Medical Therapy of Thoracic Aortic Aneurysms
Are We There Yet?

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An aneurysm is defined as a localized dilatation of a vessel of >50% of the normal diameter and includes all layers of the given vessel. Aortic aneurysms are divided into thoracic aortic aneurysms (TAAs), thoracoabdominal aortic aneurysms (a thoracic aneurysm extending into the abdomen), and abdominal aortic aneurysms (AAAs). Abdominal aortic aneurysms are reportedly more common than TAAs. Demographic studies have suggested that among people ≥65 years of age, the prevalence of AAA is ~2.5%. Occurring at a rate of 4.5 to 5.9 per 100 000 person-years, TAAs are less common. Aortic aneurysms (TAA and AAA together) remain the 13th leading cause of mortality in Western countries and are probably responsible for 15 000 to 30 000 deaths per year in the United States. TAAs are classified into 4 general anatomic categories: ascending aortic aneurysms (60%), aortic arch aneurysms (10%), descending aortic aneurysms (40%), and thoracoabdominal aneurysms (10%). It is important to understand the development, pathogenesis, and clinical course of aortic aneurysms and to develop strategies that reduce its occurrence, progression, and mortality. This review summarizes our present understanding of the available medical therapies for aortic aneurysms and attempts to determine whether medical therapy for TAA is currently a viable option. We focus on TAAs whenever possible; however, it should be mentioned that the available literature for TAA is limited, and most of the preclinical data are obtained from AAA animal models. Therefore, we use AAA data with the caveat that it is unclear that extrapolating from AAA data to TAA is limited, and most of the preclinical data are obtained from AAA animal models. Although animal models of TAAs have been described and studied intensively, it is unclear how relevant they are to the basic and clinical pathology in humans because they involve either a genetic defect that has not been described in humans or the surgical creation of thoracic aneurysms, respectively.

Origin
Aortic aneurysm is an area of medial degeneration of a focal portion of the aorta that may or may not be accompanied by inflammation. Extensive extracellular matrix degradation leads to localized weakening and dilatation of the aortic wall. In most cases, destruction of the elastic tissue of the media is found on histology. Several potential mechanisms have been proposed that lead to the final pathway of tunica media destruction.

Etiologic factors include genetic disease or mutations such as Marfan syndrome in which mutations in the gene encoding fibrillin-1 (FBN1) have been described. More than 800 FBN1 mutations that are associated with Marfan syndrome have been identified. Most mutations occur within repeated epidermal growth factor–like domains and lead to enhanced proteolytic degradation and malfunction of fibrillin-1. Marfan syndrome affects about 1 in 5000 humans. Aortic dissections and aneurysms have also been reported in people with other FBN1 sequence variations without exhibiting other Marfan properties. Other genetic diseases include Ehlers-Danlos syndrome, familial aortic dissection, and Loeys-Dietz syndrome. Ehlers-Danlos syndrome can be classified into 11 types and results in skin hyperelasticity. Type IV Ehlers-Danlos patients are at greater risk of aortic rupture owing to a defective synthesis of type III collagen; normal aorta is rich in type III collagen. The prevalence of Ehlers-Danlos syndrome is also ~1 in 5000. Familial aortic dissection results in aneurysm and dissection of the aorta at a young age. Loeys-Dietz syndrome was recently identified in patients with mutations in the transforming growth factor-β receptors 1 and 2. This disease is phenotypically similar to Marfan syndrome, and patients also develop TAAs and dissections at an early age.

The common congenital anomaly of bicuspid aortic valve, which affects 2% of the population, has been associated with TAA. From family studies, it is estimated that ~20% of TAAs are due to genetic diseases. The common method of inheritance seems to be autosomal dominant. In AAAs, the genetic predisposition is reported to be between 12% and 19%.

Among other risk factors, smoking has the strongest association with both TAA and AAA, with a relative risk of 5 for the presence of AAA. Current smoking by itself is estimated to be responsible for 0.4-mm/y additional growth rate of aortic aneurysms. Dyslipidemia and hypertension are less powerful risk factors, considered to be associated mainly with the occurrence of AAA, although newer data suggest that hypertension may actually be more closely associated with TAA, and is certainly a risk factor for dissection. Men...
are more often affected than women. Advanced age, hypertension, chronic obstructive lung disease, and coronary artery disease are also associated risk factors for both TAA and AAA, although it should be noted that not all studies identify hypertension and coronary artery disease as risk factors for AAA. They are not only risk factors for the presence of aneurysm, but also dominant determinants of aneurysm growth and rupture. Uncommon causes include bacterial endocarditis or infection of a laminar clot (from Staphylococcus aureus and S. epidermidis, Salmonella, and Streptococcus species), as well as syphilis, Takayasu arteritis, and giant-cell arteritis (temporal arteritis). Dissection is also considered a risk factor for thoracic aneurysm, and patients who undergo thoracic dissection repair are at some risk of forming aneurysms in other segments of their thoracic aorta. However, it is unclear whether dissection is a true risk factor or dissection was the first manifestation of the aneurysmal disease. Diabetes mellitus may be associated more closely with AAA than with TAA, although several other studies actually suggest an inverse association between diabetes and AAA (ie, patients with diabetes mellitus are less likely to develop AAA).2

Pathophysiology
All of the above causes and risk factors exert their effects through localized inflammatory changes, culminating in degradation of extracellular matrix and apoptosis of vascular smooth muscle cells, which used to be described as cystic medial necrosis but is now more accurately called medial degeneration of the aortic wall. Medial degeneration is a nonspecific degenerative condition that provides the anatomic background for dissection. The precise pathogenesis that leads to these changes is not fully understood. One mechanism that has been proposed is the development of reactive oxygen species that activate matrix metalloproteinases (MMPs), thereby causing an imbalance between MMPs and their inhibitors (tissue inhibitors of metalloproteinases). Found to be important in the pathogenesis of both TAA and AAAs, MMPs are a family of zinc endopeptidases that are responsible for the degradation of the extracellular matrix in aortic aneurysms. Matrix metalloproteinase-2 is produced in mesenchymal cells; MMP-9 is produced in macrophages. These are required elements of aneurysm formation.

Ejiri et al demonstrated the role of NADH/NADPH oxidase in the development of reactive oxygen species and its effect in the development of TAA. Angiotensin II has also been implicated in the development of aortic aneurysms through its NADH/NADPH activation in vascular smooth muscle cells. Transforming growth factor-β has been seen in elevated levels in certain aneurysmal segments, notably in Marfan syndrome and other inherited diseases. Transforming growth factor-β has been associated with thickening of the aortic wall and the fragmentation and disarray of elastic fibers. In a recent study, Moran et al demonstrated the role of osteoprotegerin in the growth of AAAs. Osteoprotegerin is a member of the tumor necrosis factor receptor family, Osteoprotegerin plays a role in vascular disease; its serum level increases in atherosclerosis, and it is associated with AAA size. Recombinant human osteoprotegerin inhibits vascular smooth muscle cell proliferation and induces apoptosis. Satoh et al recently identified cyclophilin A as a key factor in the development of aortic aneurysms via the inflammatory response to angiotensin II through reactive oxygen species. It is possible that all of the above-described pathways are part of a common inflammatory cascade.

Finally, the mitogen-activated protein kinase/extracellular signal-regulated kinase cascade has also been implicated in aneurysm formation. This signal transduction pathway is very complex, involves a large number of proteins, and serves to couple intracellular responses to the binding of growth factor to cell surfaces. Inhibition of this pathway with statin and extracellular signal-regulated kinase inhibitors has been shown to reduce AAA formation in experimental models. An overview of potential cellular pathways leading to aortic aneurysm is depicted in the Figure.

Biomarkers and Genetic Markers
Thoracic aortic aneurysm is a virulent, potentially lethal, but predominantly silent disease. There are significant challenges in diagnosing and following the growth of aneurysms.
Recent understanding of the pathophysiology of aneurysmal disease led to the search for potential biomarkers for both the presence and growth of aneurysms. Indicators of ongoing thrombosis, inflammatory markers, MMPs, markers of collagen turnover, genetic markers, and other potential markers have been evaluated, but the promise of biomarkers has not been realized.

As has been noted, a significant portion of TAA disease is genetic (Marfan syndrome, Loeys-Dietz syndrome, familial TAA and dissection syndrome, Ehlers-Danlos syndrome type IV). Mutations have been described in the FBN1 gene, transforming growth factor-β receptor gene type 1 and 2 (TGFBR1 and 2), and smooth muscle–specific isoforms of β-myosin and α-actin genes (MYH11 and ACTA2). Recent data have improved our understanding of the role of genetic factors in altered smooth muscle cell contraction and the pathogenesis of TAAs. The genetic predisposition for AAA is multifactorial, and recent genome-wide association studies have shown associations between AAA and loci on chromosomes 9p21.3 and 9q33.3. Genetic testing is available for family members of TAA patients, but routine screening is not yet advisable because of cost and practicality; hundreds of mutations in these genes have been associated with TAA, and the usefulness of genetic testing has not been proven.

**Clinical Course**

The major cause of mortality from aortic aneurysm is dissection and rupture. Most aneurysms are clinically silent. If symptoms are present, they can include heart failure, chest pain, myocardial ischemia, back pain, and flank pain. Compression of branch vessels can produce ischemia in the corresponding territories. According to the law of Laplace, as the size of the aneurysm increases, the wall tension rises, even though the relationship is potentially altered by the fact that there often is compensatory aortic thickening through remodeling, which may reduce the tension. There is a rising incidence of dissection and rupture with expanding aneurysm size. Studies show that the overall incidence of aortic dissection in the general population is 2.9 to 3.5 per 100,000 person-years. The growth rate of aneurysms is estimated to be between 0.1 and 0.4 cm/y, making accurate measurements of change and clinical trials challenging. The rates of dissection and rupture of TAAs are also dependent on aneurysm site (ascending or descending aorta). In the ascending aorta, we see a steep increase in complication rates once the aneurysm exceeds 6 cm in diameter. Above that diameter, the rate of aortic dissection and rupture increases to >30% a year. In descending aortic aneurysms, this happens when the diameter reaches 7 cm. The 5-year survival from untreated TAAs has been reported to be between 19.2% and 64%, whereas 8-year survival in AAA has been reported to be 75% to 80%.

**Therapy**

The recommended therapy for aortic aneurysms is dependent on aneurysm-specific factors (size, location, rate of growth, origin) and patient-specific factors (risk factors, comorbidities, presence of complications from the aneurysm). Available therapies are open and endovascular surgeries, medical therapies, and lifestyle modification.

**Open and Endovascular Surgical Therapy**

Historically, surgical repair of aortic aneurysms was suggested after it was noted that most aneurysms rupture before they reach 10-cm diameter. Current recommendations are to repair an ascending TAA at 5.5-cm diameter (5.0 cm in case of Marfan patients) and a descending TAA at 6.0 cm if repaired with open surgical technique and 5.5 cm if repaired with endovascular technique (5.5 cm for Marfan patients) or if the rate of growth is >1 cm/y. Other indications are concurrent aortic insufficiency and surgical emergencies from aneurysm complications. These recommendations are based on the inherent risk of surgery being lower than the annual risk of aortic rupture for sizes larger than the above size criteria. Open surgical repair has a surgical mortality rate of 5% to 10% for elective TAA repair and up to twice as high for nonelective operations, with lowest values for ascending aneurysm repair and highest values for thoracoabdominal aneurysm repair. Recently, low-risk thoracic aortic surgery has been reported at specialized aortic centers. The risk of spinal cord ischemia causing paraplegia is 5% to 10% with open TAA repair in descending operations only.

Covered stent grafts have been available in the United States for endovascular aneurysm repair since 2005. Current recommendations are for infrarenal AAA repair and descending TAA repair in aneurysms that are without abdominal extension. The perioperative mortality and 30-day mortality have been reported to be lower than for open repair, but the durability of benefit has been questioned. A recent systematic review of open versus endovascular TAA repair seems to confirm the lower risk of death with endovascular repair, but those authors cautioned that the quality of the studies was not good.

A review of survival data on >11,000 Medicare patients with TAAs showed a reduced 30-day mortality but similar 5-year mortality between open and endovascular repair. Recently, hybrid procedural approaches have been reported in which open and endovascular procedures are used. From randomized trial data, there is no evidence for a midterm survival benefit when comparing medical and endovascular repair for either AAA (Endovascular Aneurysm Repair-2 [EVAR-2]) or TAAs (Investigation of Stent Grafts in Aortic Dissection [INSTEAD]) or when comparing open and endovascular repair for AAAs (Dutch Randomized Endovascular Aneurysm Management [DREAM]). The EVAR-2 and DREAM trials were done in patients with AAA and compared conservative therapy with endovascular repair and open repair with endovascular repair, respectively. The INSTEAD trial, which compared medical therapy with endovascular therapy in patients with aortic type B dissection, showed no benefit of endovascular therapy over medical therapy but was underpowered for the chosen end points and was criticized because of the long period of time allowed from the time of dissection to enrollment and the high crossover rate.

The more recently introduced fenestrated endografts also enable an endovascular approach to thoracoabdominal aortic aneurysms and complex aneurysms. However, there is little evidence of the long-term durability and efficacy of this approach.
Medical Therapy

Principles and Goals of Medical Therapy
The goals of medical therapy have traditionally been to reduce shear stress on the aneurysmal segment of the aorta by reducing blood pressure and contractility (dP/dt). Although there is little evidence that cardiovascular risk factor reduction influences outcome in aortic aneurysm to a great degree, it has traditionally been recommended that cardiovascular risk factor reduction takes place. More recently, numerous reports have been published of plausible therapies that aim to affect the underlying pathophysiological changes in aortic aneurysms, thus modifying the disease process as opposed to only trying to delay its complications.

Medical Therapy in Acute Aortic Dissection
In acute aortic dissection, appropriate and immediate therapy is essential with the aim of stabilizing the patient and improving the clinical outlook. The main goals of therapy are blood pressure control, decrease of shear stress, optimization of anticoagulation, volume management, and pain control. A detailed discussion is beyond the scope of this article but can be found in excellent published reviews.55,56

Medical Therapy of Chronic Aortic Aneurysm

β-Blockers
β-Blockers may be beneficial for reducing the rate of aortic dilatation. This is thought to be due to the effect of β-blockers in reducing left ventricular dP/dt and reducing shear stress. In addition, β-blockers reduce dP/dt in the aorta and might be beneficial via this mechanism and the resultant effect on shear stress in the aorta. Several animal studies and other retrospective clinical studies have also indicated a significant inhibitory effect of β-blockers on aneurysm growth rate.57,58 In a small study of 70 patients with Marfan syndrome, propranolol-treated patients had a 73% lower rate of aortic dilatation and lower mortality than placebo-treated patients.59 However, later prospective randomized trials of β-blockers in patients with AAA failed to show a significant effect,60 although there was a trend favoring propranolol.61 These trials found a low compliance rate with propranolol (a 42% discontinuation rate in 1 trial) and a significant negative effect of propranolol on quality of life. At this time, no studies of β-blockers in patients with thoracic aortic disease (other than Marfan patients62) have been published.

Tetracyclines/Macrolides
Doxycycline is a nonspecific MMP inhibitor.63 This antibiotic has been used in conditions with MMP overexpression (eg, periodontal disease, rheumatoid arthritis).64 In animal models, doxycycline slowed elastin degradation and aneurysm development.65 In a small series of human subjects, doxycycline decreased MMP-9 levels66 and slowed the rate of progression of AAA in humans.67 The macrolide roxithromycin has also been shown to inhibit the rate of expansion of AAA in humans, possibly through a similar mechanism.68

Statins
Statins treatment is one of the cornerstone therapies in cardiovascular diseases. Statins reduce the progression of atherosclerosis and improve clinical outcomes. In addition to their lipoprotein-reducing properties, statins have a number of effects called pleiotropic effects. For instance, they reduce oxidative stress by blocking the effects of reactive oxygen species on aneurysms. This effect is independent of their lipid-lowering properties. Statins achieve these results through suppressing the NADH/NADPH oxidase system.23 These effects have been shown in both AAA and TAA specimens. Aneurysm expansion rate has also been shown to be reduced in AAA patients on statins in observational studies,69 but the largest study to date failed to show an association between statin prescription and AAA growth rate.70 At this time, no studies of statins in patients with thoracic aortic disease have been published.

Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers
Angiotensin II has been shown to have a number of biological effects on the cardiovascular system. It promotes vascular hypertrophy, cell proliferation, production of extracellular matrix, and activation of macrophages, and it activates NADH/NADPH oxidase of vascular smooth muscle cells. Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to both stimulate and inhibit MMPs and the degradation of extracellular matrix in aortic aneurysms.71 Losartan, an angiotensin I receptor blocker (ARB), seems to exert its beneficial effect through blocking transforming growth factor-β, thereby reducing matrix degradation in a Marfan syndrome mouse model.25 In Marfan and apolipoprotein E–deficient mice (in which angiotensin II is infused to induce aneurysm), ARB (losartan) prevents aneurysm formation and ACEIs do not.25 However, in other animal models of aneurysm (eg, elastase, β-aminopropionitrile monofumarate models), ACEIs prevent aortic dissection and ARB does not.72 In 1 small human study, ARB has been shown to slow the rate of progression of TAA in Marfan syndrome.73 However, Hackam et al44 found in their case-control study that ACEIs were protective but ARBs were not protective against AAA rupture, but in that study there was no dose-response effect for ACEIs and little adjustment for potential confounders. A recent report of an observational prospective study of AAA patients showed an increased growth rate of AAA diameter from 2.77 to 3.33 mm/y in patients on ACEIs.75 In a recent randomized trial, perindopril was shown to reduce the growth rate of thoracic aortic aneurysms in patients with Marfan syndrome.76 The ongoing Study of the Efficacy of Losartan on Aortic Dilatation in Patients With Marfan Syndrome (MARFANSARTAN) seeks to address the efficacy of losartan in Marfan syndrome.77 It appears that the discrepant results of ARB and ACEI efficacy in retarding aneurysm growth rate might stem from the differences among models and point toward multiple different biological pathways of aortic aneurysm development. An overview of studies reporting results of medical therapy of aortic aneurysm can be found in the Table.

Other Agents
New agents in animal studies that attempted to delay AAA development have targeted oxidative stress, proteolysis, and inflammation.78 The clinical efficacy of these approaches in TAA has yet to be tested. Transforming growth factor-β–
neutralizing antibodies have been used in animal research and have shown efficacy in delaying or avoiding the development of TAA in Marfan syndrome.25 Transforming growth factor-β antagonism therefore might represent a strategy for at least some forms of aortic aneurysm. Unfortunately, transforming growth factor-β–neutralizing antibody treatment in humans is not yet practical. In another study, a c-Jun-N-terminal kinase inhibitor was used to induce regression of AAA in mice.79 Glucocorticoid, leukocyte-depleting antibody (anti-CD 18), and indomethacin also have been used,80 and early studies with chymase inhibitors81 and aspirin82 have also shown promising results. Lifestyle modifications such as smoking cessation are also very important. Tobacco use is associated with a marked increase in general morbidity and mortality and with a 5-fold relative risk increase for the presence of AAA.83 Pregnancy is not recommended in patients with Marfan syndrome, especially if the aortic root is >4 cm.

**Conclusions**

Aortic aneurysm is still an incompletely known entity that affects a significant proportion of the population. Multiple new pathophysiological pathways have been proposed recently; however, the exact mechanisms that can induce aneurysm formation remain unclear. Surgical repair has relatively high risk because of the usually complex nature of the procedure; therefore, surgical therapy is generally reserved until the risk of rupture exceeds that of the surgery. Recent series have documented substantially increased safety of thoracic surgery, approaching the safety of traditional cardiac procedures such as coronary artery bypass graft surgery and valve replacement. Endovascular repair is a new possibility that confers less early risk to carefully selected patients, but midterm results call into question the durability of endovascular repairs of degenerative aneurysms.

To improve patient safety and outcome, it is imperative to find treatments that delay or even stop the progression of aneurysm disease. The ideal treatment would of course be one that reverses aneurysm formation. Multiple medications have been tried that are known to act on 1 or more of the proposed pathophysiological pathways of aortic aneurysm development. Only 2 randomized prospective trials have been carried out so far, both in patients with Marfan syndrome. Both trials were relatively small, and only 1 study had clinical end points. Some treatment options (eg, ACEI, ARB, β-blockers) have shown conflicting results, most likely because of the multiple causes of aneurysm formation. However, as our understanding of the disease improves, it is conceivable that we will have better medical therapies to slow the progression of thoracic aortic disease. To do so, we must be willing to randomize patients in clinical trials, and we must also consider relevant clinical end points rather than focusing solely on aneurysm expansion. Recently, the heterogeneity of the aorta itself has been raised as a plausible reason for the difference in aneurysm pathology and clinical course.6 Although it seems reasonable to treat patients with aneurysms the same way that any other patients are treated in terms of cardiovascular risk factors and prevention, the starting of medications solely to prevent aortic aneurysm expansion is
endorsed by the most recent guidelines as a reasonable option, even though an argument can be made that we should wait until we have a more thorough understanding of the etiologic diversity of aneurysm formation and of the risks and benefits of each treatment.31

Disclosures

None.

References


**Key Words:** aneurysm, aorta, aortic aneurysm, abdominal, drug therapy, aorta, thoracic, aortic aneurysm, thoracic
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Circulation. 2011;124:1469-1476
doi: 10.1161/CIRCULATIONAHA.110.006486
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/13/1469

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