Losartan for Preventing Aortic Root Dilatation in Patients with Marfan Syndrome: A Meta-Analysis of Randomized Trials

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ABSTRACT

Introduction: The role of losartan in preventing aortic root dilatation in Marfan syndrome has been evaluated in many clinical trials; however, the results are conflicting.

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Methods: We performed a computerized search of MEDLINE, EMBASE and COCHRANE databases through February 2019 for randomized clinical trials evaluating the effect of losartan in patients with Marfan syndrome. The main outcome was the change in the aortic root diameter in the losartan versus control groups.
Results: Our final analysis included seven randomized trials with a total of 1352 patients and average weighted follow-up of 37.8 months. Change in aortic root diameter was significantly smaller with losartan compared with control [weighted means: 0.44 vs. 0.58 mm, mean difference (MD) = −0.13; 95% CI −0.24 to −0.02; $p = 0.02$]. Subgroup analysis according to the control group showed no significant subgroup

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interaction when comparing losartan with beta-blockers versus with standard therapy ($p_{\text{interaction}}$= 0.27). The composite outcome of aortic surgery, dissection or mortality did not differ between the losartan and control groups (risk ratio = 1.03; 95% CI 0.72–1.49, $p = 0.86$).

Conclusion: In this meta-analysis including seven randomized trials, the use of losartan was associated with a significantly smaller change in aortic root diameter in patients with Marfan syndrome.

Keywords: Angiotensin receptor blocker; Aortic dilatation; Beta-blocker; Losartan; Marfan syndrome

INTRODUCTION

Aortic root dilatation and secondary aortic dissection is the most common cause of death among patients with Marfan syndrome [1]. However, effective medical therapy for preventing aortic dilatation is lacking. The angiotensin receptor blocker losartan emerged as a viable option for preventing aortic root dilatation via cellular and hemodynamic effects [1, 2]. This was the basis for conduction of multiple randomized trials to evaluate the clinical outcomes of losartan in patients with Marfan syndrome. Some of those clinical trials showed favorable benefits for losartan on aortic root dilatation [3, 4], while other trials failed to show beneficial effects for losartan [2, 5]. Also, those trials were underpowered to detect meaningful clinical endpoints. The only available meta-analysis of randomized trials suffered major drawbacks in its methodology with double counting subjects from one study [6]. The extended follow-up results of the LOAT (losartan vs. atenolol) trial and two other randomized trials were recently presented [1, 7, 8]. Hence, we performed a meta-analysis of the available randomized clinical trials evaluating the efficacy of losartan in the prevention of aortic dilatation.

METHODS

We performed a computerized search of MED-LINE, EMBASE and COCHRANE databases, without language restrictions, through May 2019, to identify randomized clinical trials that evaluated the effect of losartan on patients with Marfan syndrome. We further screened the bibliographies of the retrieved studies, prior meta-analyses and ClinicalTrials.gov for any relevant studies not retrieved through the initial search.

We included only randomized trials clinical trials evaluating the effect of losartan on aortic root dilatation in patients with Marfan syndrome compared with a control group. We excluded non-randomized trials and those with no endpoint assessment for aortic root dilatation. Two investigators (A.M. and M.O.) extracted data on study characteristics and main outcomes at the longest follow-up available. The main outcome was the change in the aortic root diameter in patients receiving losartan versus control. This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. The quality of the included trials was assessed on the basis of adequate description of treatment allocation, blinded outcome assessment and description of losses to follow-up [10]. In cases of an adequately described method of randomization and allocation concealment, studies were considered to be at low risk of selection bias. In cases of blinded outcomes assessment, studies were considered to be at low risk of detection bias, and in cases of complete reporting of losses to follow-up, studies were considered at low risk of reporting bias. Accordingly, the methodological quality of each study was classified as "low risk" (low risk of bias for each criteria), "high risk" (at least one criterion at high risk of bias) or "unclear risk". Data were pooled using fixed-effects and random-effects models and the Mantel–Haenszel and inverse variance methods, depending on degree of heterogeneity. Heterogeneity was assessed by I^2 statistics. Outcome measures were described using mean differences for continuous variables and risk ratio for categorical variables. *P* values were two-tailed, and were considered statistically significant at $p < 0.05$. Statistical analyses were conducted using RevMan 5.0 software (Cochrane Collaboration, Oxford, UK). This article is based on
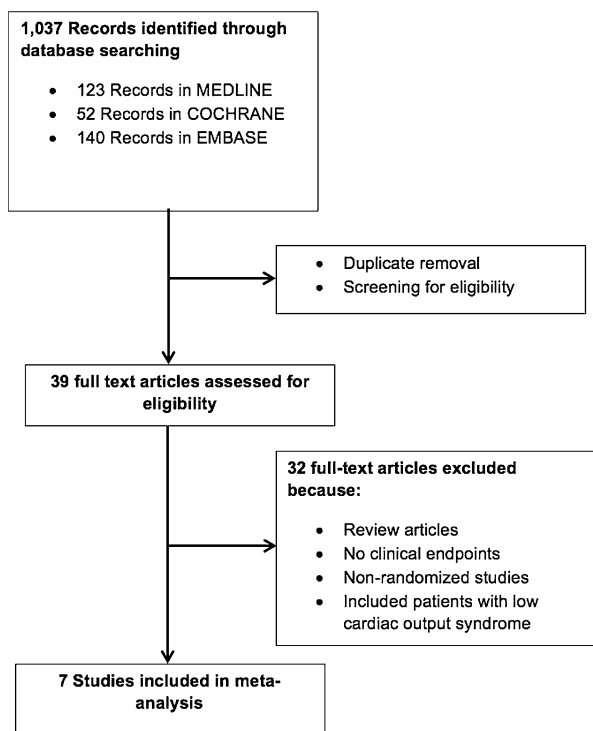
Fig. 1 Flow chart of included studies

previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

The final analysis included seven clinical trials [1–5, 7, 8], with a total of 1352 patients and average weighted follow-up of 37.8 months (Fig. 1; Supplemental Table 1). The imaging modality was cardiac magnetic resonance in two studies [1, 3] and echocardiogram in the others. After quality assessment, all included studies were classified as low risk of bias (Table 1). The baseline characteristics of the trials are presented in Table 2. Composite clinical outcomes included aortic dissection, aortic surgery, and all-cause mortality in all studies except Groenink et al., who reported cardiovascular-related mortality [3]. Change in aortic root diameter was significantly smaller with losartan compared with control [weighted means: 0.44 vs. 0.58 mm, mean difference (MD) = −0.13; 95% CI −0.24 to −0.02; $p = 0.02$], with global heterogeneity (I^2) of 98%

Table 1 Risk of bias assessment in included trials

Study	Year	Method of randomization	Blinded outcome assessment	Description of loss to follow-up?	Completion of follow-up (%)	Risk of bias
Teixido-Tura	2018	Computer-generated sequence	Yes	Yes	95.3/90.6	Low
Muiño-Mosquera	2017	Computer-generated sequence	Yes	Yes	83.3/100	Low
Bhatt	2015	Computer-generated sequence	Yes	Yes	100/100	Low
Milleron	2015	Computer-generated sequence	Yes	Yes	95.4/97.3	Low
Lacro	2014	Computer-generated sequence	Yes	Yes	87.5/88.4	Low
Chiu	2013	Computer-generated sequence	Yes	Yes	93/100	Low
Groenink	2013	Computer-generated sequence	Yes	Yes	67.2/57.3	Low

Table 2 Baseline characteristics of includes studies

Study (year)	Single/multicenter	Country of origin	Losartan group (n)	Control group (n)	Control arm	Follow-up duration	Imaging modality
Teixido-Tura (2018)	Multicenter	Spain	64	64	Atenolol	6 years	CMR
Muiño-Mosquera (2017)	Single-center	Belgium	12	10	Placebo	3 years	TTE
Bhatt (2015)	Multicenter	USA	17	17	Atenolol	6 months	TTE
Milleron (2015)	Multicenter	France	151	148	Placebo	3.5 years	TTE
Lacro (2014)	Multicenter	USA	305	303	Atenolol	3 years	TTE
Chiu (2013)	Single-center	Taiwan	15	13	Atenolol/ propranolol	35 months	TTE
Groenink (2013)	Multicenter	Netherlands	116	117	Conventional therapy	3 years	CMR
Total	Single-center n = 2/multicenter n = 5	–	680	672	–	37.8 months	CMR n = 2/TTE n = 5

Study (year)	Age, years (mean ± SD)[a]	Male (%)[a]	Weight, kg (mean ± SD)[a]	Height, cm (mean ± SD)[a]	Presence of causal FBN1 mutation (%)[a]	Prior beta-blocker (%)[a]
Teixido-Tura (2018)	25.6 ± 13.8/23.8 ± 13.6	35.9/46.9	61.5 ± 21.0/64.8 ± 20.6	171.7 ± 16.7/175.0 ± 18.8	83.3/80	0/0
Muiño-Mosquera(2017)	36.83 ± 13.81/35.4 ± 11.20	33.3/60.1	72.5/80.2	182.5/188.2	NA/NA	NA/NA
Bhatt (2015)	36 (31, 44)/34 (25, 45)[b]	41/53	77.2 ± 25.1/84.2 ± 22.0	177.2 ± 11.2/180.7 ± 12.3	NA/NA	NA/NA
Milleron (2015)	30.9 ± 15.9 28.9 ± 13.6	44/41	NA/NA	177.7 ± 11.9/178.8 ± 11.6	78.1/77.7	86/80
Lacro (2014)	11.0 ± 6.2 11.5 ± 6.5	61/59	40.5 ± 22.4/41.7 ± 22.4	149.7 ± 32.5/151 ± 33.2	31/29	57/56
Chiu (2013)	12.5 ± 5/ 13.7 ± 7.5	33.3/46.1	NA/NA	NA/NA	NA/NA	100/100

Table 2 continued

Study (year)	Age, years (mean ± SD)[a]	Male (%)[a]	Weight, kg (mean ± SD)[a]	Height, cm (mean ± SD)[a]	Presence of causal FBN1 mutation (%)[a]	Prior beta-blocker (%)[a]
Groenink (2013)	36.8 ± 12.3 38.3 ± 13.4	59.5/47	NA/NA	NA/NA	74.8/88.2	75/70.10
Total	27.1/26.5	44.0/50.4	62.9/67.7	171.8/174.7	66.8/68.7	79.5/76.5

CMR cardiac magnetic resonance imaging, *TTE* transthoracic echocardiography, *NA* not available

[a] Data are presented for losartan/control arms

[b] Data are presented as range

(Fig. 2). We conducted multiple sensitivity analyses by excluding one/two studies at a time to see which studies contributed most to the heterogeneity. The results showed a lower degree of heterogeneity by excluding the studies by Lacro et al. [2] and Chiu et al. [4] (MD = −0.07; 95% CI −0.08 to −0.05; $p < 0.001$; $I^2 = 24\%$). Subgroup analysis according to the control group showed no significant subgroup interaction when comparing losartan with beta-blockers [1, 2, 4, 7] versus with standard therapy [3, 5, 8] ($p_{\text{interaction}} = 0.27$). A change in the diameter of the ascending aorta was reported in six studies, and analysis showed no significant difference between the losartan and control groups (MD = −0.02; 95% CI −0.14 to −0.11; $p = 0.78$; $I^2 = 98\%$). There was no difference in the composite outcome for aortic surgery, dissection or mortality between the losartan and control groups (risk ratio = 1.03; 95% CI 0.72–1.49, $p = 0.86$; $I^2 = 0\%$) (Fig. 2).

DISCUSSION

The enthusiasm surrounding the use of losartan to halt aortic root dilatation in Marfan patients stems from the theoretical benefit of antagonizing transforming growth factor-beta and the initial results from animal models and small observational human studies [1]. In this meta-analysis of seven randomized trials, we found a significantly smaller (24%) change in aortic root diameter in the losartan group compared with the control group. This is even more relevant when considering the otherwise limited medical therapies to halt aortic root progression. There was a significant degree of heterogeneity in the assessment of aortic root changes; however, sensitivity analysis showed a similar benefit with losartan after excluding the studies contributing to the heterogeneity, Laro et al. and Chiu et al. Both studies comprised mainly pediatric populations with average ages of 11 and 13 years. Also, in the study by Lacro et al., the mean aortic root z scores in the losartan and atenolol groups (4.4 and 4.2, respectively) were the highest among the study populations [2]. There was no subgroup difference based on the type of control arms, i.e. beta-blockers or
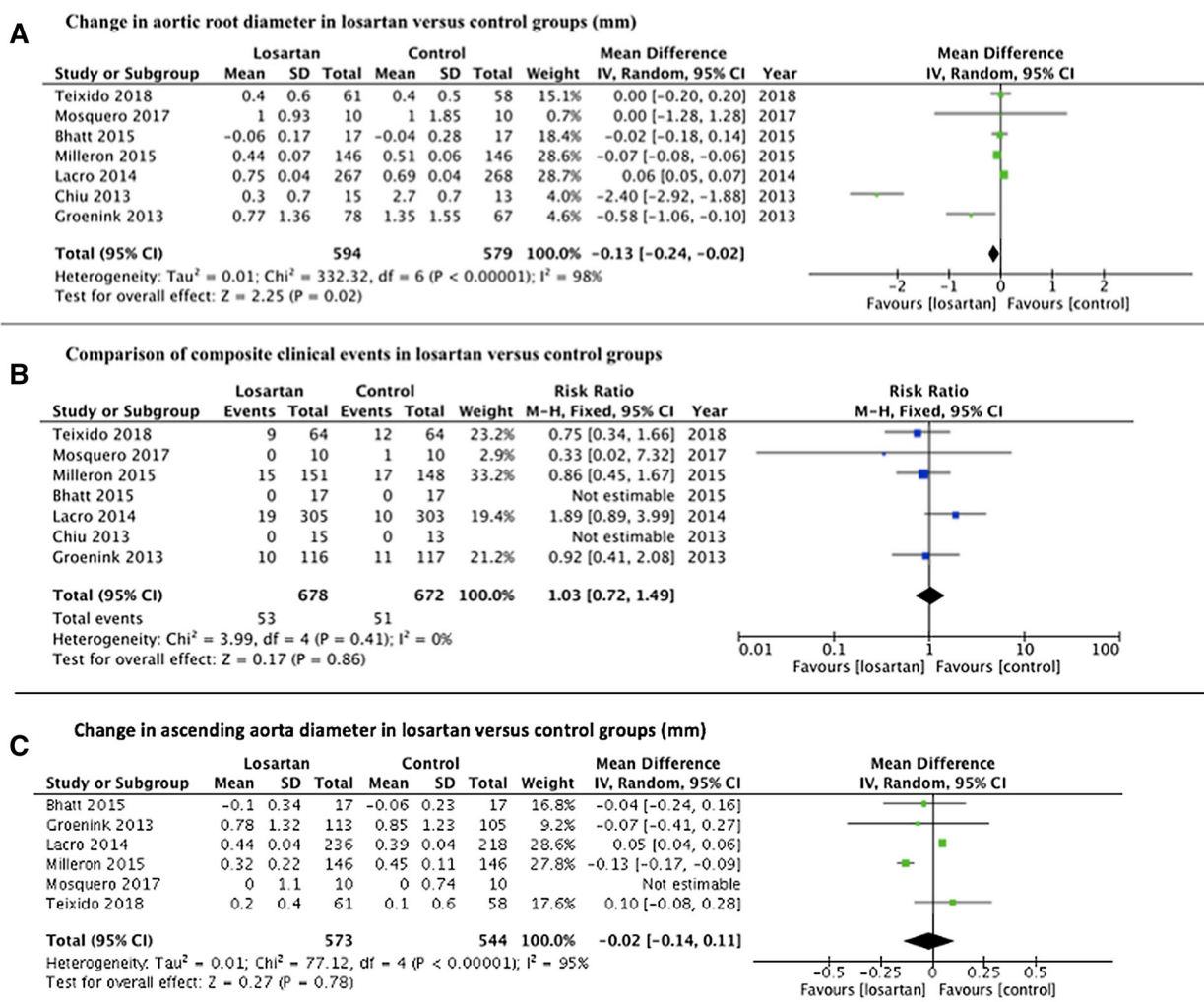
A Change in aortic root diameter in losartan versus control groups (mm)

Study or Subgroup	Losartan Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Teixido 2018	0.4	0.6	61	0.4	0.5	58	15.1%	0.00 [-0.20, 0.20]	2018
Mosquero 2017	1	0.93	10	1	1.85	10	0.7%	0.00 [-1.28, 1.28]	2017
Bhatt 2015	-0.06	0.17	17	-0.04	0.28	17	18.4%	-0.02 [-0.18, 0.14]	2015
Milleron 2015	0.44	0.07	146	0.51	0.06	146	28.6%	-0.07 [-0.08, -0.06]	2015
Lacro 2014	0.75	0.04	267	0.69	0.04	268	28.7%	0.06 [0.05, 0.07]	2014
Chiu 2013	0.3	0.7	15	2.7	0.7	13	4.0%	-2.40 [-2.92, -1.88]	2013
Groenink 2013	0.77	1.36	78	1.35	1.55	67	4.6%	-0.58 [-1.06, -0.10]	2013
Total (95% CI)			**594**			**579**	**100.0%**	**-0.13 [-0.24, -0.02]**	

Heterogeneity: Tau² = 0.01; Chi² = 332.32, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.25 (P = 0.02)

Favours [losartan] Favours [control]

B Comparison of composite clinical events in losartan versus control groups

Study or Subgroup	Losartan Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI	Year
Teixido 2018	9	64	12	64	23.2%	0.75 [0.34, 1.66]	2018
Mosquero 2017	0	10	1	10	2.9%	0.33 [0.02, 7.32]	2017
Milleron 2015	15	151	17	148	33.2%	0.86 [0.45, 1.67]	2015
Bhatt 2015	0	17	0	17		Not estimable	2015
Lacro 2014	19	305	10	303	19.4%	1.89 [0.89, 3.99]	2014
Chiu 2013	0	15	0	13		Not estimable	2013
Groenink 2013	10	116	11	117	21.2%	0.92 [0.41, 2.08]	2013
Total (95% CI)		**678**		**672**	**100.0%**	**1.03 [0.72, 1.49]**	
Total events	**53**		**51**				

Heterogeneity: Chi² = 3.99, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)

Favours [losartan] Favours [control]

C Change in ascending aorta diameter in losartan versus control groups (mm)

Study or Subgroup	Losartan Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bhatt 2015	-0.1	0.34	17	-0.06	0.23	17	16.8%	-0.04 [-0.24, 0.16]
Groenink 2013	0.78	1.32	113	0.85	1.23	105	9.2%	-0.07 [-0.41, 0.27]
Lacro 2014	0.44	0.04	236	0.39	0.04	218	28.6%	0.05 [0.04, 0.06]
Milleron 2015	0.32	0.22	146	0.45	0.11	146	27.8%	-0.13 [-0.17, -0.09]
Mosquero 2017	0	1.1	10	0	0.74	10		Not estimable
Teixido 2018	0.2	0.4	61	0.1	0.6	58	17.6%	0.10 [-0.08, 0.28]
Total (95% CI)			**573**			**544**	**100.0%**	**-0.02 [-0.14, 0.11]**

Heterogeneity: Tau² = 0.01; Chi² = 77.12, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.27 (P = 0.78)

Favours [losartan] Favours [control]

Fig. 2 Forrest plot for change in aortic root diameter, composite clinical events and ascending aorta diameter with losartan versus control

standard therapy. On the other hand, we found no significant difference between losartan and the control group in the composite outcome of aortic surgery, dissection or mortality.

The results of this meta-analysis suggest a potential benefit for losartan in reducing aortic root dilatation among Marfan patients. However, we found no significant effect on the progression of ascending aorta dilatation and no effect on the composite outcome of aortic surgery, dissection or mortality. We hypothesize that the trials conducted to date might not have been sufficiently powered to measure the beneficial effects of losartan, or that longer follow-up durations were needed to capture those

effects. In that context, further clinical trials might still be warranted to explore the real effects of losartan on aortic root dilatation and clinical endpoints in patients with Marfan, perhaps with larger samples and longer follow-up durations. The losartan doses used in human studies are lower than those in the initial mouse models that showed more pronounced benefits [1]. Efforts should also be directed to addressing the optimal dosing of losartan and the patient subsets who might benefit the most from introducing losartan.

The present study had certain limitations. Some endpoints were applicable for evaluation in only a portion of included studies. Also,

follow-up periods differed across studies. There was some variability among the included studies in patient characteristics and imaging modalities. Finally, lack of patient-level data precluded further analyses to explore the subgroups or patient characteristics which might benefit from losartan.

CONCLUSION

In this meta-analysis of seven randomized trials, the use of losartan was associated with a significantly smaller change in aortic root diameter in patients with Marfan syndrome. Further clinical trials are warranted to explore the real effects of losartan on aortic root dilatation in this patient population.

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