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# Role of Beta-Blockers on Aortic Root Growth Rate in Marfan syndrome: Meta -Analysis of 243 Patients

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## ABSTRACT

**Background:** Marfan syndrome (MS) is inherited autosomal dominant connective tissue disorder caused by mutations in the FBN1 gene encoding fibrillin-1. Aortic dilatation is present in about 80% patients with MS and is the major cause of premature mortality. The objective of our study was to determine the effect of beta-blockers on aortic root growth rate in patients with MS. **Methods:** We performed a systematic review of all randomized controlled trials and prospective cohort studies that evaluated the efficacy of beta-blockers in patients with MS. The primary outcome of the study was aortic root growth rate. Secondary outcome was composite of death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery. **Results:** Five prospective trials were identified with similar comparable groups, with a total of 243 patients. In our study mean patient age was 12 years with a mean follow-up 86.5 months. There was a significant reduction in aortic root growth rate (SMD -0.86, 95% CI -1.23 to -0.48, p <0.001) with the use of beta-blockers. No significant difference was observed in secondary outcomes in the beta-blocker group as compared to placebo (OR = 1.80, 95% CI 0.21-15.53). **Conclusion:** Beta-blockers were associated with a significant reduction in aortic root growth rate with reduction in morbidity and mortality.

***Keywords:*** Marfan syndrome, beta-blockers, aortic root growth rate.

## INTRODUCTION

Marfan syndrome is inherited autosomal dominant connective tissue disorder caused by mutations in the FBN1 gene encoding fibrillin-1. The incidence of classic Marfan's syndrome is approximately 2-3 per 10000 individuals, although this estimate depends on recognition of all affected and genetically predisposed individuals.[1] Aortic dilatation is present in about 80% patients with Marfan disease and is the major cause of premature mortality.

The therapeutic options for reduction of aortic root growth include β-blockers and angiotensin II receptor-1 blockers (ARBs). Over the past 3 years, mixed results have been obtained regarding the comparative effect of β-blockers and ARBs. In a small retrospective cohort of 18 pediatric patients, losartan was shown to reduce aortic root dilatation rate with a severe MS.[2] In addition, a randomized controlled trial of 233 patients; losartan was shown to reduce the aortic arch dilatation rate after aortic root replacement.[3] However, in another randomized controlled trial of 608 patients, Lacro et al demonstrated no difference between atenolol and losartan in the aortic-root dilatation rate between the two treatment groups over a 3-year period.[4] Additionally, Milleron et al demonstrated no affect on aortic dilatation over a period of 3-years in a randomized, large-scale, double blind, losartan versus placebo-controlled trial (n=303).[5] Based on these findings, it was suggested that β-blockers remain the first-line therapy in patients with Marfan's syndrome.

The beneficial effects β-blockers are thought to be due to their effect in reducing left ventricular and aortic dP/dt and reducing shear stress. Several animal studies and retrospective clinical studies have indicated a significant reduction in aortic root aneurysm growth rate with use of β-blockers.[6-8] However, later prospective randomized trials of β-blockers failed to show a significant effect with these agents.[9,10] In order to address the discrepancy of their effects, Gersony et al and Gao et al conducted meta-analyses on this topic, which showed contradicting results. Gersony et al demonstrated no reduction in aortic root enlargement in patients with MS with β-blockers and Gao et al demonstrated reduction in aortic dilatation with β-blockers

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therapy.[11,12] However, both these meta-analyses included data from retrospective studies introducing a potential for bias.

In order to address this issue, we performed a meta-analysis of all prospective trials evaluating the role of β-blockers in young patients with Marfan syndrome.

## MATERIALS AND METHODS

The present review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.

**Search Strategy**

We searched PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science and CINAHL databases from the inception through June 3, 2018. All randomized controlled trials and prospective cohort studies of pediatric population with comparable groups (beta-blockers and placebo) were included in the analysis. We combined the terms ("beta-blockers") AND ("Marfan syndrome") as keywords or medical subject heading terms. Two reviewers (RG and RC) independently extracted the data from the eligible trials on study design, patient characteristics, congestive heart failure, aortic root growth rate, aortic regurgitation, aortic dissection, cardiovascular surgery, death and medications (beta-blockers or placebo). Discrepancies between the two reviewers were resolved by discussion and consensus. Final results were reviewed by senior investigators [Figure 1]. All references of the retrieved articles were reviewed for further identification of potentially relevant studies. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

**Eligibility criteria**

The eligibility criteria for our systematic review and meta-analysis included (1) human subjects with Marfan syndrome comparing β-blockers with placebo; (2) reported aortic root growth rate, and complications; (3) literature published in English and (4) either randomized controlled trials (RCTs) or prospective cohort studies. Studies that did not have randomized or matched cohorts were excluded. Retrospective studies, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded. We used the longest available follow-up data from individual studies for our analysis.

**Outcomes**

The primary outcome of interest was final aortic root diameter and aortic root growth rate. Secondary outcome of our study was composite of death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery. The longest available follow up data from the individual trials were used.

**Statistical Analysis**

Random effects model was used to estimate the odds ratio (OR) and respective 95% confidence intervals (CI) using Cochrane Collaborative software, RevMan 5.3. Measure of heterogeneity between the studies was assessed using the chi square test and was considered significant if I2>50%. All p values were 2-sided, and p value of <0.05 was considered significant.

**Quality appraisal and publication bias**

Assessment of risk of bias for each selected study was performed according to PRISMA 2009 guidelines. Qualitative evaluation of bias using the following key parameters were performed for each study: 1) clear definition of study population; 2) clear definition of outcomes and outcome assessment; 3) independent assessment of outcome parameters; 4) sufficient duration of follow-up; 5) selective loss during follow-up; and 6) important confounders and prognostic factors identified. Evidence of publication bias was investigated using funnel plots and analyzed using Egger and Begg methods.

## RESULTS

A total of 21 studies were identified after exclusion of duplicate or irrelevant references [Figure 1]. After a detailed evaluation of these studies, 5 relevant studies were included, that incorporated a total of 243 participants (149 in the treatment group and 94 in placebo group) with Marfan syndrome undergoing therapy with beta-blockers. Of these, 2 were randomized controlled trials and 3 were prospective observational studies.[8,13-15] The characteristics of these trials are described in [Table 1].

The data from Salim et al.[15] was used as two studies in our analysis as this study included patients from two centers and compared the effects of two beta-blockers on the aortic root growth rate, with only one common control group (i.e placebo) for comparison.

**Description of included studies**

Five prospective trials with a total of 243 patients were included in the analysis. Patients were categorized by treatment status (beta-blocker) or untreated (i.e. no beta-blocker). There was one study that assessed any beta- blockers, another evaluated atenolol/propranolol, and rest assessed propranolol. Rossi-Foulkes et al,[14] evaluated the use of all beta-blockers types versus no treatment and demonstrated a significant reduction in aortic root growth rate (mm/year) in the beta-blockers group versus the control group (0.9 ± 1.3 versus 1.8 ± 0.9 mm/year, respectively, p <0.02). Three

patients in the beta-blocker arm had aortic dissection and/or rupture. In another trial Salim et al,[15] demonstrated slower aortic growth rate in the propranolol/atenolol arm (1.1 mm/year, p<0.006) and atenolol only arm (0.7mm/year, p<0.03) as compared to the control group (2.1 mm/year). Five patients in the treatment group underwent elective surgery as compared to no patients in control group. Tahernia et al,[13] described six patients with Marfan syndrome, three of which were treated with propranolol (<1 mg/kg/body weight per day in two divided dose). There were no medication related side effects during the follow-up period. In a trial of 70 patients with Marfan syndrome, Shores et al,[8] (propranolol versus no treatment), demonstrated a significant difference in the rate of change in the aortic ratio, defined as the measured aortic diameter divided by the diameter predicted by patient's height, weight, and age, between the beta blockers arm (0.023/year) and control arm (0.084/year) (p <0.001). Five patients in the treatment arm (of which 2 patients never took their propranolol) and seven patients in the control arm reached the secondary clinical end point [Table 1].

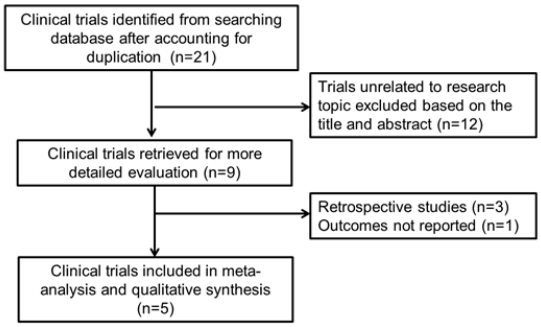


**Figure 1: Process of study selection for randomized and prospective trials (PRISMA Statement).**

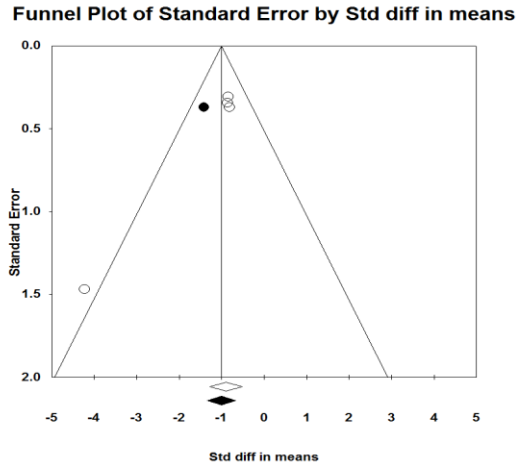


**Figure 2: Funnel plots to assess publication bias**
**a) Aortic root growth**

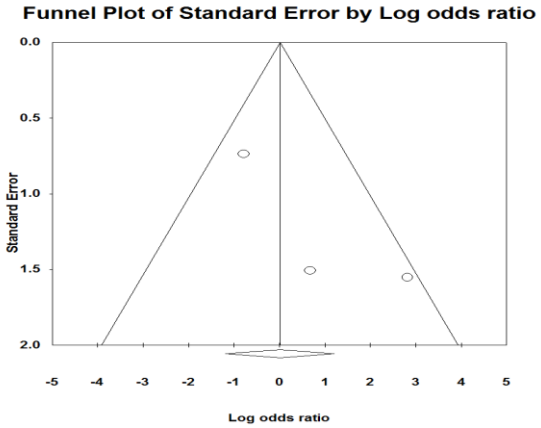


**Figure 2: (Solid circle in (b) indicates imputed study and solid diamond at the bottom shows the result after incorporation of imputed study)**
**b) Secondary outcome (composite of death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery)**

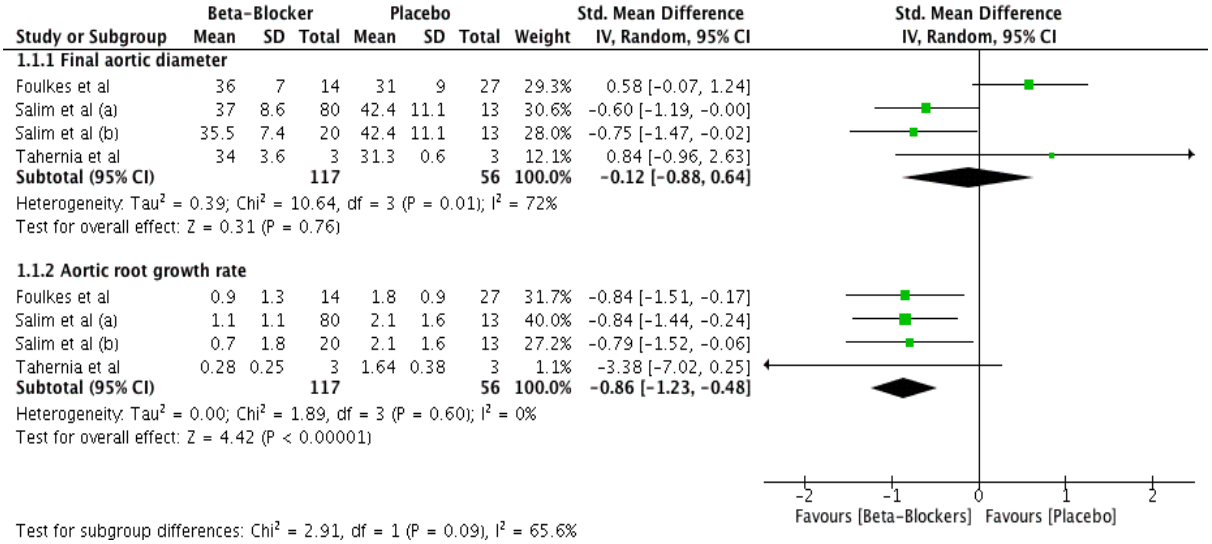


**Figure 3: Forest plot demonstrating primary outcomes - final aortic diameter and aortic root growth rate in patients with Marfan syndrome treated with beta-blockers versus placebo**

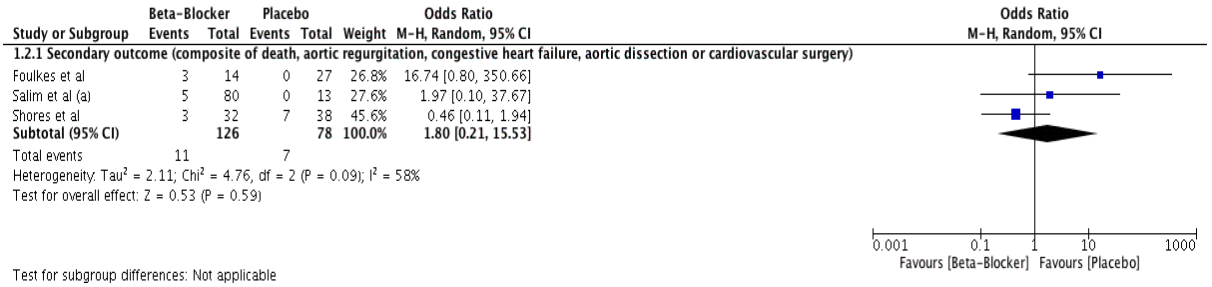


**Figure 4: Forest plot demonstrating secondary outcomes in patients with Marfan syndrome treated with beta-blockers versus placebo**

**Table 1: Descriptive characteristics of studies**

| Trials | Study Design | Treatment | Aortic root growth rate mm/year | Death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery |
|---|---|---|---|---|
| Shores et al[8] | Prospective randomized | Propranolol (n=32), control (n=38) | N/A | Treatment: 3/30<br>Control: 7/38 |
| Tahernia et al,[13] | Prospective randomized | Propranolol (n=3), control (n=3) | Treatment: 0.28 ± 0.25<br>Control: 1.64 ± 0.38 | Treatment: 0/3<br>Control: 0/3 |
| Rossi-Foulkes et al,[14] | Prospective nonrandomized | Any beta-blockers (n=14), control (n=27) | Treatment: 0.9 ± 1.3<br>Control: 1.8 ± 0.9 | Treatment: 3/14<br>Control: 0/27 |
| Salim et al,[15*] | Prospective nonrandomized | Propranolol/atenolol (n=80), control (n=13) | Treatment: 1.1 ± 1.1<br>Control: 2.1 ± 1.6 | Treatment: 5/80<br>Control: 0/13 |
| Salim et al,[15*] | Prospective nonrandomized | Atenolol (n=20), control (n=13) | Treatment: 0.7 ± 1.8<br>Control: 2.1± 1.6 | Treatment: 0/20<br>Control: 0/13 |

* The data from Salim et al. was used as two studies in our analysis as this study included patients from two centers and compared the effects of two beta-blocker on the aortic root growth rate, with only one common control group for comparison

**Table 2: Summary of Egger's and Begg's test for publication bias**

| Outcomes | Egger's test p-value | Begg's test p-value |
|---|---|---|
| Final Aortic root diameter | 0.58 | 1.00 |
| Aortic root growth rate | 0.02 | 0.73 |
| Secondary Outcome | 0.28 | 0.29 |

P value of <0.05 indicates publication bias

## Quality assessment and publication bias

Overall, there were clear definitions of the study population, outcomes, and assessment in most component studies, but blinded assessment of outcomes was not reported in all studies resulting in potential bias. A significant publication bias was observed with aortic root growth diameter in Egger's test. However, after adjustment of the bias the standard mean difference continued to be significantly in favor of reduction in aortic growth rate with use of beta-blockers (standard mean difference [SMD] -1.05, 95% CI -1.52 to -0.59 after adjustment compared to -0.95, 95% CI -1.50 to -0.41 before adjustment). No significant publication bias was observed in other outcomes using funnel plots (Egger's test and Begg's test had p values >0.05 for all analyses) [Table 2, Figure 2].

## Baseline characteristics

In the participant studies, there were no significant differences between the two groups in terms of age, gender and baseline aortic root diameters. Patients on beta-blocker therapy had more weight and height compared to placebo group (p<0.05). No significant heterogeneity was observed for both weight and height [Table 3]. The mean patient age was 12 years and a mean follow-up period of 86.5 months.

## Primary outcome

Four studies reported outcome data on aortic root growth rate and final aortic root diameter. There was a significant reduction in aortic root growth rate (SMD -0.86, 95% CI -1.23 to -0.48, p <0.001) with the use of beta-blockers [Figure 3]. No significant heterogeneity was observed. However, no significant difference was observed in the final aortic root diameter between the two groups (SMD -0.12, 95% CI -0.88 – 0.64). Test of heterogeneity was significant (I2=72%) [Figure 3].

## Secondary outcome

Of 3 clinical trials that reported data on secondary outcome (i.e. composite of death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery), no statistical significant difference was observed in the beta-blocker arm as compared to placebo (OR = 1.80, 95% CI 0.21-15.53, p=0.09, I2 = 58%) [Figure 4].

# DISCUSSION

This systemic review and meta-analysis incorporated 243 patients with MS and demonstrated that beta-blockers when compared to placebo were associated

with significant reduction in aortic root growth rate. Also, no significant differences were observed between the two arms in final aortic root diameter and secondary outcome (i.e composite of death, aortic regurgitation, congestive heart failure, aortic dissection or cardiovascular surgery). This is the first updated meta-analysis of currently available randomized controlled and prospective cohort trials comparing beta-blockers versus placebo in patients with MS.

Beta-blockade is currently considered as standard of care in patients with Marfan syndrome in order to delay aortic dissection or rupture. It is presumed that reduction in heart rate, blood pressure and central aortic pressure during left ventricular ejection explains the beneficial effects of beta-blockade in patients with Marfan syndrome.[16] The reduction in vascular complication in Marfan syndrome was not confirmed until 1994, when Shores et al demonstrated a significant reduction in rate of aortic dilatation with use of beta-blockers.[8] Another potential mechanism includes an effect on elastic properties of aorta, although studies have varied in results. Haouzi et al,[17] demonstrated that 8 of 13 patients treated with beta-blockers resulted in reduced aortic stiffness and increase aortic distensibility, however these findings were inconsistent as 38% of the study subjects demonstrated worsening of these indices on beta-blockers. Studies have also shown variable hemodynamic response to beta-blockers. Yin et al demonstrated that intravenous beta-blockers during cardiac catheterization in Marfan syndrome patients resulted in reduced arterial compliance, with no reduction in maximum acceleration of blood into ascending aorta.[18] In addition, Rios et al demonstrated an increase in peripheral vascular resistance in patients on beta-blockers, which in turn can result in an increase in central aortic pressure and wall stress in patients with Marfan syndrome.[19]

Atenolol is more beta-1 selective blocker as compared to propranolol, and hence may be of greater benefit in patients with Marfan syndrome (although there have been no studies directly comparing atenolol to propranolol or any other beta-1 selective antagonist to date).[8] Prior meta-analyses on this subject have been conducted by Gersony et al and Gao et al have demonstrated contradicting results. Gersony et al demonstrated no reduction in aortic root enlargement in patients with MS with β-blockers and Gao et al demonstrated reduction in aortic dilatation with β-blockers therapy.[11,12] However, both these meta-analyses included data from retrospective studies introducing a potential for bias.

There are few limitations to our findings in this study. All studies included in our analysis had a small sample size. Also aortic root growth suggests 2 processes, a) body growth and b) aortic dilatation. Thus it is prudent that aortic measurements should be indexed to body surface area, which was lacking in all the trials. However, in order to avoid any heterogeneity in between the studies, we only included prospective trials and excluded any retrospective study design (unlike other meta-analysis).[12] No significant difference was observed in the final aortic root diameter between the two groups.

## CONCLUSION

Our study suggests that use of beta-blockers was associated with a significant reduction in aortic root growth rate. Although there was no statistical significant reduction in morbidity and mortality, further trials are required to address this question.

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