JAMA Cardiology | Review

# Update on Clinical Trials of Losartan With and Without β-Blockers to Block Aneurysm Growth in Patients With Marfan Syndrome
## A Review

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**IMPORTANCE** Thoracic aortic aneurysms leading to acute aortic dissections are a major cause of morbidity and mortality despite significant advances in surgical treatment, which remains the main intervention to prevent type A dissections. In the past 2 decades progress had been made toward a better understanding of molecular mechanisms that lead to aneurysm formation and dissections of the thoracic aorta. This focused review emphasizes the results of clinical trials using β-blocker, losartan potassium, and irbesartan in patients with Marfan syndrome and comments briefly on mechanisms of aortic remodeling, including fibrosis and transforming growth factor β signaling.

**OBSERVATION** The major risk factors for the disease are increased hemodynamic forces, typically owing to poorly controlled hypertension, and heritable genetic variants. The altered genes predisposing to thoracic aortic disease have been shown or are predicted to decrease vascular smooth muscle cell contraction, decrease transforming growth factor β signaling, or alter the extracellular matrix. Preclinical models of Marfan syndrome showed promising results for losartan as a potential therapy to attenuate aortic dilation in mice. However, several clinical trials did not conclusively confirm that losartan attenuated aortic aneurysm expansion better than β-blockers. Most importantly, clinical trials assessing whether losartan therapy not only reduces aortic growth but also improves adverse aortic outcomes, including dissection, need for surgery, and death, have not been conducted. The largest trial to date to our knowledge, the Pediatric Heart Network trial, sponsored by the National Heart, Lung, and Blood Institute, showed a nonsignificant increase in adverse aortic outcomes, with almost a doubling of adverse events in patients randomized to losartan treatment compared with β-blockers, suggesting that this study was underpowered to assess adverse aortic outcomes. On the other hand, the evidence for β-blocker therapy to reduce morbidity and mortality in Marfan syndrome is limited to a single small, prospective randomized and nonblinded clinical trial.

**CONCLUSIONS AND RELEVANCE** Taken together, these data emphasize the need for clinical trials adequately powered to assess both aortic aneurysm growth and adverse aortic outcomes to identify effective medical therapies for Marfan syndrome and other aortopathies.

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Thoracic aortic aneurysms leading to acute aortic dissections are a major cause of morbidity and mortality despite significant advances in surgical treatment, which remains the main intervention to prevent type A dissections. Progress toward a better understanding of molecular mechanisms that lead to aneurysm formation and dissections of the thoracic aorta has led to targeted drug interventions.

The first drug shown to alter thoracic aortic disease was a β-blocker. An increased susceptibility to aortic dissection can be induced in turkeys by feeding them β-aminopropionitrile, a lysyl oxidase inhibitor, and treatment with propanolol hydrochloride significantly reduced dissection rates from 74% to 8%.[1] Hydralazine decreased blood pressure to the same extent, but increased dissection rates in β-aminopropionitrile–fed turkeys.[2] Subsequently, an open-label randomized clinical trial of propranolol in patients with Marfan syndrome involving 70 patients (mean age at enrollment, 14.5 years for the control group, 15.4 years for the treatment group) showed a significant reduction in aortic root growth and clinical events in the 32 patients treated with propranolol who were followed for a mean of 10.7 years.[3] Based in part on these data, β-blocker was the drug of choice in the 2010 American College of Cardiology/American Heart Association guidelines for treatment of patients with thoracic aortic disease.[4] This recommendation is in agreement with the 2017 practice guidelines for management of hypertension, which recommend β-blocker as the preferred antihypertensive drug class in patients with hypertension and thoracic aortic disease.[5]

A second possible drug to treat aortic disease in Marfan syndrome emerged from studies using a mouse model with an *Fbn1* missense mutation. In this Marfan syndrome mouse model, aneurysms form but rarely dissect. These mice show evidence of increased transforming growth factor β (TGF-β) signaling based on increased Phosphor-Smad2 (Cell Signaling Technology) immunostaining in the aneurysmal aorta. Neutralizing antibodies against TGF-β (R&D System) attenuated aortic dilatation in this Marfan syndrome mouse model.[6] Thus, blocking TGF-β signaling became a pharmacological target to prevent aneurysm formation.

In the quest for an oral agent to prevent aneurysms, losartan potassium was selected based on its ability to inhibit TGF-β signaling and subsequent tissue fibrosis in animal models of chronic renal insufficiency and cardiomyopathy.[7] Moreover, losartan has minimal adverse effects, and cardiologists are comfortable prescribing the drug. When initiated prenatally or at age 7 weeks, losartan was shown to be better than propanolol at reducing both aortic growth and medial thickening and fibrosis of the aortic wall in the Marfan syndrome mouse model.[6] Losartan is an angiotensin 1 receptor (AT1R) blocker, and the effectiveness in the Marfan syndrome mouse model may not be exclusively the result of TGF-β inhibition; rather, it also inhibits AT1R-mediated cellular signaling events and selectively stimulates the $AT_2$ receptor.[8]

## Clinical Trials With Losartan

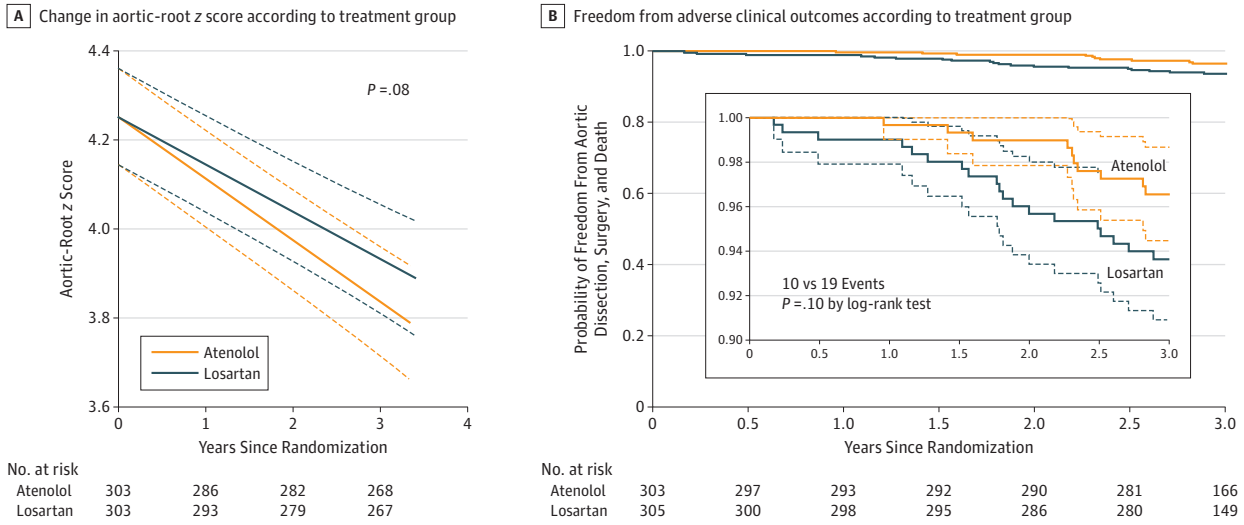
The initial publication of the Marfan syndrome mouse data in 2006, along with publication of a nonrandomized trial of 18 pediatric patients with severe Marfan syndrome that reported reduction in the rate of aortic enlargement with losartan,[9] led physicians worldwide to prescribe losartan to prevent aneurysm growth in individuals with Marfan syndrome, well before randomized clinical trials of losartan were initiated. In fact, losartan was widely prescribed instead of β-blockers for patients with thoracic aortic disease in general (**Table**). The first prospective trial was the Dutch Cozaar in Marfan Patients Reduces Aortic Enlargement (COMPARE) trial,[12] which assessed 233 patients older than 18 years with Marfan syndrome, who were assigned to receive losartan or no additional medications beyond usual therapy, which commonly included a β-blocker. After mean (SD) follow-up of 3.1 (0.4) years, losartan significantly reduced the rate of aortic root dilation compared with usual therapy, with the caveat that more patients in the losartan group than in the usual care group took β-blockers.[12] A substudy of COMPARE analyzed 117 patients with Marfan syndrome with characterized *FBN1* mutations and determined that individuals with haploinsufficiency mutations (n = 38), but not individuals with missense mutations (n = 79), had a statis-

**Table. Summary of Prospective Randomized Clinical Trials of Losartan or Irbesartan in Marfan Syndrome**

| Trial | Drugs Compared | Number Enrolled | Enrollment Age, y | Follow-up, y | Primary Outcome | Results | *P* value | Notes |
|---|---|---|---|---|---|---|---|---|
| Pediatric Heart Network[10] | Losartan vs atenolol | 608 | 0.5-25 | 3.0 (SD, 0.1) | Rate of change in root *z* score | −0.107 vs −0.139 Z/y | .08 | Genetic substudies pending |
| Marfan Sartan[11] | Losartan vs placebo | 299 | >10 | 3.5 | Rate of change in root *z* score | −0.01 vs −0.03 Z/y | .68 | 86% In both groups received β-blockers |
| COMPARE[12] | Losartan vs usual care | 233 | >18 | 3.1 (SD, 0.4) | Change in absolute root diameter | 0.77 vs 1.35 mm | .01 | Significant only for *FBN1* haplo-insufficiency[13] |
| Aortic Irbesartan Marfan Study (AIMS) | Irbesartan + β-blocker vs placebo + β-blocker | 192 | 6-40 | 5 | Rate of change in absolute root diameter | + 0.53 mm vs +0.74 mm | .03 | Unpublished study, presented at 2018 European Society of Cardiology meeting[14] |
| Spanish[15] | Losartan vs atenolol | 140 | 5-60 | 3.0 | Change in root *z* score or absolute diameter | −0.01 vs −0.04 *Z*/y | .19 | None |
| Taiwanese[16] | Losartan + β-blocker vs β-blocker | 28 | None specified | 3 | Rate of change in absolute root diameter | 0.10 vs 0.89 mm/y | .02 | Pilot study open label |
| Ghent Marfan Trial[17] | Losartan + β-blocker vs placebo + β-blocker | 22 | >10 | 3 | Rate of change in absolute root diameter or *z* score | 1 mm/3 y in both groups | >.99 | Difficulties with recruitment[17] |
| Italian | Losartan vs nebivolol vs losartan + nebivolol | Not reported | 1-55 | 4 | Rate of change in absolute root diameter or *z* score | Unpublished | Unpublished | Unpublished study[37] |

Abbreviation: ESC, European Society for Cardiology.

Figure. Primary and Secondary Outcome of the Pediatric Heart Network Trial




A, Baseline adjusted rate of change in the aortic-root *z* score across the 3-year period (solid lines), with 95% CIs (dashed lines) according to treatment. B, Freedom from adverse clinical outcomes according to treatment group. The graph shows the estimated probability of freedom from aortic dissection, aortic root surgery, and death (solid lines) with 95% CI (dashed lines). A total of 543 participants completed the 3-year follow-up visit.

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tically significant reduction in the rate of aortic root dilation with losartan treatment.[13]

The US Pediatric Heart Network trial, the largest of the losartan trials,[10] enrolled 608 patients with Marfan syndrome between the ages of 6 months and 25 years who met the Ghent diagnostic criteria for Marfan syndrome and had an aortic root enlargement with a *Z* score greater than 3.0. The 2 arms of the randomized trial were atenolol (started at 0.5 mg/kg/d and increased on the basis of hemodynamic response to a maximum of 4 mg/kg/ d) and losartan (started at 0.4 mg/kg/d and increased on the basis of hemodynamic response to a maximum of 1.4 mg/kg/d). The mean doses for young adults were 151 mg of atenolol per day and 85 mg of losartan per day. Echocardiography did not show any significant difference in the rate of aortic root growth between the groups. In this trial, the echocardiographic images were analyzed by 2 core laboratory readers with excellent interobserver agreement, and the mean interobserver difference ranged from 0.5 to 2.0 mm for the aortic measurements.[18] Similarly, a smaller randomized double-blind Spanish clinical study of 140 patients with the same design comparing losartan with atenolol showed no effect of losartan in limiting aortic dilatation.[15] Moreover, 128 patients from the Spanish study continued to receive the initial treatment assignment and were followed up for a mean (SD) duration of 6.7 (1.5) years in an open-label extension study; still, there was no difference in aortic dilatation rate or presence of clinical events between treatment groups.[19]

These trials did not fulfill the promise raised by the preclinical murine models. The favorable results from the COMPARE study raised the possibility that losartan as an add-on therapy to β-blockers could be beneficial, whereas the Pediatric Heart Network trial and the Spanish trial indicated that losartan did not perform better than atenolol. This question was addressed by the French Marfan Sartan study,[11] which randomized 299 patients already receiving standard therapy (with 86% receiving β-blocker at baseline) to losartan or placebo. This study showed that adding losartan had no effect in limiting aortic dilatation. The Ghent study enrolled 22 patients between 2009 and 2011, with 12 patients receiving β-blocker plus losartan and 10 patients receiving β-blocker plus placebo. There was no difference in aortic dilatation after 3 years' follow-up, and 2 of 12 losartan-treated patients stopped losartan therapy either because of aortic growth or pregnancy.[17] In contrast, a small open-label pilot study in 28 patients with Marfan syndrome reported a reduced rate of aortic dilation with losartan added to β-blockade therapy.[16] The Aortic Irbesartan Marfan Study (AIMS) randomized 192 patients with Marfan syndrome receiving standard medical therapy (56% taking a β-blocker) to either irbesartan or placebo, and results were reported in 2018.[14] The irbesartan group showed a statistically significant reduction of 0.22 mm in aortic dilatation, together with a significant reduction of approximately 12 mm Hg in systolic blood pressure. We have to await the final publication to determine whether the echocardiographic measurements of reduced aortic dimension measured in systole are mediated by the lower blood pressure in the irbesartan group; at minimum, aortic dimensions should be measured in diastole. Collectively, these 4 randomized controlled double-blind clinical studies[10,11,15,17] did not confirm a beneficial effect of angiotensin receptor blocker as had been suggested by the animal studies[6,8] and small nonrandomized clinical trials.[9,16] Another clinical study initiated in Italy is ongoing, and results have not been published.[37]

Although the Pediatric Heart Network trial found no difference in aortic root growth as the primary outcome (**Figure**, A), adverse clinical outcomes, defined as the 3-year rates of aortic root surgery, aortic dissection, death, and a composite of these events, were

reached in 10 of 268 atenolol-treated patients and in 19 of 267 losartan-treated patients. Although event rates were not statistically different ($P$ = .10), adverse events were almost 2-fold greater in the losartan-treated patients (Figure, B). In an analysis that combined the 2 treatment arms, adverse clinical outcome was significantly higher in adults and in participants with a baseline aortic root $z$ score of 4.5 or greater. The study was not powered to examine clinical end points of dissection, death, and aortic root surgery, in part because these events are rare in a pediatric and young adult cohort. However, this combined secondary outcome with a doubling of clinically relevant event rates raises an important point; future clinical studies cannot focus on aortic dilatation alone and must include clinically important outcomes such as dissection and aortic surgery. No signal of harm was seen in the Spanish study[19] or in the AIMS study. Therefore, the low frequency of events and nonsignificant $P$ value precludes definitive conclusions about the potential for harm with losartan treatment. A meta-analysis of all recent trials is required and may be able to shed light into this controversy.

The Pediatric Heart Network trial did not include a placebo group, because when the study protocol was developed, most of the trial subcommittee members concluded that a placebo arm would not be acceptable to many patients, families, study investigators, and primary cardiologists.[20] Therefore, without a placebo arm, the trial was not able to evaluate the efficacy of each of the therapies independently and only assessed the efficiency of atenolol therapy relative to losartan therapy. All other studies also lacked a true placebo arm, and patients were randomized to receive an angiotensin receptor blocker, usual care (which commonly included a β-blocker), or atenolol (Table).

There are reasons to be concerned about the potential of increased aortic events with losartan treatment. Both TGF-β and angiotensin II signaling drive vascular fibrosis, and angiotensin type I receptor blockers and angiotensin-converting enzyme inhibitors have antifibrotic effects.[21] Angiotensin II blockade with enalapril maleate was recently reported to slow the progression of cardiac fibrosis in patients with Duchenne and Becker muscular dystrophy.[22,23] Although reducing cardiac or renal fibrosis might improve the function of these organs, it could be disadvantageous for the aorta, where tensile strength is required to withstand the force of pulsatile blood flow. Fibrosis of the medial and adventitial layers of the aorta is commonly observed in early stages of aneurysmal thoracic aortic disease; most likely, this thickening of the medial layer and increased fibrosis is a physiologic response to increased wall stress and potentially protective to prevent dissection or rupture. Hence, blocking aortic fibrosis driven by TGF-β or AT1R signaling may not be the correct pharmacologic target, especially in the absence of β-blocker treatment, as was done in the US Pediatric Heart Network trial. The concern about blocking TGF-β or AT1R signaling in thoracic aortic disease is supported by multiple observations. First, mutations in genes that encode proteins in the TGF-β canonical signaling pathway that lead to decreased TGF-β signaling cause heritable thoracic disease.[24] It is counterintuitive to further block TGF-β signaling in these individuals to prevent aortic disease. Second, blocking TGF-β signaling in the Marfan syndrome mouse model through knockout of the TGF-β type II receptor or knockdown of TGF-β2 has been shown to increase aneurysm formation.[25,26] In fact, TGF-β inhibition using the same neutralizing antibodies increased dissection deaths in an alternative Marfan syndrome mouse model, which progresses to dissection and treatment with losartan delays but does not prevent dissection deaths.[27] Third, blocking TGF-β signaling while infusing angiotensin II, a method to induce aortic aneurysm formation in mice, increases the penetrance and severity of aneurysms and deaths due to aortic rupture.[28] Finally, loss-of-function mutations of lysyl oxidase, an enzyme-mediating collagen crosslinking and mechanical stability of extracellular matrix and fibrosis, has been associated with thoracic aortic aneurysms and dissections, indicating that proper collagen and elastin crosslinking is important in maintaining the structural integrity of the aorta.[29,30] Thus, blocking TGF-β signaling or preventing proper collagen maturation disrupts the integrity of the thoracic aorta.

## Conclusions

To summarize, initial studies found that the β-blocker propranolol prevented dissection deaths in the β-aminopropionitrile–fed turkeys. Studies of a Marfan syndrome mouse model that rarely dissects found that blocking either TGF-β signaling or treatment with losartan blocked aneurysm formation. At the same time, similar studies in another Marfan syndrome mouse model that progresses to dissection found blocking TGF-β signaling early increased dissection deaths and losartan delayed but did not prevent dissection deaths. It is important to remember that aneurysms are typically asymptomatic whereas dissections can cause sudden death in up to 50% of individuals in whom they occur.[31] Therefore, there is no benefit in blocking aneurysm formation if the risk for dissection is not decreased. Although the secondary outcome of dissection, death, and aortic repair in the US Pediatric Heart Network trial was not statistically significant between Losartan and β-blocker, and the the study was not powered sufficiently to assess for this secondary outcome despite being the largest clinical trial of Marfan Syndrome, we raise our concern regarding use of losartan over β-blockers as a first-line therapy for thoracic aortic disease until further data are available. For now, we propose the use of β-blockers as a first-line therapy in patients with Marfan syndrome, and losartan only if β-blockers are not tolerated. However, we acknowledge that the evidence for β-blocker preventing aortic dissections in Marfan syndrome is limited to 1 small clinical trial of 70 patients randomly assigned to propranolol or no treatment for an mean duration of 10.7 years.[3] Accordingly, a 2017 Cochrane review concluded that based on 1 low-quality randomized clinical trial, no definitive conclusion for clinical practice can be drawn.[32] Similarly, a 2007 meta-analysis of 6 studies that enrolled a total of 802 patients with Marfan syndrome found no difference between β-blocker therapy and no treatment with regard to clinical outcomes of mortality and morbidity.[33]

Finally, it is important to remember that the management of hypertension remains a central target for all physicians caring for patients with thoracic aortic disease. Hypertension often develops later in life and is associated with thoracic aortic disease. An elegant study by Kim et al[34] examined 4654 nonsyndromic adults with moderately dilated ascending aorta and found that hypertension was the strongest risk factor for dissection, with a hazard ratio of 2.76. A study of 50 patients with Marfan syndrome showed that the absence of a family history of Marfan syndrome and a higher body mass index were independent predictors of adverse out-

come, defined as an aortic root diameter of 55 mm requiring surgical intervention or aortic dissection.[35] In that study, smoking, hyperlipidemia, and the presence of 2 or more cardiovascular risk factors were associated with risk, but not independently after controlling for family history and body mass index.[35] Thus, hypertension, increased body mass index, and other factors that increase biomechanical forces on the thoracic aorta promote the progression to dissection in patients with thoracic aortic aneurysms. It is reasonable to use β-blockers as a first-line therapy for thoracic aortic disease with the addition of losartan or other angiotensin receptor blockers only if a second drug is needed for blood pressure control. There is evidence that drugs that lower blood pressure by decreasing smooth muscle cell contraction (eg, hydralazine, calcium channel blockers) should not be considered the first line of therapy.[2,36] Taken together, the evidence for β-blocker to reduce morbidity and mortality in Marfan syndrome is limited to a single small prospective randomized trial, and we urgently need larger well-powered clinical studies to access clinical outcomes beyond aortic dilation to address optimal medical therapy for Marfan syndrome and other aortopathies.

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