Abdominal aortic aneurysm (AAA) is a common condition of increasing prevalence, particularly among older men. Aneurysm-related mortality is responsible for approximately 15,000 deaths in 2010 in the USA. Although there are approximately 55,000 patients who undergo AAA repairs annually, the overall incidence of AAA is probably estimated to be higher. AAA occurs in 4–9% of the population over the age of 65 years according to the screening studies, and affects approximately 1.7 million individuals in the USA. Many groups have researched the pathophysiology of AAA with the intent to discover an effective medical treatment through a biological or molecular approach. Matrix metalloproteinase (MMP) is a key proteinase mechanism in the development and growth of AAA. Effective medical treatment for AAA has not been established yet; however, it would be beneficial to avoid the invasive interventions and it would be expected to reduce the medical cost. We reviewed the current treatment options and potential medical treatment for AAA.

Etiology and Pathogenesis of AAA
AAA is hypothesized to be caused by multifunctional degenerative processes, including extracellular matrix remodeling, vascular smooth muscle cell apoptosis/necrosis, oxidative stress and infiltration of inflammatory cells. Genetic disorder, inflammation, infection and connective tissue disease are also causal underlying factors of destructive degeneration of the aortic wall. While the precise etiology of AAA hasn’t been fully understood yet, it is certain that the progression of atherosclerosis involves destructive remodeling of the aortic wall. Elastin is one of the key structural proteins of extracellular matrix in the aortic wall and maintains the integrity of the wall. Numerous studies suggest that proteolytic degradation of elastin in the medial layer leads to weakening and dilatation of the aortic wall while collagen degradation accounts for the rupture of the aneurysm. The elastin and collagen degradation in the aneurysm wall is contributed by the matrix metalloproteinase (MMP) family such as collagenase-I (MMP-1), stromelysin-1 (MMP-3), the 72-kDa gelatinase (MMP-2) and the 92-kDa gelatinase (MMP-9), macrophage elastase (MMP-12) and collagenase-3 (MMP-13). MMPs are structurally related metalloendopeptidases that can degrade the extracellular matrix and play important roles in normal tissue development and remodeling. Abnormal expression of MMPs is associated with various pathological processes such as osteoarthritis, rheumatoid arthritis, tumor invasion and metastasis, pulmonary emphysema and atherosclerosis. Regulation of MMP activities has been attempted (to prevent the tissue degradation) by controlling them at different levels of the activation processes. The tissue inhibitor of metalloproteinases (TIMPs) are physiological inhibitors of MMP activity. Several studies suggested that atheroma tissue has an imbalance between MMPs and TIMPs. The MMP-2, MMP-9, and MMP-12 have been shown to be related to human aneurysm with their activity against elastin. MMP-9 has been proven to be the most abundant elastolytic proteinase. It is expressed by infiltrating macrophages.
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Table 1. Current Status of Potential Medical Treatments for AAA in the Format of the ACC/AHA Practice Guidelines

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect on AAA growth</th>
<th>Level of Evidence</th>
<th>Class of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>No inhibition</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Inhibition</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Inhibition</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Statins</td>
<td>Inhibition</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>No inhibition</td>
<td>B and C</td>
<td>IIb</td>
</tr>
<tr>
<td>AR blockers</td>
<td>Animal data</td>
<td>C</td>
<td>IIb</td>
</tr>
</tbody>
</table>

AAA, abdominal aortic aneurysm; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; AR, angiotensin-receptor.

Table 2. SVS Guideline Recommendation in the Medical Management of AAA During the Surveillance Period

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Quality of Evidence</th>
<th>Level of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Angiotensin blockers</td>
<td>Low</td>
<td>Weak</td>
</tr>
</tbody>
</table>

SVS, Society for Vascular Surgery. Other abbreviations as in Table 1.

Medical Treatments for AAA

The current available treatments of AAA, which is either open surgical repair or endovascular aneurysm repair, are based upon a mechanical concept. If the medical treatment can delay or even arrest the growth of AAA, it would prevent those invasive procedures and could reduce patients’ stress and cut the medical cost. In addition, several reports suggest that patients with small AAA under surveillance have impaired quality of life. Effective medical treatment for these patients with small AAA might potentially become a beneficial option by improving their quality of life.

A promising potential molecular target of pharmacological treatment for AAA is MMPs. Many studies suggested the inhibition of MMP would be a feasible means to suppress the progression of aneurysmal degeneration. Other potential medical treatments include anti-hypertensives, statins, and antibiotics, some of which might work as MMP inhibitors. Tables 1 and 2 show the current recommendations associated with the medical treatments for AAA, which have been categorized in the format of the ACC/AHA and SVS practice guidelines.

Beta-Blockers

Propranolol might affect the growth of an aneurysm by lowering blood pressure and its biochemical effects on matrix proteins. Several animal studies have indicated that propranolol reduces the growth of an aneurysm and rupture risk. There are several clinical trials that were focused on the effects of...
propranolol for aneurysm expansion. Leach et al and Gadowski et al have retrospectively investigated patients with AAA and showed that β-blockers might be associated with a decreased AAA growth rate. In contrast, Lindholt et al performed a prospective randomized double-blinded trial of patients with AAA comparing propranolol and a placebo and showed only minor inhibition of the expansion of AAA. The Propranolol Aneurysm Trial Investigators in Canada performed a prospective randomized control trial and also demonstrated no significant difference between the 2 groups in the growth rate of AAA. In addition, they showed a significant negative effect in quality of life that was assessed by using SF-36. These 2 prospective studies also indicated a high drop-out rate due to low compliance and adverse events including life-threatening diseases. The 2005 ACC/AHA guidelines rate this as a Class IIb (level of evidence B) recommendation. As an aside, the perioperative administration of β-blockers is rated as a Class I (Level of Evidence A) recommendation in the sense of reducing the risk of adverse cardiac morbidities.

Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors) and Angiotensin Receptor Blockers (ARB)

A number of animal experiments reported the relationship between angiotensin II (Ang II) and aneurysm development and the preventive effect of ACE inhibitors. ACE inhibitors have found to both stimulate and inhibit MMPs depending on cell types and animal models. Hackam et al reported a large population-based case-control study showing a preventive association between ACE inhibitors and rupture in patients with abdominal aortic aneurysms. They analyzed linked administrative databases from Ontario, Canada and compared ruptured AAAs with non-ruptured AAAs from 1992 to 2002. Patients who were administered an ACE inhibitor before admission were significantly less likely to present with ruptured aneurysms (odds ratio 0.82, CI 0.74–0.90). In contrast, several cohort studies suggested that there were no association between ACE inhibitors and growth of AAA. Transforming growth factor-β (TGF-β) plays an important role in the pathogenesis of Marfan syndrome. Losartan, an ARB and also TGF-β antagonist suppressed the progressive matrix degradation in the mouse model of Marfan syndrome. There are several cohort clinical trials that associate ARB with AAA growth; these results were also inconsistent.

Because one of the causes of these dissociated conclusions about studies of ACE inhibitors and ARBs is due to difficulty to exclude confounding bias, further randomized control studies are necessary. Clinical trials of losartan in adult patients with Marfan syndrome have shown a striking effect of it in reducing aortic root growth. Another randomized controlled trial that is designed to compare the effects of perindopril and amlopidine on small AAA growth has started recruitment in the UK.

Statin

Statin is a widely used gold standard therapy, not only in terms of lipid lowering but also for preventing the progression of atherosclerosis and reducing the risk of adverse events in patients with cardiovascular diseases. It has pleiotropic effects such as anti-inflammatory activities and has the ability to stabilize plaque as well as to control serum lipid levels. Several studies have suggested that high total serum cholesterol is one of the risk factors of AAA. A number of studies suggest the influence of statins on AAA expansion. Steinmetz et al showed that in an experimental AAA mice model after infusion of elastase, simvastatin reduced the diameter of the aorta and AAA, and suppressed the expression of MMP-9 and preserved the medial elastin and smooth muscle cells in the aortic wall. In a study involving humans, Evans et al measured MMP-9 levels in the AAA wall, which were excited from patients who underwent elective aortic surgery, and showed a 40% reduction in MMP-9 levels in patients who randomly did or did not receive preoperative simvastatin administration. There are several cohort studies with respect to the relationship between growth of AAA and statin use. Schlosser et al performed measurements of the abdominal aortic diameter in 230 observational patients with an initial AAA diameter between 30 and 55 mm, and demonstrated that statins are associated with significantly lower AAA growth rates. Other cohort studies showed the reducing growth rate of AAA. In contrast, Ferguson et al demonstrated no association between statin prescription and AAA expansion. Several meta-analyses have obtained inconsistent results. Although statins are expected to be one of the promising drugs for the medical treatment of AAA, further studies are still needed to establish the evidence of their beneficial effects. However, because statins have been indicated for most of the patients with cardiovascular diseases, it could be difficult to perform a large-scale, randomized controlled study to assess the association between statins and growth of AAA.

Macrolides

Infection is regarded as the one of the causal components of AAA, hence, certain types of antibiotics are reported as potential medical therapy for AAA. Several studies have reported that Chlamydia pneumoniae (C. pneumoniae) has been associated with the atherosclerotic lesions of arteries and with abdominal aortic aneurysms by immunocytochemistry, polymerase chain reaction (PCR) and electron microscopy. Lindholt et al investigated the antibodies against C. pneumoniae in blood samples that were taken from patients with an AAA before surgery. The results showed that a high proportion of men with an AAA had antibodies to C. pneumoniae, and that expansion of the AAA was significantly correlated with the positive antibodies to C. pneumoniae. Vammen et al performed a randomized clinical trial in which 43 patients who were administered with roxithromycin once daily for 28 days were compared with 49 patients who were administered with a placebo. The expansion rate of AAA was significantly reduced in the intervention group compared with the placebo group (1.56 mm and 2.75 mm per year, respectively, P=0.02). Hogh et al performed a randomized clinical trial with roxithromycin and the results showed that roxithromycin treatment significantly reduced aneurysm growth (P=0.014). In another macrolide study, Karlsson et al performed a larger randomized clinical trial using azithromycin and showed no beneficial effect of it on AAA expansion. These discrepant studies did not clarify the pharmacological mechanism in respect to the development of AAA, and therefore further investigation is required.

Tetracycline (Doxycycline)

Tetracycline (Doxycycline) is well-known for its use as an antibiotic, but it is also indicated for the treatment of periodontal disease as an inhibitor of matrix metalloproteinases (MMP). There are numerous reports with respect to the suppressive effects on MMP by tetracycline. Petrinec et al showed that treatment with doxycycline inhibits the development of AAA in the experimental elastase-induced rodent model of AAA, and suggested that tetracycline might have a selective inhibitive mechanism of elastolytic MMP expression in infiltrating inflammatory cells rather than having antibiotic effects. Their
Medical Treatment for Abdominal Aortic Aneurysm

effects were obtained using even lower circulating doxycycline levels. A number of studies have reported the inhibitory effect on MMPs with doxycycline in human samples as well. Baxter et al performed a phase II study of the prolonged administration of doxycycline in patients with small aneurysms and achieved the results that included a high rate of compliance, minor side effects and a reduction of plasma MMP-9.

Table 3. Doxycycline Clinical Trial (N-TA^2CT)

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients 55 years of age or older.</td>
</tr>
<tr>
<td>2. Infrarenal abdominal aortic aneurysm with a diameter larger than 35 mm and no greater than 50 mm in men, and larger than 35 mm and no greater than 45 mm in women.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Renal artery involvement or suprarenal extension of the aneurysm.</td>
</tr>
<tr>
<td>3. Iliac artery occlusive disease.</td>
</tr>
<tr>
<td>4. Known genetic syndrome (e.g., Marfan Syndrome, Ehlers-Danlos Syndrome).</td>
</tr>
<tr>
<td>5. Stage II hypertension.</td>
</tr>
<tr>
<td>6. Creatinine &gt;2.0 g/dl or creatinine clearance &lt;30 ml/min.</td>
</tr>
<tr>
<td>7. Allergy or intolerance of tetracyclines.</td>
</tr>
<tr>
<td>8. Use of tetracyclines within the past 6 months.</td>
</tr>
<tr>
<td>10. Current or planned treatment with chemotherapy or radiation therapy.</td>
</tr>
<tr>
<td>11. Current or planned treatment with systemic immunosuppressive agents.</td>
</tr>
<tr>
<td>12. Chronic infection managed with long-term antibiotics.</td>
</tr>
<tr>
<td>13. Prognosis of survival less than 2 years.</td>
</tr>
</tbody>
</table>

Figure 2. Study designs of the Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^2CT) are shown. The study aims to enroll 248 patients with a small aneurysm and randomly assign them into a doxycycline group and a placebo control group.

The group also demonstrated that both doxycycline and several chemically modified tetracyclines dose-dependently inhibit the development of AAA in the rat model of elastase-induced AAA. In another experimental AAA model, Prall et al demonstrated that doxycycline inhibits aortic growth in the AAA murine model, which was induced by the application of CaCl₂ in the periadventitial abdominal aorta; similar inhibitory effects were obtained using even lower circulating doxycycline levels.
levels. Circulation J. Vol.77, December 2013

Curci et al. reported that they randomized patients before AAA surgery into 2 groups: treatment with doxycycline or a control 7 days prior to the surgery and investigated the expression of MMPs in the aneurysmal wall. They concluded that the expression of MMP-9 mRNA was significantly reduced in the patients who were treated with doxycycline.

Doxycycline might have diverse effects on AAA. Abdul-Hussien et al. performed a clinical trial in which 60 patients scheduled for elective open aneurysm repair were randomly assigned to receive 50, 100 or 300 mg doxycycline per day or a placebo, and showed a significantly reduced expression of MMP-3 and MMP-25 and an increasing level of protease inhibitor. Cystatin C and TIMP-1 (tissue inhibitor of metalloproteinase 1), as well as a reduced expression of MMP-8 and MMP-9 in the aortic tissue. In addition, doxycycline also suppressed the neutrophil content of the aortic wall. Furthermore, their group demonstrated that doxycycline suppressed cytotoxic T-cell content, interleukin (IL)-6, IL-8, IL-13 and granulocyte colony-stimulating factor protein levels, as well as the upstream regulators of these interleukins such as AP-1 and C/EBPα in the major inflammatory pathways. Neutrophils might have an important role in AAA progression as a main source of MMP. Therefore, doxycycline might have potentially multiple beneficial effects on the growth of AAAs.

There was one clinical prospective randomized controlled trial involving doxycycline that studied the growth of an abdominal aortic aneurysm. Mosorin et al. performed the trial in which 32 patients with small AAAs were randomly assigned to receive either doxycycline or a placebo and showed that the growth rate of AAAs in the doxycycline group was significantly lower than that in the placebo group during the 6–12 month and 12–18 month period. However, the randomization was imbalanced with more smokers in the placebo group.

In addition, doxycycline might potentially become an adjunct treatment to improve the long-term clinical success rate after endovascular aneurysm repair (EVAR). Several authors have reported that aortic neck dilatation after EVAR can occur and cause type 1 endoleak because of device migration. Therefore, we should monitor this tendency of neck dilatation. Moreover, the persistent shrinkage of the aneurysmal sac is one of the most important indicators of clinical success after EVAR. Hackmann et al. performed the clinical randomized controlled trial using doxycycline after EVAR. In the results, plasma MMP-9 decreased significantly in the doxycycline group compared with the placebo group at 6 months, and doxycycline significantly reduced the aortic neck dilatation at 6 months and decreased the maximum aneurysmal diameter compared with the placebo among endoleak-free patients. Although this trial has several limitations (it was small in size and had a short follow up), these results suggest the potential beneficial effects on EVAR and provided an alternative clue, other than a mechanical approach, to resolve the specific problem of EVAR such as durability, migration or endoleak. If doxycycline can reduce the maximum aneurysmal diameter compared with the placebo group, these results suggest the potential beneficial effects on EVAR and provided an alternative clue, other than a mechanical approach, to resolve the specific problem of EVAR such as durability, migration or endoleak. If doxycycline can reduce the maximum aneurysmal diameter compared with the placebo group, these results suggest the potential beneficial effects on EVAR.

**Conclusions**

We reviewed the pathophysiology of AAA, the current concept of medical treatment for AAA, and the clinical trial structure of the ongoing N-TA3CT for small AAA. The conclusion of this trial will provide valuable insight into the potential medical treatment for AAA.

**Disclosures**

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**Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA3CT)**

Since the first clinical trial of doxycycline was small and might contain confounding factors, the evidence level is still Level B according to ACC/AHA clinical practice guidelines. Therefore, a larger randomized controlled trial of doxycycline for AAA (ie, Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial, N-TA3CT) has started in July 2012 in multiple centers in the USA. The overall objective of this trial is to investigate doxycycline treatment (100 mg p.o. twice a day) in patients with a small aneurysm (3.5–5.0 cm in men, and 3.5–4.5 cm in women). The primary hypothesis is 40% slowing of the aneurysm growth by CT imaging. Many secondary aims are directed at studying biomarkers, and other morphologic endpoints. The inclusion and exclusion criteria for this trial are shown in Table 3. The study is planning to enroll 124 patients in each arm (Figure 2). The successful enrollment and analysis of this randomized, prospective, double-blind trial will provide clear evidence for whether doxycycline is an effective treatment for AAA. While a 40% reduction in growth is a modest clinical effect, mechanistic proof of an effective medical therapy for AAA might lead to renewed interest in the pharmacologic development of stronger and more specific metalloproteinase inhibitors.
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