the measurements (A.A.A.) was blinded to treatment allocation.

### Echocardiography

Two-dimensional, M-mode, and Doppler echocardiograms were obtained with a commercially available cardiac ultrasound system, using a 2.5-MHz transducer. Aortic root measurements were made in 2-dimensional parasternal long-axis view at end-diastole (peak of R wave on electrocardiogram) and at end-systole (T wave on electrocardiogram) at the level of the left ventricular outflow tract, sinuses of Valsalva, supra-aortic ridge, and proximal ascending aorta 1 to 2 cm above the supra-aortic ridge according to the method of Roman et al.<sup>20</sup> All measurements were made using the

leading edge technique on up to 5 cycles and averaged. The severity of aortic and mitral regurgitation was graded semiquantitatively using color

Doppler jet area criteria.<sup>21</sup> Echocardiographic evidence of mitral valve prolapse was evaluated using established echocardiographic criteria.<sup>22</sup> A single

**Table 1.** Baseline Characteristics of the Study Population<sup>a</sup>

Characteristics	Placebo Group (n = 7)	Perindopril Group (n = 10)	P Value <sup>b</sup>
Demographics			
Age, mean (SD), y	31 (2)	34 (5)	.47
Sex ratio, male/female	5/2	8/2	.46 <sup>c</sup>
Height, m	1.84 (0.02)	1.83 (0.02)	.73
Weight, kg	74 (1)	76 (1)	.49
Body surface area, m <sup>2</sup>	1.8 (1)	1.9 (1)	.71
Body mass index <sup>d</sup>	22 (1)	21 (1)	.23
Heart rate, beats/min	64 (2)	67 (2)	.24
Brachial blood pressure, mm Hg			
Systolic	118 (4)	122 (2)	.36
Diastolic	71 (2)	73 (2)	.41
Mean arterial pressure	83 (2)	81 (1)	.46
Pulse pressure	47 (4)	49 (3)	.75
Lipids, mg/dL			
Total cholesterol	207 (10)	198 (7)	.42
HDL-C	49 (5)	50 (4)	.75
LDL-C	116 (5)	112 (9)	.75
Triglycerides	134 (9)	126 (13)	.99
Preexisting valvular conditions, No. (%)			
Aortic regurgitation	2 (28)	3 (30)	.76 <sup>c</sup>
Mitral valve prolapse	4 (57)	5 (50)	.81 <sup>c</sup>
Mitral valve regurgitation	3 (43)	3 (30)	.62 <sup>c</sup>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. SI conversions: To convert total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; and to convert triglycerides to mmol/L, multiply by 0.0113.

<sup>a</sup>Data are presented as mean (SEM) unless otherwise specified.

<sup>b</sup>By unpaired *t* test.

<sup>c</sup>By  $\chi^2$  test.

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

**Table 2.** Effects of Perindopril on Blood Pressure and Arterial Stiffness Parameters

Parameter	Mean (SEM)				$\Delta$ in Placebo Group	$\Delta$ in Perindopril Group	P Value <sup>a</sup>
	Placebo Group		Perindopril Group				
	Baseline	24 Weeks	Baseline	24 Weeks			
Brachial, mm Hg							
Systolic BP	118 (4)	119 (3)	122 (2)	118 (2)	1 (1)	-4 (1)	<.001
Diastolic BP	71 (2)	72 (4)	73 (2)	69 (2)	1 (2)	-4 (2)	<.001
Mean arterial pressure	83 (2)	84 (3)	81 (2)	80 (1)	1 (1)	-1 (1)	.004
Pulse pressure	47 (4)	49 (3)	49 (3)	48 (2)	2 (1)	-1 (1)	.94
Heart rate, beats/min	64 (2)	65 (3)	67 (1)	66 (2)	1 (1)	-1 (3)	.65
Carotid, mm Hg							
Systolic BP	113 (3)	117 (2)	124 (6)	120 (6)	4 (1)	-4 (1)	<.001
Pulse pressure	45 (1)	47 (1)	52 (6)	51 (5)	2 (1)	-1 (1)	.03
SAC, mL/mm Hg <sup>b</sup>	0.30 (0.01)	0.29 (0.01)	0.33 (0.01)	0.54 (0.04)	-0.01 (0.03)	0.2 (0.1)	.004
Pulse wave velocity, m/s							
Central	7.1 (0.5)	7.5 (0.5)	7.6 (0.4)	5.9 (0.3)	0.4 (0.1)	-1.6 (0.2)	<.001
Peripheral	11.7 (0.3)	11.9 (0.3)	10.9 (0.4)	8.7 (0.4)	0.2 (0.1)	-2.2 (0.2)	<.001

Abbreviations: BP, blood pressure; SAC, systemic arterial compliance.

<sup>a</sup>Analysis of covariance on change in parameters with baseline values as covariates. When controlling for mean arterial pressure, *P* value for SAC was .006; *P* values for pulse wave velocities did not change.

<sup>b</sup>SAC measurements were not obtained in 5 patients with aortic regurgitation (2 in the placebo group and 3 in the perindopril group).

sonographer blinded to the clinical data and treatment assignment (K.M.D.) performed the analysis, and all echocardiograms were also assessed by 2 experienced cardiologists blinded to patient identity and treatment (A.A. and A.J.W.). Excellent comparability (and no systematic differences) in measures of aortic root diameters both in end-diastole and end-systole between readers was observed ( $r=0.88-0.97$ ). Results are expressed

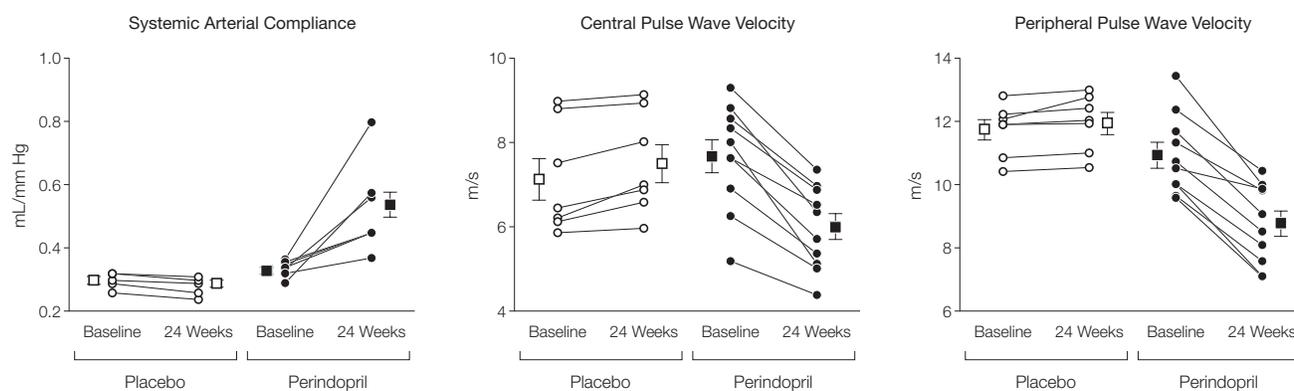
relative to body surface area calculated according to Roman et al.<sup>20</sup>

**Biochemical Analyses**

Venous blood samples were drawn from each patient at baseline and following 24 weeks of therapy. Samples were subsequently analyzed for active and latent TGF- $\beta$  using enzyme-linked immunosorbent assay (ELISA, TGF- $\beta$  Emax ImmunoAssay System, Promega Corporation, Madi-

son, Wisconsin). A fluorokine MAP-Human MMP Base Kit (R&D Systems, Minneapolis, Minnesota) was used to measure MMPs on a BioPlex platform (BioRad Laboratories Inc, Hercules, California); this assay consists of multiplexed sandwich ELISA for the quantitative measurement of MMP-2 and MMP-3. Each sample was assayed twice and averaged. The coefficient of variation between all duplicate assays was less than 5%

**Figure 2.** Individual Patient Values for Systemic Arterial Compliance and Central and Peripheral Pulse Wave Velocities



Squares indicate mean (SEM) values. *P* values for change in placebo vs change in perindopril were calculated using analysis of covariance with baseline values as covariates ( $P=.004$  for systemic arterial compliance and  $P<.001$  for central and peripheral pulse wave velocities). Systemic arterial compliance measurements were not obtained in 5 patients with aortic regurgitation (2 in placebo group and 3 in perindopril group).

**Table 3.** Effects of Perindopril on Echocardiographic Parameters

Parameter <sup>a</sup>	Mean (SEM)				$\Delta$ in Placebo Group	$\Delta$ in Perindopril Group	<i>P</i> Value <sup>b</sup>
	Placebo Group		Perindopril Group				
	Baseline	24 Weeks	Baseline	24 Weeks			
LVID, cm/m <sup>2</sup>							
Systole	1.98 (0.07)	1.97 (0.09)	1.99 (0.05)	2.02 (0.06)	-0.01 (0.03)	0.03 (0.03)	.72
Diastole	3.12 (0.08)	3.14 (0.07)	3.12 (0.07)	3.21 (0.07)	0.02 (0.03)	0.09 (0.02)	.02
LVOT, mm/m <sup>2</sup>							
Systole	21.3 (1.2)	22.5 (1.2)	22.4 (0.8)	23.0 (0.8)	1.3 (0.3)	0.6 (0.1)	.03
Diastole	20.2 (1.3)	20.8 (1.4)	20.7 (0.8)	19.3 (0.8)	0.6 (0.2)	-1.5 (0.2)	<.001
Sinuses of Valsalva, mm/m <sup>2</sup>							
Systole	22.6 (0.9)	24.9 (0.7)	22.9 (0.6)	23.3 (0.6)	2.3 (0.5)	0.4 (0.1)	<.001
Diastole	20.9 (0.8)	21.6 (1.0)	21.1 (0.6)	19.2 (0.5)	0.7 (0.1)	-1.8 (0.2)	<.001
Supra-aortic ridge, mm/m <sup>2</sup>							
Systole	18.6 (1.0)	19.9 (0.7)	20.0 (0.7)	20.2 (0.6)	1.5 (0.3)	0.2 (0.1)	.001
Diastole	17.3 (1.1)	17.7 (1.0)	18.1 (0.6)	15.1 (0.6)	0.6 (0.1)	-3.0 (0.2)	<.001
Ascending aorta, mm/m <sup>2</sup>							
Systole	19.9 (0.6)	21.1 (0.6)	20.3 (0.4)	20.5 (0.3)	1.2 (0.3)	0.3 (0.1)	.01
Diastole	19.0 (0.8)	19.4 (0.6)	18.8 (0.5)	17.5 (0.5)	0.4 (0.2)	-1.2 (0.2)	<.001

Abbreviations: LVID, left ventricular internal diameter; LVOT, left ventricular outflow tract.

<sup>a</sup>Aortic diameters are indexed to body surface area.

<sup>b</sup>Analysis of covariance on change in parameters with baseline values as covariates. *P* values were unchanged when mean arterial pressure was added as a covariate.

and therefore results were averaged to obtain a single value for each sample. Unique standard curves were constructed for each bead and sample analyte concentration determined. This approach delivers the sensitivity of ELISA.

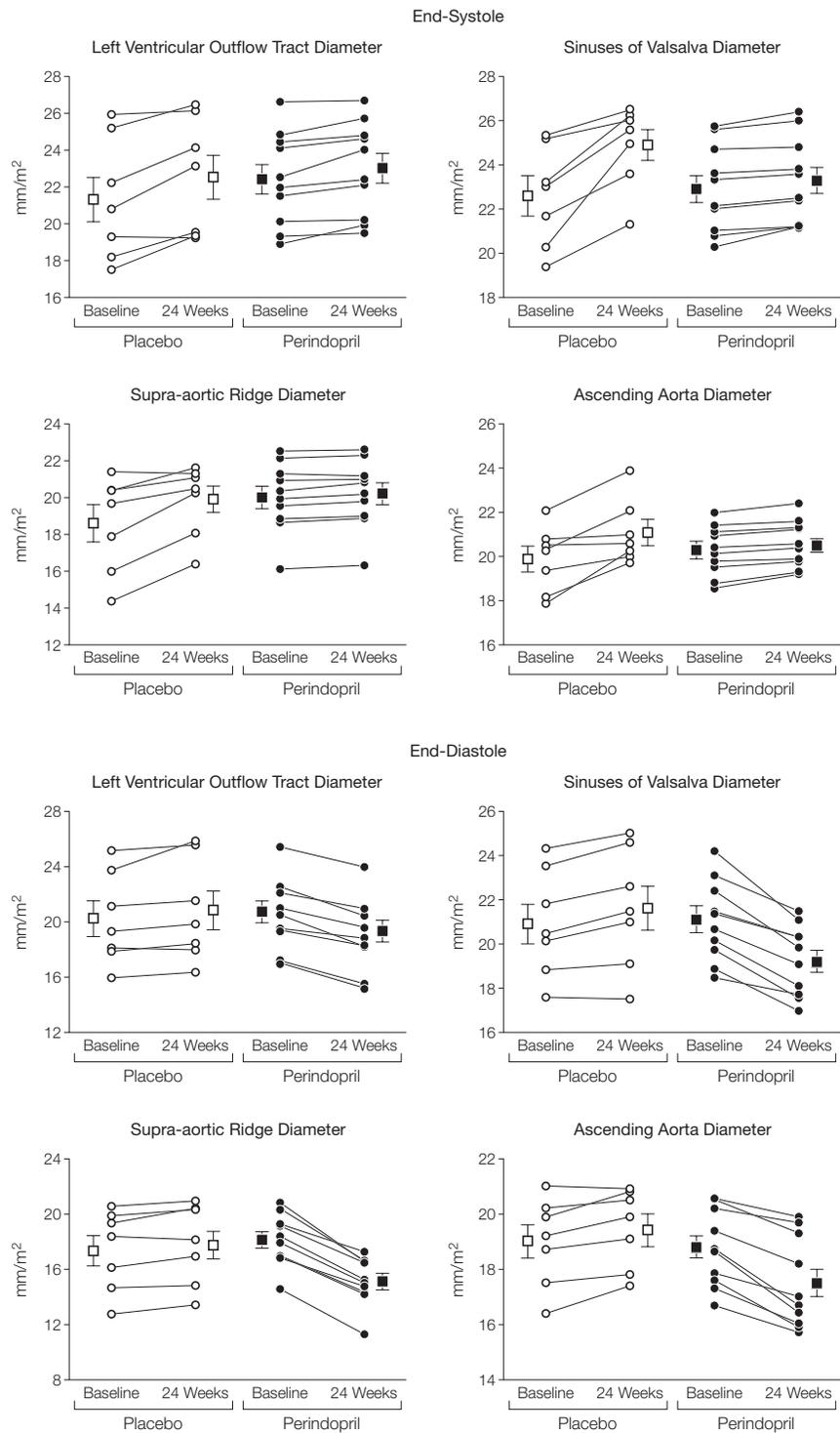
### Statistical Analysis

Demographic and hemodynamic indices at baseline were compared in the perindopril and placebo groups by  $\chi^2$  tests (categorical variables) and unpaired *t* tests (continuous variables). Replicates were meaned to obtain a single value for each patient at each time point (baseline and postintervention). All data are presented as mean (SEM) except age, which is mean (SD). The change in all arterial stiffness indices and echocardiographic parameters from baseline to 24 weeks was compared between the perindopril and placebo groups using an analysis of covariance model. Although groups were matched for all baseline parameters, these were included in all covariate analyses. In addition, because the change in mean arterial pressure was greater in the perindopril group compared with the placebo group, this variable was also included in covariate analyses. *P* values did not change when change in mean arterial pressure was included as a covariate except as otherwise noted. All statistical analyses were performed by using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). *P* < .05 was considered to be significant. The statistician performing the analyses was blinded to treatment group.

### RESULTS

The perindopril and placebo groups were similar in age, body mass index, body surface area, and other cardiovascular risk factors (TABLE 1). The presence of mild aortic regurgitation, mitral valve prolapse, and mitral valve regurgitation was comparable between the 2 groups. The type and dose of  $\beta$ -blocker did not vary between groups. In the perindopril group, 5 patients were taking 200 mg/d of atenolol, 3 patients were taking 100 mg/d of atenolol, 1 patient was taking 240

**Figure 3.** Individual Patient Values for End-Systole and End-Diastole Aortic Root Diameters



Squares indicate mean (SEM) values. *P* values for change in placebo vs change in perindopril were calculated using analysis of covariance with baseline values as covariates (for end-systole: *P* = .03 for left ventricular outflow tract diameter, *P* < .001 for sinuses of Valsalva diameter, *P* = .001 for supra-aortic ridge diameter, and *P* = .01 for ascending aorta diameter; and for end-diastole: *P* < .001 for all).

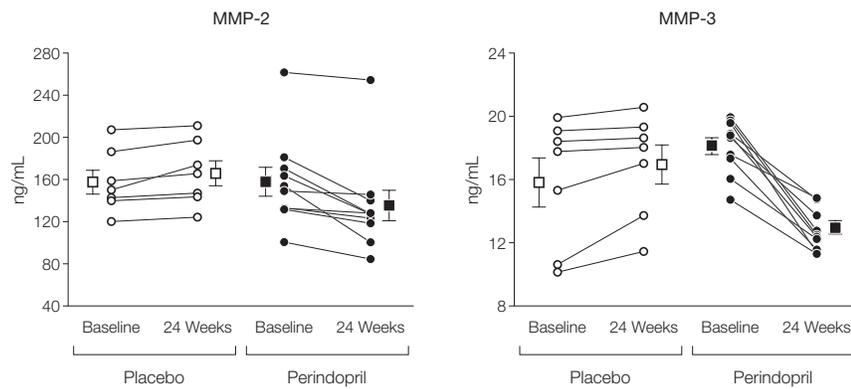
mg/d, and 1 patient was taking 200 mg/d of propranolol. In the placebo group, 3 patients were taking 200 mg/d of atenolol, 2 patients were taking 100 mg/d of atenolol, 1 patient was taking 240 mg/d, and 1 patient was taking 160 mg/d of propranolol. None of the above doses were changed during the trial. One patient in the perindopril group and 2 patients in the placebo group were taking lipid-lowering therapy. None of the patients were taking any other cardiovascular-active drugs. No adverse events were reported throughout the trial.

**Blood Pressure and Arterial Stiffness**

Perindopril therapy increased mean systemic arterial compliance by 0.2 (SEM, 0.1) mL/mm Hg and was significantly different from placebo (-0.01 [0.03] mL/mm Hg,  $P=.004$ ) (TABLE 2 and FIGURE 2). Consistent with these findings, perindopril also reduced central pulse wave velocity (-1.6 [0.2] m/s for perindopril vs 0.4 [0.1] m/s for placebo,  $P<.001$ ) and peripheral pulse wave velocity (-2.2 [0.2] m/s for perindopril vs 0.2 [0.1] m/s for placebo,  $P<.001$ ) (Table 2 and Figure 2).

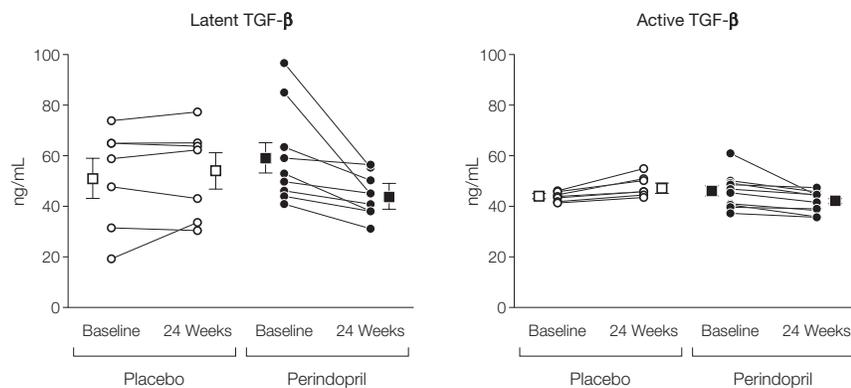
In young healthy individuals, central systolic and pulse pressure are normally lower than the corresponding brachial pressure; however, due to the increase in arterial stiffness in MFS,<sup>23</sup> this differential was not evident. Relative to placebo, perindopril significantly reduced both carotid and brachial systolic blood pressure as well as brachial diastolic blood pressure; however, these changes were small (reduction of 1-4 mm Hg from baseline,  $P<.001$  vs placebo) (Table 2). Although brachial pulse pressure was unaffected by the perindopril intervention, carotid pulse pressure was reduced compared with placebo ( $P=.03$ ). The reduction in mean arterial pressure was small but significant (mean [SEM], -1 [1] mm Hg for perindopril vs 1 [1] mm Hg for placebo;  $P=.004$ ). Importantly, the observed changes in arterial stiffness parameters remained significant ( $P=.001-.006$ ) when mean arterial pressure was included as a covariate. There was no significant difference in resting heart rate between the 2 groups (Table 2).

**Figure 4.** Individual Matrix Metalloproteinase (MMP)-2 and MMP-3 Protein Levels



Squares indicate mean (SEM) values.  $P<.001$  for both plots.

**Figure 5.** Individual Transforming Growth Factor  $\beta$  (TGF- $\beta$ ) Plasma Levels



Squares indicate mean (SEM) values.  $P=.01$  for latent and  $P=.02$  for active TGF- $\beta$  comparisons.

**Echocardiographic Data**

At the initial examination, all echocardiographic variables were comparable between the 2 groups (TABLE 3). Aortic root diameters during systole increased during the placebo intervention, and this increase was significantly attenuated in the perindopril group for all diameters (Table 3 and FIGURE 3). During diastole, aortic root diameters in the placebo group increased marginally, while perindopril therapy led to a reduction (1.2-3.0 mm/m<sup>2</sup>) in end-diastolic diameters compared with the placebo group (Table 3 and Figure 3). The differences in changes in aortic diameters remained significant ( $P<.001$ ) when mean arterial pressure was included as a covariate.

**MMP-2, MMP-3, and TGF- $\beta$  Levels**

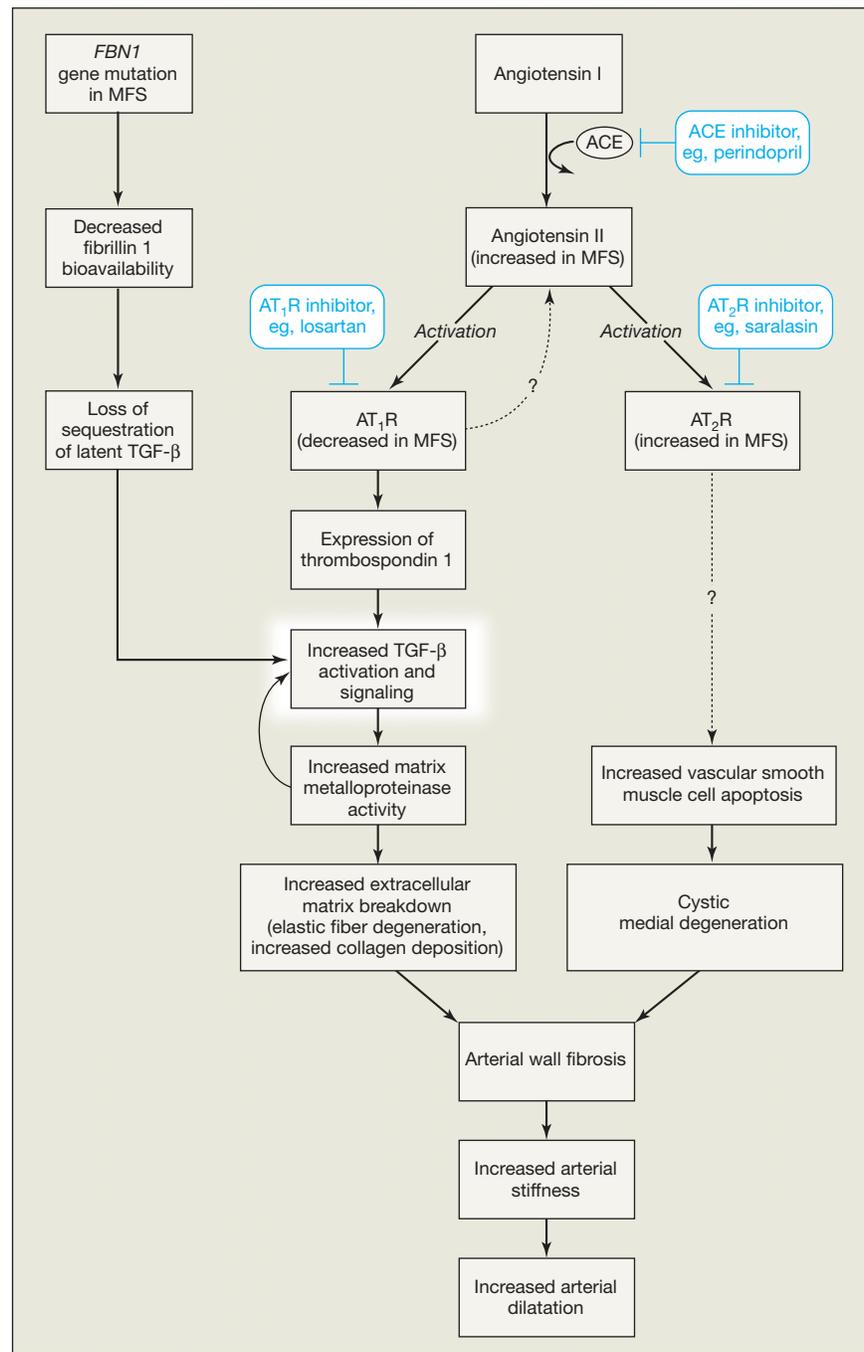
Perindopril reduced total MMP-2 protein levels (mean [SEM], 157 [14] ng/mL at baseline to 135 [14] ng/mL at 24 weeks; decrease of 22 [6] ng/mL

in the perindopril group vs increase of 8 [3] ng/mL in the placebo group,  $P < .001$ ) and total MMP-3 protein levels (18 [1] ng/mL at baseline to 13 [1] ng/mL at 24 weeks; decrease of 5 [1] ng/mL in the perindopril group vs increase of 2 [1] ng/mL in the placebo group,  $P < .001$ ) (FIGURE 4). Perindopril also reduced latent TGF- $\beta$  levels (59 [6] ng/mL at baseline to 45 [3] ng/mL at 24 weeks; decrease of 14 (4.5) ng/mL), which was significantly different from placebo (51 [8] ng/mL at baseline to 54 [7] ng/mL at 24 weeks; increase of 2 [2.3] ng/mL,  $P = .01$ ) (FIGURE 5). Active TGF- $\beta$  levels were also reduced following perindopril therapy (46 [2] ng/mL at baseline to 42 [1] ng/mL at 24 weeks; decrease of 4 [1] ng/mL in the perindopril group vs increase of 3 [1] ng/mL in the placebo group,  $P = .02$ ) (Figure 5).

## COMMENT

The major novel finding of our study was that perindopril therapy for 24 weeks reduced aortic diameters relative to placebo in both systole and diastole in patients with MFS taking standard  $\beta$ -blocker therapy. In systole, perindopril reduced the progression of aortic dilatation observed in the placebo group. However, in diastole, perindopril actually reduced aortic diameters below baseline levels by an average of between 1.2 and 3.0 mm/m<sup>2</sup>. Aortic root dilatation and associated aortic regurgitation, dissection, and rupture is the major life-threatening complication of MFS. Prophylactic repair of the aorta with a composite valve and graft is effective therapy once the ascending aorta becomes widely dilated.<sup>24</sup> The current indication for surgery is an aortic root diameter of 50 mm.<sup>25</sup> However, even after surgery, approximately 10% of patients develop complications of the residual aorta.<sup>24</sup> In addition, some patients will have a major complication (ie, dissection or rupture), even though the aortic root dimension is less than 50 mm.<sup>25</sup> Postoperatively, the patient is required to remain on

**Figure 6.** Proposed Effect of ACE Inhibition on Pathogenesis of Aortic Stiffness in Patients With MFS



Marfan syndrome (MFS) is associated not only with increased transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling through the angiotensin II type 1 receptor (AT<sub>1</sub>R),<sup>10</sup> but also with cystic medial degeneration through the angiotensin II type 2 receptor (AT<sub>2</sub>R).<sup>11</sup> Blockade of the renin-angiotensin system with an angiotensin-converting enzyme (ACE) inhibitor rather than an AT<sub>1</sub>R or AT<sub>2</sub>R inhibitor does not only inhibit downstream effects of increased TGF- $\beta$  signaling, such as increased matrix metalloproteinase activity, increased extracellular matrix breakdown, arterial wall fibrosis, and ultimately increased arterial dilatation, but it also leads to a reduction in vascular smooth muscle cell apoptosis, the principle characteristic of cystic medial degeneration. Thus, ACE inhibition provides additional clinical benefit because it attenuates detrimental effects mediated through both the AT<sub>1</sub>R and AT<sub>2</sub>R. Dashed pathways indicate that an exact mechanism is not yet known.

life-long warfarin treatment and has the risk of prosthetic valve endocarditis. Thus, there is a great deal of interest in medical therapy for MFS, which protects the aorta and prevents or delays surgery. The current use of  $\beta$ -blockers as standard therapy may not directly address the underlying pathobiology of aortic wall degeneration.<sup>3-5</sup>

In MFS, there is good evidence that angiotensin II is increased<sup>11</sup> and that signaling through both the AT<sub>1</sub><sup>10</sup> and AT<sub>2</sub><sup>11</sup> receptor pathways contributes to aortic degeneration. Specifically, in a mouse MFS model, the AT<sub>1</sub> receptor antagonist losartan reduced aortic growth rate and prevented elastic fiber degeneration, presumably through hemodynamic actions and effects on TGF- $\beta$  signaling.<sup>10</sup> Angiotensin II also stimulates Smad-2 dependent signaling in vascular smooth muscle cells and vessel wall fibrosis in a mouse model by an AT<sub>1</sub> receptor-dependent but TGF- $\beta$ -independent mechanism.<sup>26</sup> In addition, AT<sub>2</sub> receptor mechanisms are associated with cystic medial degeneration in MFS and contribute to aortic rupture.<sup>11</sup> As ACE inhibitors reduce angiotensin II production, they act via both AT<sub>1</sub> and AT<sub>2</sub> dependent pathways (FIGURE 6). The effect of inhibiting both pathways in the context of MFS was unknown<sup>27</sup> before the current study.

Our data indicate that adjunct therapy with the ACE inhibitor perindopril reduced large artery stiffness and aortic diameter in patients with MFS taking standard  $\beta$ -blocker therapy. This likely occurred by reducing signaling through both the AT<sub>1</sub> and AT<sub>2</sub> receptors (Figure 6). The observed reduction in TGF- $\beta$  and MMP-2 and MMP-3 are probably secondary to reduced AT<sub>1</sub> receptor signaling.<sup>10</sup> Reduction in AT<sub>2</sub> receptor signaling may provide additional benefit through protection from cystic medial degeneration.<sup>11</sup> Based on our data and previous literature, we therefore suggest that ACE inhibition will provide greater efficacy in aortic root

protection in MFS than specific blockade of either of the angiotensin II receptors alone.

Whether our findings represent an effect specific to perindopril or a more broad class effect cannot be determined. ACE inhibitors vary in lipophilicity, tissue binding, duration of action, and metabolism, which may contribute to variable efficacy with regard to arterial actions.<sup>28</sup> An extensive literature exists regarding the beneficial effects of perindopril on large artery properties<sup>29-31</sup>; however, whether perindopril has greater efficacy than other ACE inhibitors due to its relative lipophilicity or other properties will require direct comparisons.

This study was limited because of its small sample size and relatively short duration. However, it provides a valid basis for further investigation in a larger clinical trial.

In conclusion, therapy with perindopril reduced both aortic stiffness and aortic root diameter in patients with MFS taking standard  $\beta$ -blocker therapy. These findings warrant further investigation in a larger, longer-term clinical trial.

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**Analysis and interpretation of data:** Ahimastos, D'Orsa, White, Dart, Kingwell.

**Drafting of the manuscript:** Ahimastos, Dart, Kingwell.  
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**Statistical analysis:** Ahimastos, Kingwell.

**Obtained funding:** Kingwell.

**Administrative, technical or material support:** D'Orsa, Formosa.

**Study supervision:** Aggarwal, Savarirayan, Dart, Kingwell.

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With all our varied instruments of precision, useful as they are, nothing can replace the watchful eye, the alert ear, the tactful finger, and the logical mind, which correlates the facts obtained through all these avenues of information, and so reaches an exact diagnosis.

—William W. Keen (1837-1932)