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Effects of resveratrol on aortic growth in patients with Marfan syndrome: a single-arm open-label multicentre trial

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ABSTRACT

Background Resveratrol, a dietary supplement that intervenes in cellular metabolism, has been shown to reduce aortic growth rate in a mouse model of Marfan syndrome (MFS), a condition associated in humans with life-threatening aortic complications, often preceded by aortic dilatation. The primary objective of this study was to investigate the effects of resveratrol on aortic growth rate in patients with MFS .

Methods In this investigator-initiated, single-arm open-label multicentre trial, we analysed resveratrol treatment in adults aged 18–50 years with MFS. The primary endpoint was the change in estimated annual aortic growth at five predefined levels in the thoracic aorta after 1 year of resveratrol treatment, evaluated using a linear mixed model. Aortic diameters were measured by cardiac MRI at three time points to analyse the annual aortic expansion rate before and after initiation of treatment. Additionally, annual aortic growth was compared with growth in a previously conducted losartan randomised clinical trial.

Results 898 patients were screened of which 19% (168/898) patients met the inclusion criteria. 36% (61/168) patients signed informed consent and 93% (57/61) aged 37±9 years, of which 28 males (49%) were included in the final analysis of the study. 46% (26/57) had undergone aortic root replacement prior to the study. Aortic root diameters remained stable after 1.2±0.3 years of resveratrol administration. A trend towards a decrease in estimated growth rate (mm/year) was observed in the aortic root (from 0.39±0.06 to −0.13±0.23, p=0.072), ascending aorta (from 0.40±0.05 to −0.01±0.18, p=0.072) and distal descending aorta (from 0.32±0.04 to 0.01±0.14, p=0.072).

Conclusion Resveratrol treatment for 1 year may stabilise the aortic growth rate in adult patients with MFS. However, a subsequent randomised clinical trial with a longer follow-up duration and a larger study cohort is needed to establish an actual long-term beneficial effect of this dietary supplement in patients with MFS.

Trial registration number NL66127.018.18.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Resveratrol, a dietary supplement, is known to reduce the aortic dilatation rate in a Marfan syndrome mouse model. The effect on the aortic dilatation rate in human Marfan syndrome patients is currently unknown.

WHAT THIS STUDY ADDS

⇒ Daily treatment with resveratrol, a dietary supplement, may lead to a decrease in the aortic dilation rate in humans with Marfan syndrome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A larger randomised clinical trial is needed to assess the observed beneficial effect of resveratrol on aortic dilation rate in humans with Marfan syndrome. Hereafter, resveratrol may be added to the limited arsenal of therapeutic options to slow down aortic dilatation in Marfan syndrome.

INTRODUCTION

Marfan syndrome (MFS) is an inherited connective tissue disorder caused almost exclusively by mutations in the fibrillin-1 (FBN1) gene at an incidence of ∼1/5000.[1] Alterations or shortages of the extracellular matrix protein FBN1 are at the basis of the biological processes that lead to an increased risk of sudden death due to aortic dissection or rupture, mostly preceded by aortic growth.[2] Life expectancy for patients with MFS has improved due to the establishment of early diagnosis, advanced techniques for elective aortic surgery and potentially by treatment with β-blockers (BB) and/or angiotensin-II receptor blockers (ARB).[3 4] Despite these advancements, cardiovascular morbidity in this patient cohort remains a major concern.

It is noteworthy that in this era of drug development, no pharmacological treatment strategy has been identified to effectively inhibit aortic disease in patients with MFS. However, as our understanding of the pathophysiological process in MFS increases, new potential medical treatment options are emerging. We have previously shown that natural polyphenol resveratrol slows the aortic growth rate in an MFS mouse model ($Fbn1^{C1041G/+}$ mice) by reducing aortic smooth muscle cell death

and elastic lamina damage.[5] The primary aim of the RESVcue Marfan study was to determine whether resveratrol could reduce the aortic growth rate at any predefined thoracic aortic level in adult patients with MFS measured by cardiovascular magnetic resonance imaging (CMR).

METHODS

Study design and participants

The design of the RESVcue Marfan study was a single-arm open-label multicentre trial (see online supplemental file 1 for the study protocol). Patients were enrolled from December 2018 to November 2020. Patients were identified in four Dutch university hospitals with specialised multidisciplinary Marfan screening clinics (Amsterdam UMC, Amsterdam; Radboud University Medical Center, Nijmegen; University Medical Center Groningen, Groningen; Leiden University Medical Center, Leiden) and by using the CONgenital CORvita (CONCOR) Dutch national registry for adult congenital heart disease.[6] Eligible patients were adults (≥18 years) who were diagnosed with MFS according to the revised Ghent criteria, with a known FBN1 mutation and at least one CMR scan of their aortic trajectory >1 year prior to our study. Patients were ineligible if they (1) had an aortic root diameter >50 mm, (2) had a history of aortic dissection, (3) had more than one vascular prosthesis, (4) had aortic surgery in the last 6 months prior to inclusion or (5) were likely to have aortic surgery within 6 months of inclusion. Moreover, patients were ineligible if they (6) were known to have mental retardation or (7) had planned to become pregnant within the following year. First, all patients with MFS treated in one of the expert centres or present in the CONCOR registry were screened, and eligible patients were contacted by telephone. Informed consent was then signed by all participants during the baseline visit. The local ethics boards approved the study.[7] While the current study was not a randomised controlled trial (RCT), we included available aortic growth rate data from patients of the losartan intervention arm of the previously published COMPARE RCT, in which the effect of losartan on aortic growth rate was investigated, hereinafter referred to as the COMPARE trial group.[8]

Sample size calculation

Measured by CMR, the average annual growth of the aortic root in patients with MFS is approximately 0.35 mm/year with an SD of 0.49.[8] With 100 patients, the width of the 95% CI of the average annual growth rate with resveratrol treatment is approximately 0.2 (4×0.49/10), which we judged to be sufficient to be used as a basis for decision making for a randomised phase IIb or phase III study. With 100 patients, there will be 80% power and a statistically significant Cohen's effect size of about 0.3 or more. Such a large effect has not been observed so far with pharmacological interventions in patients with MFS, but Cohen's effect size of 0.3 is considered to be moderate.

Intervention with resveratrol

All patients prospectively enrolled in the RESVcue study started on 500 mg resveratrol (EHF Production, Rotterdam, The Netherlands) daily, directly after the baseline visit. The COMPARE trial group had not received resveratrol during participation in the COMPARE trial. We did not anticipate side effects, based on other studies using a similar dose; however, when unexpected effects likely due to resveratrol occurred, treatment was discontinued for at least 1 week to examine if the complaints disappeared. Resveratrol treatment was continued after 1 or 2 weeks, and treatment was terminated if side effects reoccurred.

Assessment and outcome

Participating patients started resveratrol treatment after baseline examinations. At baseline and after approximately 1 year of follow-up, we examined patients' medical history and performed CMR of the entire aorta. Every 3 months, patients were interviewed for side effects, changes in medication use and clinical events. The primary endpoint of this study was the change in annual aortic growth rate at five predefined aortic levels, measured by means of CMR, after 1 year of follow-up. To demonstrate a change in growth rate after starting resveratrol, aortic diameters were also measured in the most recent clinically obtained CMR from the participating centre, made at least 12 months prior to inclusion. Using these three diameter measurements, estimated aortic growth rates before and during resveratrol administration were compared. In a separate analysis, we compared the estimated annual aortic growth rate after resveratrol administration in the RESVcue cohort, with the estimated annual aortic growth rates of the COMPARE trial group.

Cardiac magnetic resonance imaging

All RESVcue MFS patients underwent a 3 Tesla CMR (Ingenia, Philips, Best, The Netherlands) examination using a 16-channel torso and 8-channel posterior coil. CMR scans at the baseline visit and after 1 year of resveratrol use were performed at one centre (Amsterdam UMC). The aorta was imaged using an end-diastolic, non-contrast-enhanced, ECG-gated and respiratory navigator-gated 3D mDixon sequence. The acquired spatial resolution was 0.73×0.73×1.25 mm. Aortic diameters were assessed on five cross-sections of the mDixon water images: the aortic root at the level of the sinus of Valsalva; the ascending aorta at the level of the pulmonary artery bifurcation or superior to the aorta graft in patients with a history of aortic root replacement; the aortic arch in between the left carotid and left subclavian artery; the proximal descending aorta at the level of the pulmonary artery bifurcation and the distal descending aorta at the level of the diaphragm (figure 1). The largest diameter measured at each level was used for analysis. Four observers evaluated aortic measurements. First, all measurements were performed by MMvA. Next, positioning and acquisition of the diameter measurements were checked by DB. In case of disagreement about position or diameter, MG decided on the final measurement. Additionally, DB and RM independently evaluated aortic diameters in 10 random CMR examinations each to assess inter-observer and intra-observer variability.

Statistical analysis

Statistical analyses were performed using SPSS V.26 (IBM) and R V.4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The analysis was conducted according to the intention-to-treat principle. Categorical data were reported in numbers and percentages. Continuous data were reported as mean and SEor as mean and SD. Differences in aortic growth rates of patients enrolled in the RESVcue study before and during the clinical trial were evaluated using a linear mixed model analysis. We specified aortic diameter as the dependent variable. The model included follow-up time between examinations, resveratrol use and their interaction. Finally, a random intercept on the subject level was added to the model. Differences in aortic growth rate between the resveratrol and the COMPARE trial groups were also evaluated using a linear mixed model analysis with diameter as the dependent variable. The model included follow-up time between examinations, treatment group and their interaction. An adjustment was made for baseline aortic

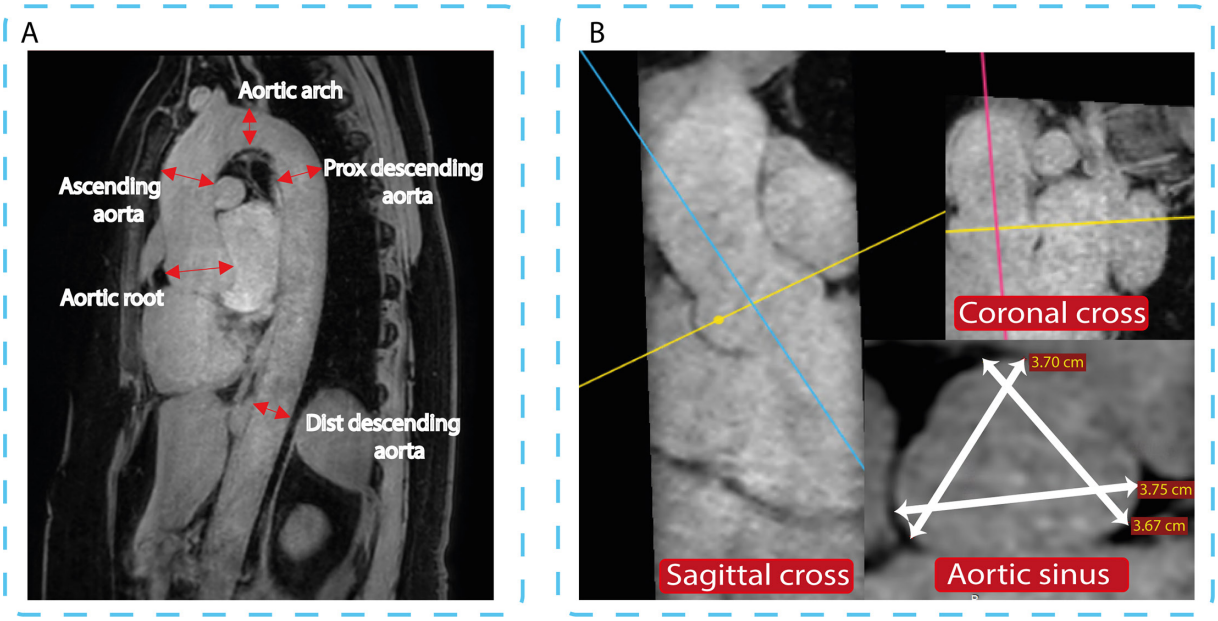

Figure 1 Overview of five levels of thoracic aortic measurements on the diastolic mDixon CMR scan (A) and an example of cusp-to-cusp aortic root dimension measurement (cusp-to-cusp) on the level of the aortic root (B).

diameter, mean arterial pressure (MAP) and body surface area (BSA), and a random intercept on the subject level was added to the model. Aortic growth rates were estimated using the linear mixed effect models. An independent-sample t-test was used for group comparisons of baseline continuous variables. Fisher's exact test or χ^2 test was used to test for baseline group differences in nominal variables. A paired t-test was used to compare baseline and follow-up patient characteristics. Inter-observer and intra-observer variability were reported using the intraclass correlation coefficient (ICC) with 95% CI based on an absolute agreement two-way random effects model. A p value <0.05 (adjusted using the Benjamini-Hochberg procedure in case of multiple testing) was considered significant.

Patient and public involvement

Patients were involved in the design and funding of the study. The authors intend to disseminate the study results to the patients included in the study, as well as healthcare professionals caring for the patients included in the study.

RESULTS

Study population

From March 2018 until November 2020, 57 patients with confirmed MFS were enrolled in the study (figure 2). Patient characteristics at baseline visit are shown in table 1. The mean age at inclusion was 37±9 years, and approximately half of the patients were male (49%). Twenty-six (46%) patients had undergone aortic root replacement prior to the study. The mean time between baseline and follow-up visit was 423 days (range: 283–752). Continued resveratrol treatment was achieved in 55 patients (96%) during the entire follow-up. Resveratrol treatment was ceased within 2 months in two patients due to side effects: skin rash (n=1) and itching skin (n=1). Cardiovascular medicinal treatment regimens did not change during the study between baseline and follow-up. MAP (mm Hg) was not different at baseline versus follow-up in the RESVcue study cohort (baseline: 84±9, follow-up: 83±8, p=0.346).

Baseline visit characteristics of the COMPARE trial group (n=101) are presented in table 1. Both systolic and diastolic blood pressures (mm Hg) were higher for the COMPARE trial group versus the RESVcue group (124±13 vs 116±13, p<0.001 and 74±11 vs 67±10, p<0.001, respectively). BSA (m^2) was higher for the RESVcue group compared with the COMPARE trial group (2.11±0.30 vs 2.02±0.20, p=0.023).

Primary endpoint—aortic growth rate

Aortic growth rate evaluation was possible by CMR in 57 patients. Pre-trial RESVcue CMR sequences used for aortic dimension analysis were 3D steady-state free precession (59.6%), 3D angiography (22.8%), triggered CT angiography (7.0%), mDixon (7.0%), bright blood (1.8%) and dark blood (1.8%). An overview of aortic dimensions pre-trial, at baseline and follow-up and estimated aortic growth in the RESVcue cohort is presented in table 2.

Pre-trial CMR was acquired at mean 1186 (range: 371–3107) days before the inclusion of CMR. We found no significant change in estimated growth rates at any of the aortic levels. However, a trend towards a decrease in estimated aortic growth rate (mm/year) was observed in the aortic root (from 0.39±0.06 to −0.13±0.23, p=0.072), ascending aorta (from 0.40±0.05 to −0.01±0.18, p=0.072) and distal descending aorta (from 0.32±0.04 to 0.01±0.14, p=0.072). Adding baseline cardiac medication use (BB, ARB or both), male sex or age at the baseline visit to the interaction term in the model did not modify the effect of resveratrol on aortic growth rate on any of the aortic levels. Similarly, adding a history of aortic surgery to the interaction term of the model did not influence the effect of resveratrol on aortic growth rate in the ascending (p=0.698), arch (p=0.461), proximal (p=0.461) and distal descending aorta (p=0.698).

In the COMPARE trial group, aortic diameters of the aortic root and the ascending aorta were available only for patients with MFS without a history of aortic root surgery (n=70). A comparison of aortic diameters and estimated aortic growth

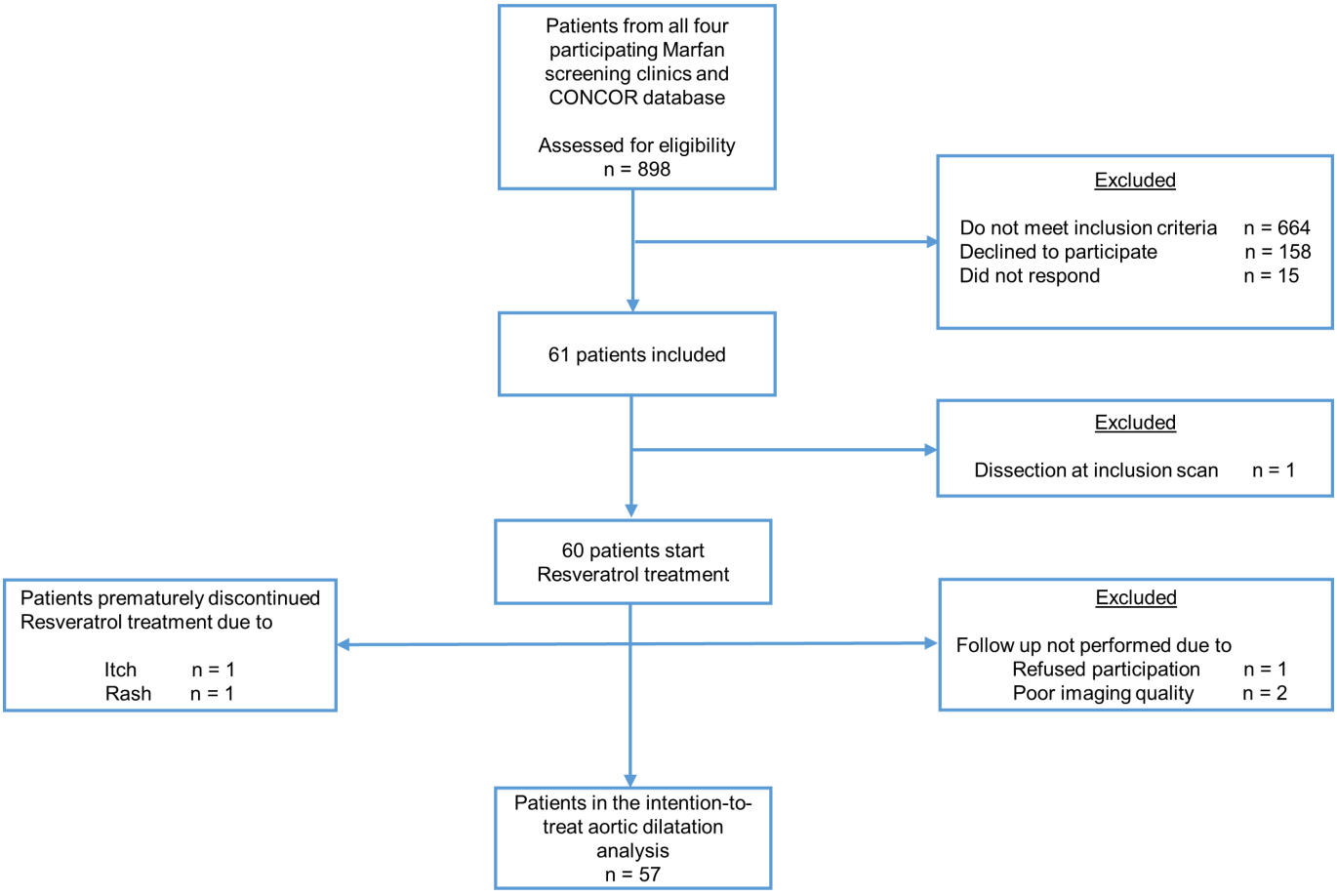

Figure 2 Inclusion and follow-up flowchart for the RESVcue study.

Table 1 Baseline demographics and clinical characteristics of the patients with Marfan syndrome in the RESVcue study and COMPARE trial group

	RESVcue n=57	COMPARE n=101
General features		
Age at inclusion (years)	37±9	38±12
Sex (male)	28 (49%)	59 (58%)
Body surface area (m^2)	2.11±0.3	2.02±0.2*
FBN1 mutation		
Dominant-negative	25 (44%)	47 (46%)*
Haploin sufficient	26 (46%)	27 (26.7%)*
Unknown effect	6 (10%)	27 (26.7%)*
Cardiac medication	44 (72%)	101 (100%)*
β-blocker	33 (58%)	74 (73%)
Losartan	37 (71%)	101 (100%)*
β-blocker and losartan	25 (44%)	74 (73%)*
History of aortic root surgery	26 (46%)	31 (31%)
Bicuspid aortic valve	0 (0%)	1 (1%)
Systolic BP (mm Hg)	116±13	124±13*
Diastolic BP (mm Hg)	67±10	74±11*
Days between baseline and follow-up (range)	423 (283–752)	1150 (669–1631)
Days between pre-trial and inclusion (range)	1186 (371–3107)	NA

*P value <0.05 comparing RESVcue study participants and the COMPARE trial participants.
NA, not applicable.

rates is presented in table 3. All aortic diameters of the RESVcue cohort were significantly different at both baseline and follow-up compared with the COMPARE trial group, except for the ascending aorta diameter (mm) at follow-up (29.8±0.6 vs 29.1±0.5, p=0.322). No significant differences in estimated aortic growth rates corrected for differences in follow-up duration, baseline aortic diameter, BSA and MAP were observed at any of the aortic levels.

Assessment of intra-observer variability in 10 scans showed a mean absolute difference of 1.5±1.05 mm with an ICC of 0.969 (95% CI: 0.918 to 0.986). The mean absolute difference was 2.0±1.55 mm in the inter-observer variability analysis in 10 scans with an ICC of 0.944 (95% CI: 0.870 to 0.973).

DISCUSSION

In this study, we were unable to demonstrate a significant effect of 1.2 years of resveratrol treatment on aortic growth rate in a cohort of adult patients with MFS. However, we did observe a trend towards aortic growth rate decrease on three of the five aortic levels investigated.

Resveratrol is a plant-based compound present in certain plant roots, grapes, berries and nuts, where it is generated in response to injury.[9] Its primary cardiovascular protective effects in humans are considered to reduce oxidative stress and promote cellular survival, as demonstrated in cellular and animal models.[10]

We previously investigated the effect of resveratrol on aortic growth rate in the MFS $Fbn1^{C1041G/+}$ mice, which decreased aortic growth by improving smooth muscle and endothelial cell function.[5 11] In these studies, treatment with resveratrol resulted

Table 2 Overview of aortic diameters and growth rates pre-trial and during the trial period in patients enrolled in the RESVcue study

n=57	Diameter (mm) Mean±SE			Estimated annual growth rate (mm/year) Mean±SE		
Aortic level	Pre-trial	Baseline	Follow-up	Pre-trial	During trial	P value adj†
Root (n=31)	40.3±0.9	41.6±0.8*	41.4±0.8	0.39±0.06	−0.13±0.23	0.072
Ascending	29.0±0.4	30.7±0.4*	30.7±0.4	0.40±0.05	−0.01±0.18	0.072
Arch	25.2±0.4	26.6±0.4*	26.8±0.4	0.29±0.06	0.15±0.21	0.523
Proximal descending	25.9±0.6	26.7±0.6*	26.6±0.6	0.21±0.06	0.07±0.21	0.523
Distal descending	20.8±0.4	22.0±0.3*	22.0±0.3	0.32±0.04	0.01±0.14	0.072

For root diameter analysis, only patients with a native aortic root were analysed. Aortic growth rates and differences in aortic growth rates were estimated using a linear mixed model, correcting for differences in follow-up duration with a random intercept on the subject level .
*P value <0.05 after adjustment for multiple testing using the Benjamini-Hochberg procedure comparing pre-trial and baseline diameter.
†P value after adjustment for multiple testing using the Benjamini-Hochberg procedure.

in decreased smooth muscle cell death, preserving elastin fibres and restoring endothelial nitric oxide synthase function. This reduction in aortic growth rate after resveratrol treatment may involve reduced redox stress[10] and/or normalised TGF-β signalling,[12] promoting aortic repair. Recently, mitochondrial dysfunction has been shown in MFS mice[13] and in MFS aortic smooth muscle cells,[14] which could be reversed by nicotinamide riboside treatment in MFS mice, preventing aneurysm formation. This may be a key downstream pathological pathway impairing aortic repair, which is beneficially affected by resveratrol. Resveratrol is known as sports mimetic for its ability to improve mitochondrial function in many animal studies[15] and also in skeletal muscle in human subjects in two different trials.[16 17] As it is not known which resveratrol metabolite may be beneficial, and which of the pathways are targeted specifically, it appears that the processes that are affected by resveratrol are interconnected. Therefore, all aforementioned pathways are relevant as drug targets to treat vasculopathy in humans with MFS.

Table 3 Aortic dimensions and estimated aortic growth—RESVcue vs COMPARE trial group

	RESVcue (n=57)	COMPARE (n=101)	
Aortic level	Mean±SE	Mean±SE	P value adj*
Baseline (mm)			
Root†	41.6±0.8	44.0±0.6	0.027
Ascending†	29.7±0.6	28.2±0.4	0.041
Arch	26.6±0.4	23.9±0.3	<0.001
Proximal descending	26.7±0.6	23.8±0.4	<0.001
Distal descending	22.0±0.30	20.5±0.3	0.001
Follow-up (mm)			
Root†	41.4±0.8	44.8±0.6	0.003
Ascending†	29.8±0.6	29.1±0.5	0.322
Arch	26.8±0.4	24.5±0.3	<0.001
Proximal descending	26.6±0.6	24.4±0.4	0.001
Distal descending	22.0±0.3	20.8±0.3	0.009
Annual growth rate (mm/year)			
Root†	−0.15±0.22	0.27±0.05	0.365
Ascending†	−0.06±0.22	0.28±0.05	0.365
Arch	0.06±0.15	0.19±0.04	0.470
Proximal descending	0.10±0.16	0.19±0.05	0.615
Distal descending	−0.04±0.13	0.10±0.04	0.470

Estimated aortic growth rates and differences in aortic growth rates were estimated using a linear mixed model, correcting for differences in follow-up duration, baseline aortic diameter, baseline body surface area and mean arterial pressure, with a random intercept on the subject level.
*P value after adjusted for multiple testing using the Benjamini-Hochberg procedure.
†For root and ascending diameter analysis, only patients with a native aorta were analysed (RESVcue, n=31, COMPARE group, n=70).

To our knowledge, only one other study has used resveratrol for the duration of 1 year in human subjects. This study included 60 patients with atherosclerosis who received 100 mg/day and observed normalisation of blood pressure and cholesterol levels due to resveratrol.[18] We did not observe a reduction in blood pressure in our MFS cohort, which might be explained by the fact that patients with MFS have normal blood pressure levels, as shown at baseline, also controlled by the blood pressure-lowering drugs that most of them receive as standard therapy.

According to a recent meta-analysis evaluating the effect of BB and ARB in seven MFS trials, the mean aortic root growth rate is 0.38–0.52 mm/year depending on the medicinal regimen received: BB, ARB or both.[19] The annual aortic root growth rate prior to the inclusion of our current study population was comparable (0.39 mm/year). The mean estimated annual growth rate during the RESVcue trial was −0.15 mm, which is well below the reported growth rates in these studies.

The current RESVcue Marfan study lacked a true MFS control group. However, we compared the aortic growth rates of the RESVcue study with the patients who participated in the COMPARE trial in the losartan arm performed within the same institutions.[8]

Although not statistically significant, the mean baseline characteristic-corrected annual growth rate was lower for the RESVcue cohort compared with the COMPARE trial group.

The observation that only trends, rather than significant changes, in aortic growth rate were noted after resveratrol administration across four specialised Marfan screening clinics underscores the need for international collaboration to conduct an RCT with a larger MFS cohort and a longer follow-up period to accurately assess the impact on aortic growth rate.

Limitations

A major limitation of the current RESVcue Marfan study is our inability to include the originally established total sample size of 100 patients, partly due to our strict inclusion and exclusion criteria and also to the restricted use of our infrastructure during the COVID-19 pandemic.[7] This might have resulted in the failure to observe statistically significant growth rate changes in parts of the aorta, in which a true biological difference might have been present. This is further emphasised by the near statistically significant growth rate differences on three of five measured aortic levels in the pre-treatment and post-treatment analysis.

Additionally, the follow-up period of our study was limited to 1 year. This relatively short follow-up period also hampered the statistics for the investigation of clinical endpoints (aortic surgery, aortic dissections, aortic ruptures or death).

Furthermore, the CMR examinations prior to study inclusion used for the analysis were not all mDixon sequences. Despite this, variability in aortic dimensions due to a variation in standard CMR sequences with comparable spatial resolution was previously found to be low.[20–22]

In the current study, we included patients with a native aorta and with a history of aortic root replacement because this is a normal representation of an adult MFS population. Furthermore, excluding patients with a history of aortic root surgery would have resulted in the exclusion of patients with a more severe phenotype and a history of aortic root surgery is an independent risk factor for type B aortic dissections.[23] To acquire actual aortic growth rates, measurements of aortic diameter were performed only in areas with native aortic tissue. However, it is known that haemodynamics and biomechanical properties change in native aortic tissue distal to the aortic graft and/or replaced aortic valve.[24 25] Nevertheless, adding a history of aortic root surgery to the linear mixed model did not significantly affect estimated growth rates.

CONCLUSION

Treatment with resveratrol in adult patients with MFS did not significantly change the aortic growth rate. However, we did observe trends towards a decreased aortic growth rate. Therefore, in a world with limited medicinal options for the treatment of aortopathy in MFS, resveratrol, as a new treatment option, warrants further investigation through a larger RCT with longer follow-up.

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Contributors MMvA made substantial contributions to the conception and design of the study, performed all CMR examinations, measurements and made a substantial contribution to drafting the manuscript. DB performed CMR measurements and data analysis and made a substantial contribution to the writing of the manuscript. RM performed CMR measurements and contributed to the writing of the manuscript. PvO, MG, VdW, DR-V, AJN, BM and EMS made substantial contributions to the conception and design of the study and critically revised the manuscript. AHZ advised and participated in the statistical analysis. RRLvK, AS and MGD were responsible for local patient recruitment and critically revised the manuscript. VdW and MG organised the funding for this project. VdW is the guarantor. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by MREC Amsterdam UMC: NL66127.018.18. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets analysed during the current study will become available from the corresponding author on reasonable non-commercial request.

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REFERENCES

1 Judge DP, Dietz HC. Marfan's syndrome. *Lancet* 2005;366:1965–76.
2 Sakai LY, Keene DR, Renard M, *et al*. FBN1: The disease-causing gene for Marfan syndrome and other genetic disorders. *Gene* 2016;591:279–91.
3 Shores J, Berger KR, Murphy EA, *et al*. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335–41.
4 Pitcher A, Spata E, Emberson J, *et al*. Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials. *Lancet* 2022;400:822–31.
5 Hibender S, Franken R, van Roomen C, *et al*. Resveratrol Inhibits Aortic Root Dilatation in the Fbn1C1039G/+ Marfan Mouse Model. *Arterioscler Thromb Vasc Biol* 2016;36:1618–26.
6 van der Velde ET, Vriend JWJ, Mannens MMAM, *et al*. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol* 2005;20:549–57.
7 Andel MM van, Ooij P van, Scholte AJ, *et al*. The effect of resveratrol on aortic function in patients with marfan syndrome – rationale and design of the resvcue marfan trial. *In Review* [Preprint].
8 Groenink M, den Hartog AW, Franken R, *et al*. Losartan reduces aortic dilatation rate in adults with Marfan syndrome: a randomized controlled trial. *Eur Heart J* 2013;34:3491–500.
9 Langcake P, Pryce RJ. The production of resveratrol by Vitis vinifera and other members of the Vitaceae as a response to infection or injury. *Physiol Plant Pathol* 1976;9:77–86.
10 van Andel MM, Groenink M, Zwinderman AH. Insights from Rodent-Based Animal Studies. *Int J Mol Sci* 2019;20:1122.
11 Mieremet A, van der Stoel M, Li S, *et al*. Endothelial dysfunction in Marfan syndrome mice is restored by resveratrol. *Sci Rep* 2022;12:22504.
12 Guo S, Zhou Y, Xie X. Resveratrol inhibiting TGF/ERK signaling pathway can improve atherosclerosis: backgrounds, mechanisms and effects. *Biomed Pharmacother* 2022;155:113775.
13 Oller J, Gabandé-Rodríguez E, Ruiz-Rodríguez MJ, *et al*. Extracellular Tuning of Mitochondrial Respiration Leads to Aortic Aneurysm. *Circulation* 2021;143:2091–109.
14 Verhagen JMA, Burger J, Bekkers JA, *et al*. Multi-Omics Profiling in Marfan Syndrome: Further Insights into the Molecular Mechanisms Involved in Aortic Disease. *Int J Mol Sci* 2021;23:438.
15 Guerrieri D, Moon HY, van Praag H. Exercise in a Pill: The Latest on Exercise-Mimetics. *Brain Plast* 2017;2:153–69.
16 Timmers S, de Ligt M, Phielix E, *et al*. Resveratrol as Add-on Therapy in Subjects With Well-Controlled Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Care* 2016;39:2211–7.
17 Mankowski RT, You L, Buford TW, *et al*. Higher dose of resveratrol elevated cardiovascular disease risk biomarker levels in overweight older adults - A pilot study. *Exp Gerontol* 2020;131:110821.

18 Lixia G, Haiyun Z, Xia Z. The clinical effects of resveratrol on atherosclerosis treatment and its effect on the expression of NADPH oxidase complex genes in vascular smooth muscle cell line. *Cell Mol Biol (Noisy-le-grand)* 2021;67:148–52.
19 Saeyeldin A, Zafar MA, Velasquez CA, *et al*. Natural history of aortic root aneurysms in Marfan syndrome. *Ann Cardiothorac Surg* 2017;6:625–32.
20 Potthast S, Mitsumori L, Stanescu LA, *et al*. Measuring aortic diameter with different MR techniques: comparison of three-dimensional (3D) navigated steady-state free-precession (SSFP), 3D contrast-enhanced magnetic resonance angiography (CE-MRA), 2D T2 black blood, and 2D cine SSFP. *J Magn Reson Imaging* 2010;31:177–84.
21 von Knobelsdorff-Brenkenhoff F, Gruettner H, Trauzeddel RF, *et al*. Comparison of native high-resolution 3D and contrast-enhanced MR angiography for assessing the thoracic aorta. *Eur Heart J Cardiovasc Imaging* 2014;15:651–8.
22 Kourtidou S, Jones MR, Moore RA, *et al*. mDixon ECG-gated 3-dimensional cardiovascular magnetic resonance angiography in patients with congenital cardiovascular disease. *J Cardiovasc Magn Reson* 2019;21:52.
23 den Hartog AW, Franken R, Zwinderman AH, *et al*. The Risk for Type B Aortic Dissection in Marfan Syndrome. *J Am Coll Cardiol* 2015;65:246–54.
24 Palumbo MC, Redaelli A, Wingo M, *et al*. Impact of ascending aortic prosthetic grafts on early postoperative descending aortic biomechanics on cardiac magnetic resonance imaging. *Eur J Cardiothorac Surg* 2022;61:860–8.
25 Palumbo MC, Rong LQ, Kim J, *et al*. Prosthetic aortic graft replacement of the ascending thoracic aorta alters biomechanics of the native descending aorta as assessed by transthoracic echocardiography. *PLoS One* 2020;15:e0230208.