

# Is Losartan the True Panacea for Aneurysm Disease? CON

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## KEYWORDS

- Aortic aneurysm • Angiotensin
- Angiotensin receptor blocker • Medical therapy

## INCIDENCE, PREVALENCE, PATHOGENESIS, AND CLINICAL COURSE OF THORACIC AORTIC ANEURYSM

An aortic aneurysm is defined as a localized dilatation of the aorta, 50% more than the normal diameter, and it includes all 3 layers of the vessel (intima, media, adventitia).<sup>1</sup> Aortic aneurysms are the thirteenth leading cause of death in Western countries.<sup>2</sup> Thoracic aortic aneurysms (TAA) are less common than abdominal aortic aneurysms (AAA). The incidence of TAA is estimated to be between 4.5 and 5.9 per 100,000 person-years.<sup>3,4</sup> Overall, 5-year survival with TAA has been reported to be 64%,<sup>4</sup> with some studies reporting much lower rates.<sup>3</sup> This rate is significantly less than the survival with AAA (75%–80% over 8 years).<sup>5</sup> Risk factors include male gender, age, cigarette smoking, hypertension, chronic obstructive lung disease, and coronary artery disease.<sup>6,7</sup> Atherosclerotic disease, although associated with AAA, is not a well-established risk factor for TAA.<sup>8</sup> Genetic predisposition is another etiologic factor, and has a higher impact in TAA than in AAA. Approximately 20% of TAAs are attributed to a genetic syndrome.<sup>4</sup> The most common of these is Marfan syndrome (MFS), a connective tissue disorder affecting about 1 in 5000 persons.<sup>9</sup> Ehlers-Danlos syndrome type IV preferentially causes dilatation of the thoracic aorta.<sup>4</sup> Loeys-Dietz syndrome and the familial TAA and dissection

syndrome are caused by mutations in growth factor receptors, which predispose patients to TAA.<sup>10,11</sup> The common congenital anomaly, bicuspid aortic valve, which affects 2% of the population, has also been associated with TAA. Much less common are certain inflammatory and infectious causes such as Takayasu arteritis, giant cell arteritis (temporal arteritis), and syphilis.

The pathogenesis of TAA is not well understood; however, it seems that aortic aneurysm is a chronic-inflammatory state of a focal portion of the aorta. All of these causes and risk factors exert their effects through localized-inflammatory changes culminating in cystic medial necrosis (degradation of extracellular matrix) and the apoptosis of vascular smooth muscle cells (VSMCs). Cystic medial necrosis is a nonspecific degenerative condition, which provides the anatomic background for dissection.<sup>12</sup> Numerous pathways have been proposed that can lead to these changes. One proposed mechanism is the development of reactive oxygen species (ROS) in response to the inflammatory state. ROS in turn can cause an imbalance between matrix metalloproteinases (MMPs) and their inhibitor proteins: tissue inhibitors of matrix metalloproteinases. MMPs (especially MMP2 and MMP9) are responsible for the degradation of extracellular matrix in aortic aneurysms.<sup>13</sup> The role of NADH/NADPH oxidase has also been shown in the development of ROS and its effect in the development of

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TAA.<sup>14</sup> Elevated levels of transforming growth factor (TGF)- $\beta$  have been found in certain aneurysmal segments, notably in MFS and other inherited diseases.<sup>15</sup> Two more possible pathways have been shown to participate in aneurysm formation: osteoprotegerin seems to be associated with VSMC proliferation and apoptosis in AAA, and its levels are associated with aneurysm size.<sup>16</sup> Satoh and colleagues<sup>17</sup> recently identified cyclophilin A as a key factor in the inflammatory response to angiotensin II through ROS in the development of aortic aneurysms.

The major cause of mortality from aortic aneurysms is dissection and rupture. The incidence of rupture increases with expanding aneurysm size.<sup>4,18</sup> The overall incidence of aortic dissection is 2.9 to 3.5 per 100,000 per year.<sup>19,20</sup> The rate of growth of aneurysm diameter is between 0.1 cm/y and 0.4 cm/y.<sup>5,21</sup> In the ascending aorta the complication rate steeply increases to about 30% once the diameter reaches 6 cm; in the descending aorta this increase occurs at 7 cm.<sup>22</sup>

## PRINCIPLES AND GOALS OF THERAPY

The recommendation of therapy depends on the location and size of the aneurysm, its cause, and the patient's comorbidities. For aneurysms that are at high risk for rupture, surgical repair is recommended. Historically the risk of surgery has been associated with 5% to 10% surgical mortality for elective cases and at least 20% mortality for emergency procedures.<sup>23</sup> The consensus is that when the 1-year mortality risk from complications of aneurysm surpasses the surgical mortality risk, surgery is recommended. Medical therapy has traditionally been targeted to reduce the growth rate of aneurysm and delay surgery. The reduction of shear stress on the aneurysm along with the reduction of heart rate and blood pressure has been the one approach that has been shown to accomplish this.<sup>24</sup> More recently, the authors have gained better insight into the mechanisms of pathophysiologic changes that occur within aortic aneurysms. This has opened the door to possible therapies that would not only slow the expansion of aneurysm but also possibly affect the underlying disease process, from certain causes at least.<sup>15,16</sup>

### *Surgical Therapy*

Open surgical repair became available in the early 1950s. Since then, the emphasis has been to determine the diameter that requires surgery.<sup>25</sup> Current recommendations are to perform surgical repair on an ascending TAA at 5.5 cm diameter (5.0 cm in case of patients with MFS) and 6.5 cm

for descending TAA (6.0 cm for patients with MFS), or if the rate of growth is more than 1 cm per year. Other indications for surgery are aortic insufficiency and surgical emergencies from aneurysm complications.<sup>26</sup> In 2005 the Food and Drug Administration approved the Gore TAG thoracic endoprosthesis (W.L. Gore and Associates Inc, Flagstaff, AZ, USA), which opened the possibility for thoracic endovascular repair, with the aim of reducing perioperative mortality and spinal cord ischemia<sup>27</sup> as well as hospital length of stay. Major problems are graft endoleak and dealing with branch vessels of the aorta. Current recommendations for endovascular repair are for infrarenal aorta and descending TAA without abdominal extension.<sup>28</sup> New approaches have been investigated for treating aortic aneurysms in which branch vessels are involved.<sup>29</sup>

### *Medical Therapy*

#### ***$\beta$ -BLOCKERS, TETRACYCLINES, AND MACROLIDES; STATINS; ANGIOTENSIN-CONVERTING ENZYME INHIBITORS; OTHER AGENTS***

The mainstay of medical therapy in patients with aortic aneurysm has been  $\beta$ -blocking drugs.<sup>24</sup>  $\beta$ -Blockers have been shown to reduce the rate of thoracic aortic dilatation, especially in patients with MFS.<sup>30</sup> For AAA the results are more controversial, with animal studies and retrospective data reports suggesting benefit, and prospective trials showing no significant benefit.<sup>31-33</sup> These trials also showed a significant negative effect on the quality of life among patients taking  $\beta$ -blockers and a high discontinuation rate.

Doxycycline can stop or slow elastin degradation and can decrease MMP levels in the aortic wall; it can also slow aneurysm development in animal models and in a small series of human subjects.<sup>34-36</sup> Roxithromycin, a macrolide, has also been shown to inhibit the rate of expansion of AAA.<sup>37</sup>

Statins reduce the progression of atherosclerosis through their lipid-lowering effects as well as through their so-called pleiotropic (eg, inflammatory and immunology response modulating) effects, and are one of the mainstays of therapy in cardiovascular diseases. Statins also reduce oxidative stress via the NADP/NADPH oxidase system.<sup>14,38</sup> Reduction of expansion rate of aneurysm by statins has been reported in AAA<sup>39</sup> but not in TAA.

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to stimulate and inhibit MMPs, as well as to stimulate and inhibit the degradation of extracellular matrix in aortic

aneurysms.<sup>40,41</sup> TGF- $\beta$  neutralizing antibodies have shown their efficacy by delaying or avoiding the development of TAA in MFS.<sup>15</sup>

Other agents that act on specifically proposed pathogenetic mechanisms have been tested in animal models of AAA, but not TAA; these include c-jun-N-terminal kinase inhibitor, glucocorticoids, leukocyte-depleting antibody (anti-CD18), and indomethacin. Lifestyle modifications, such as smoking cessation and other cardiovascular risk factor reduction, are also very important.

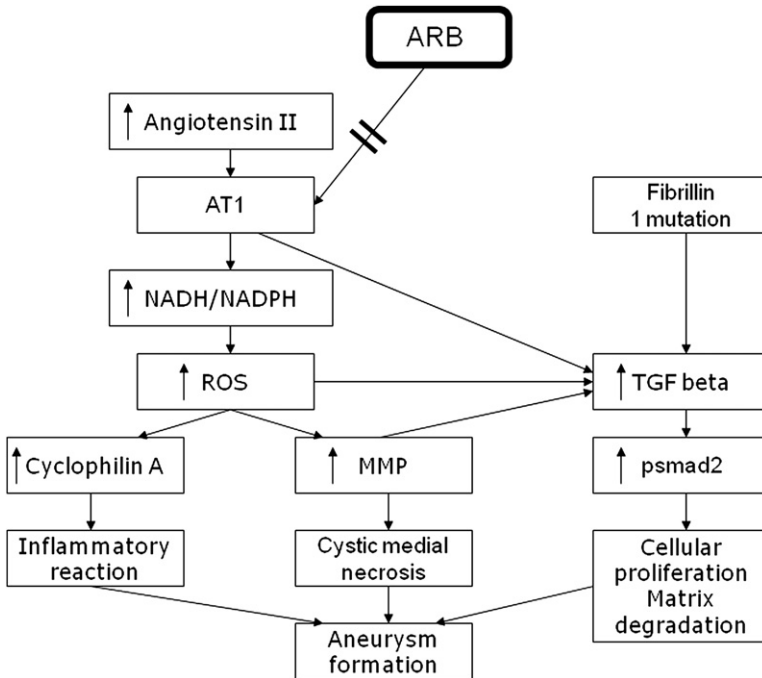
### **Angiotensin II receptor blockers in the treatment of TAA**

**Biology of angiotensin and mechanisms of action** Angiotensin was discovered in the 1930s. An oligopeptide, it is a component of the renin-angiotensin system and increases aldosterone levels. Angiotensin is derived from its precursor, angiotensinogen, which is produced in the liver. Angiotensinogen levels are increased by corticosteroids, estrogen, thyroid hormone, and angiotensin II itself. Angiotensin occurs in 4 forms. Angiotensin I, formed by the action of renin on angiotensinogen, is a precursor of angiotensin II and appears to have no biologic effect. In addition to increasing blood pressure, angiotensin II promotes vascular hypertrophy, cell proliferation, production of extracellular matrix, activation of macrophages, and activation of NADH/NADPH oxidase of VSMCs. Angiotensin II is derived from angiotensin I via angiotensin-converting enzyme (ACE), mainly in the lung capillaries. Angiotensin II is degraded to angiotensin III and IV; both have some pressor and aldosterone-producing activities. There are 4 angiotensin (AT) receptors. AT1 mediates vasoconstriction, aldosterone production, vasopressin secretion, cardiac hypertrophy, VSMC proliferation, renin inhibition, and extracellular matrix formation. AT2 modulates cell growth (inhibition), fetal tissue development, extracellular matrix, apoptosis, and cellular differentiation. Although AT2-receptor density is highest in fetal tissue and decreases significantly after birth, enhanced expression has been reported in adults in the settings of atherosclerosis, hypertension,<sup>42</sup> and MFS.<sup>43</sup> AT2 has been shown to mediate VSMC apoptosis in tissue culture experiments with cells obtained from patients with MFS.<sup>43</sup> AT3 and AT4 are as yet poorly characterized subtypes.

ACEIs were first discovered in 1975. ACEIs not only inhibit the RAS pathway but also inhibit the breakdown of bradykinin and in turn activate nitric oxide synthetase. There are alternative pathways of angiotensin II production; through serine proteases, such as kallikrein, cathepsin, and chymase,

which are not blocked by ACEIs. Angiotensin II receptor blockers (ARBs) block angiotensin's effect on the AT1 receptor. ARBs have a 1000- to 20,000-fold affinity for AT1 versus AT2. In MFS, a mutation occurs in the gene encoding fibrillin-1 (Fbn1), a component of the extracellular matrix microfibril,<sup>44</sup> which in turn leads to various Marfanoid manifestations including TAA. In mouse models low levels of Fbn1 produces an MFS-like syndrome. Fbn1 not only has important structural function but also regulates TGF- $\beta$ . TGF- $\beta$  has been associated with thickening of the aortic wall and the fragmentation and disarray of elastic fibers.<sup>15</sup> TGF- $\beta$  influences cellular proliferation, differentiation, and survival of different cell types. ARBs are known to inhibit the effects of TGF- $\beta$ . Angiotensin II has also been shown to activate the NADH/NADPH oxidative system in VSMC cultures<sup>45</sup> that produce ROS and induce oxidative stress. Angiotensin II plays a role in aneurysm development possibly by activating MMPs and cyclophilin A (**Fig. 1**).

**Preclinical evidence** ARBs, and specifically losartan, have been studied for TGF- $\beta$  antagonizing effects in human and animal models of cardiomyopathy and renal insufficiency.<sup>46,47</sup> Ejiri and colleagues<sup>14</sup> demonstrated that ARBs suppressed the expression of NADH/NADPH oxidase in human thoracic aneurysmal segments and ACEI did not, suggesting an AT1-mediated pathway. Habashi and colleagues<sup>15</sup> found that in a mouse model of MFS losartan inhibited elastic-fiber fragmentation, but propranolol did not (**Table 1**). This group provided evidence that losartan achieved its effect through AT1 receptor blockade, mediated via downstream TGF- $\beta$  signaling inhibition. The effect of losartan was comparable to TGF- $\beta$  neutralizing antibody. Daugherty and colleagues<sup>48</sup> found that signaling through AT2 receptors antagonizes any effects of AT1. In theory this would mean that while AT1 blockade should produce a beneficial effect on TAAs, ACE blockade, which blocks AT1 as well as AT2 effects, should at least have a smaller effect or no effect at all. The effects of angiotensin II on aneurysm formation were observed in the apolipoprotein (Apo) E-deficient mouse model.<sup>49</sup> Nagashima and colleagues<sup>50</sup> found that  $\beta$ -aminopropionitrile monofumarate (BAPN)-induced aortic dissection is not prevented by ARBs, but by ACEIs. These findings suggested that instead of AT1 receptor participation, AT2 receptor expression is upregulated in organ culture of aortic aneurysm, and also indicate that ACEIs and not ARBs block VSMC apoptosis.<sup>43</sup> In the case of elastase-induced AAA in the rat model, Liao and colleagues<sup>51</sup> also found that ACE inhibition but



**Fig. 1.** Angiotensin II and ARB in aneurysm formation. Angiotensin promotes aneurysm formation through AT1 receptors. Increased angiotensin II causes an increase of ROS through the NADH/NADPH system, which in turn increases cyclophilin A and MMP levels. This promotes inflammatory reaction and subsequent cystic medial necrosis, leading to aneurysm formation. Fibrillin gene mutation causes elevated signaling of TGF- $\beta$ , resulting in cellular proliferation and matrix degradation probably through signaling via the psmad2 system. ARBs are believed to inhibit the above pathways via inhibition of the AT1 receptors.

not AT1 blockade suppressed aneurysm formation.

**Clinical evidence** To date there has been one retrospective study on 18 subjects with MFS who were followed for at least 1 year after ARB therapy initiation. The patients were followed for a median length of 26.1 months. The mean rate of aortic root

enlargement before ARB therapy was  $3.54 \pm 2.87$  cm/y and after ARB therapy,  $0.46 \pm 0.62$  cm/y.<sup>52</sup> Other clinical data pertain to AAA. Hackam and colleagues<sup>53</sup> analyzed a database in Ontario, Canada and found that use of ACEI but not the use of ARBs had a beneficial effect in preventing rupture of AAA (see **Table 1**). Another report from this dataset suggested that the

**Table 1**  
Preclinical and clinical studies of angiotensin receptor blockers in aortic aneurysms

First Author <sup>Ref</sup>	Model/Population	Subject Number	Findings
Habashi <sup>15</sup>	Mouse, Marfan	10	ARB prevented aneurysm formation
Daugherty <sup>49</sup>	Mouse, apoE deficient, AAA	15	AT1 blockade (losartan) prevented aneurysm formation, AT2 blockade promoted it
Nagashima <sup>50</sup>	Rat, $\beta$ -aminopropionitrile monofumarate-induced cystic medial degeneration and aortic dissection	15	ACEI but not ARB prevented cystic medial degeneration and aortic dissection
Liao <sup>51</sup>	Rat, elastase-induced, AAA	9	ACEIs but not ARB suppressed AAA formation
Brooke <sup>52</sup>	Human, Marfan (retrospective)	18	ARB significantly slowed aortic root dilatation
Hackam <sup>53</sup>	Human, AAA (retrospective)	15326	ACEIs were, but ARBs not protective against aortic aneurysm rupture

discontinuation of ACE inhibitor prior to admission had a deleterious effect on aneurysm rupture.<sup>54</sup>

**Potential benefits of ARB therapy in TAA** The use of ARB in TAA has the theoretical benefit of blood pressure lowering and subsequent shear force reduction. In animal models of MFS and ApoB deficiency, ARBs preferentially blocked extracellular-matrix degradation and VSMC apoptosis, and slowed or arrested aneurysm expansion and formation. This was thought to be achieved by blocking TGF- $\beta$  signaling by preferentially blocking AT1 receptors. Other potential benefits could be exerted through blocking the NADH/NADPH oxidase system and reducing ROS production.

**Potential risks of ARB therapy in TAA** Some of the preclinical studies of the effects of ARB on aortic aneurysms have produced conflicting results. Some animal models (elastase and BAPN) suggested that AT2 receptor signaling was more important in the development of aneurysms than AT1 receptor signaling. In these models ARBs did not produce any beneficial results, whereas ACEIs (dual AT1 and AT2 blockade) did. This result suggests that whereas ARBs could be beneficial in some cases of TAAs, in other cases they could have little or no effect.

There are also contraindications to ARB use in the general population (eg, pregnancy, allergy), and without more knowledge of ARB action in TAA from different causes, it is impossible to know if there are more specific contraindications in these patients. Also, it is impossible to know if any ARB effect would be sustained over a longer period of time or if their long-term effects are equal, worse, or better than  $\beta$ -blockers.

## SUMMARY

TAA is a significant health problem with potentially devastating consequences. More is known about the genetics and molecular genesis of the disease than ever before, and potential treatments are on the horizon. The results of AT1-receptor blocker treatments in MFS are exciting. However, only retrospective data from a small number of individuals with only one subtype of aneurysm is available. The underlying biochemical and molecular mechanisms of aneurysm formation are varied, and a full understanding of the different mechanisms that contribute to the different causes is needed. Although it is tempting to generalize, caution should be used. The tendency to extrapolate the scant available data should be avoided to prevent any harm that can be caused to patients. There are many unknowns, and the answers will come from ongoing or future

studies; but for now losartan (and ARBs in general) cannot be regarded as a panacea for all patients with thoracic aortic disease.

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