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Medical Management of Small Abdominal Aortic Aneurysms

B. Timothy Baxter, MD; Michael C. Terrin, MD, MPH; Ronald L. Dalman, MD

Abstract—Abdominal aortic aneurysm is a common condition that may be lethal when it is unrecognized. Current guidelines suggest repair as the aneurysm diameter reaches 5.0 to 5.5 cm. Most aortic aneurysms are detected incidentally when imaging is done for other purposes or through screening programs. Ninety percent of these aneurysms are below the threshold for intervention at the time of detection. A number of studies have sought to determine factors that lead to progression of aneurysmal disease that might be amenable to intervention during this period of observation. We review these studies and make recommendations for the medical management of small abdominal aortic aneurysms. On the basis of our current knowledge of the causes of aneurysm, a number of approaches have been proposed to prevent progression of aneurysmal disease. These include hemodynamic management, inhibition of inflammation, and protease inhibition. The American College of Cardiology/American Heart Association clinical practice guidelines rules of evidence have helped to define strength of evidence to support these approaches. Level A evidence (from large randomized trials) is available to indicate that observation of small aneurysms in men is safe up to a size of 5.5 cm and that propranolol does not inhibit aneurysm expansion. Level B evidence (from small randomized trials) suggests that roxithromycin or doxycycline will decrease the rate of aneurysm expansion. A number of studies agree that tobacco use is associated with an increased rate of aneurysm expansion. Level B and C evidence is available to suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may inhibit aneurysm expansion. There are animal data but no human data demonstrating that angiotensin-converting enzyme inhibitors or losartan, an angiotensin receptor blocker, will decrease the rate of AAA expansion. A pharmacological agent without important side effects that inhibited aneurysm expansion could change current approaches to aneurysm treatment. Additional studies are needed to clarify the potential role of doxycycline, roxithromycin, and statin therapy in the progression of aneurysmal disease. (*Circulation*. 2008;117:1883-1889.)

Key Words: aneurysm ■ aorta ■ pharmacology ■ antibiotics ■ tetracycline

Aneurysmal degeneration of the abdominal aortic and iliac arteries (referred to as abdominal aortic aneurysm, or AAA) is a common and frequently lethal age-related disease process. The prevalences of unsuspected, asymptomatic AAA in men and women over the age of 60 years are 4% to 8% and 0.5% to 1.5%, respectively.¹⁻⁷ Advanced age, history of cigarette smoking, male gender, and family history have been the most frequently recognized AAA risk factors in prior screening studies.^{8,9} Of these, smoking is the most important.^{10,11} In a recent cohort study of >100 000 health maintenance organization participants, after a median 13-year follow-up, additional factors associated with subsequent AAA development include treated and untreated hypertension, high total serum cholesterol, known coronary artery disease, and intermittent claudication.¹² Black race and Asian race are inversely associated with AAA risk in men.^{2,12}

Ruptured AAA and complications after surgical treatment are responsible for at least 15 000 deaths per year in the United States, but some estimate the actual rate may be as

high as 30 000 deaths per year, a mortality rate that approaches those associated with prostate and breast cancer.⁷ Open surgical repair for larger aneurysms is effective in preventing rupture but is morbid; newer endovascular exclusion strategies are less morbid but may require additional interventions and do not always prevent aneurysm rupture.^{13,14} Most investigators agree that AAA disease, in its initial stage, is an inflammatory condition associated with benign dilation. At some point, typically when the aneurysm enlarges beyond 5 cm, progressive degenerative changes predominate, which leads, in some cases, to mechanical failure. Although research involving genetically deficient mice has identified key proteins involved in experimental aneurysm formation, a detailed pathophysiological understanding of human disease is still incomplete. Major clinical challenges in AAA disease include the absence of diagnostic biomarkers and effective nonsurgical therapies to prevent progression of early-stage disease. Biomarkers indicative of progression or efficient imaging indices to monitor metabolic

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activity will be important in guiding suppressive medical therapies for small aneurysms.

The abdominal aorta between the renal arteries and the iliac bifurcation is the most common extracranial site of aneurysm formation. Although aneurysms are generally defined by a 50% increase in native vessel diameter, aortic diameter increases with age even in the absence of overt disease.^{15,16} Consequently, some controversy exists as to when a large infrarenal aorta becomes an AAA. Some investigators have used an absolute aortic diameter of 3 cm.^{2,4,17} This distinction has limitations, however, because it falls within the upper limits of the normal aortic diameter related to the body habitus and advancing age.¹⁶ Because of these limitations, others have used relative measures compared with nondiseased aortic segments or adjacent vertebral bodies. Relative aortic indices (eg, 1.5 or 2.0×) are, however, less useful in the setting of diffuse arteriomegaly or generalized aortic enlargement. An absolute diameter of 3.5 cm or greater represents a practical compromise, separating the large aorta with age-related changes that will not progress from frank aneurysmal disease.

Current Treatment Modalities

Mechanical intervention is currently the only treatment shown to be effective in preventing AAA rupture and aneurysm-related death; it is reserved for AAA ≥ 5.5 cm in diameter for men and ≥ 5.0 cm in women.^{18,19} Although smaller aneurysms do rupture, the likelihood of aneurysm-related death only exceeds treatment risks above these thresholds. This conclusion in men is based on data from 2 large-scale randomized clinical trials.^{18,19} These studies did not have a sufficient number of women to precisely identify the size threshold for repair. The threshold of 5 cm, used by most clinicians for women, is based on a higher rate of rupture of 5- to 5.5-cm aneurysms in women.^{18,20} In the United States, elective AAA repairs, generally performed for asymptomatic or medically stable patients, averaged 87.7 per 100 000 Medicare patients between 2000 and 2003.²¹ In the last decade, endovascular aneurysm repair has gained acceptance as an alternative to open surgical repair, with reduced periprocedural risks.^{13,14} Several Food and Drug Administration–approved commercial endovascular aneurysm repair devices are currently available and in use. A reflection of the impact of endovascular aneurysm repair strategies and devices is that perioperative (30 day) mortality for all elective AAA repairs declined from 5.0% to 3.7% ($P < 0.001$) between 2000 and 2003 with no change in outcome for open repairs alone. By 2003, endovascular repair accounted for 41% of elective AAA repairs.²¹

Although treatment outcomes have clearly improved for surgical patients in the endovascular aneurysm repair era, evidence from prospective screening studies on 3 continents suggests that a substantial window of opportunity exists for earlier intervention in AAA disease. After congressional passage of the Screening for Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Amendment in 2006, the Centers for Medicare and Medicaid Services in the United States added a screening AAA ultrasound examination to the Initial Preventative Physical Examination, or IPPE, for new pro-

gram enrollees as they turn 65 years of age. This benefit is extended to men between the ages of 65 and 75 years who have smoked at least 100 cigarettes in their lifetime and men and women in this age range with a family history of AAA disease. The IPPE must be completed within 6 months of Medicare eligibility. This benefit was justified on the basis of a review by the US Preventive Services Task Force that concluded that ultrasound screening may reduce AAA mortality by 43% in men aged 65 to 75 years.²² The potential utility of intervention in smaller (< 5.5 cm) AAAs was considered, but the risks of surgical repair greatly outweighed the potential benefit of reduced AAA rupture, even when the likelihood that widespread screening would identify thousands of new patients with smaller AAAs was taken into account.²² In the largest previous US screening study, 90% of AAAs identified were < 5.5 cm in diameter.⁸ In the next several years, increasing awareness of AAA disease driven by provider and patient education related to this new screening benefit could dramatically increase the pool of small AAA patients seeking treatment options for early-stage disease.

Measuring Aneurysm Progression

Traditionally, aneurysm diameter has been used as the principal surrogate marker for disease progression. For purposes of population-based disease screening studies and to determine the timing of surgical intervention, abdominal ultrasound imaging has proven accurate and reproducible.^{23,24} Although more is being learned about AAA biology and progression, aneurysm diameter remains the most important clinical determinant for risk of rupture.^{25,26} Interpretation of ultrasonic diameter data is frequently complicated by lengthening of and increased angulation from the axial plane during disease progression. This variability may be overcome in part in the course of serial examinations.²³ CT imaging protocols may be reproducible to within a millimeter when a standardized technique is used in their interpretation. The computerized reconstruction available with CT images provides accurate 3D images that allow for planning of operative repair, but the cost, risk, and inconvenience associated with CT imaging do not lend themselves to screening and surveillance applications.

Factors That Influence Aneurysm Progression

The most common method of AAA detection is an abdominal imaging study obtained for an unrelated problem. The mean growth rate for small AAAs (≤ 5.5 cm) is 2.6 to 3.2 mm per year, which increases with aneurysm diameter.^{17,19} Studies of AAA expansion and the factors associated with expansion have been limited by sample size or a limited number of serial observations. In the United Kingdom Small Aneurysm Trial (UK SAT), AAA expansion in 1743 patients followed up for up to 7 years was most strongly associated with diameter at baseline.²⁷ No association with growth rate was noted for age or gender. Self-reported cigarette smoking status was associated with an incrementally increased growth rate of 0.4 mm per year, which persisted after adjustment for potential confounding variables. Of other potential risk factors considered in the UK SAT, including hypertension, peripheral arterial occlusive disease, total or high-density lipoprotein

plasma cholesterol concentration, and diabetes mellitus, only the presence of peripheral arterial disease or diabetes influenced aneurysm growth, with peripheral arterial disease decreasing it by 0.2 mm per year for each 0.2 change in ankle brachial index (95% CI -0.03 to 0.25) and diabetes reducing the growth rate by 0.79 mm per year (95% CI 0.27 to 1.33 mm). On the basis of these data, investigators calculated that screening intervals of 36, 24, 12, and 3 months for patients with AAA diameters of 35, 40, 45, and 50 mm, respectively, yielded less than a 1% chance of the AAA unexpectedly exceeding 55 mm in diameter between examinations. In clinical practice, examination intervals vary but rarely exceed more than 12 months, with increasing frequency associated with progressive enlargement.²⁷ Part of the reason for the more frequent studies is reassurance for both the patient and physician. Quality-of-life surveys indicate that diagnosis without treatment of AAA can be associated with significant anxiety.²⁸

Although not considered in the analyses of most AAA trials, lifelong patterns of lower-extremity exercise may provide some protection from AAA. Computational flow-modeling studies of hemodynamic conditions in the distal aorta suggest that the decreased flow from prolonged sedentary existence may promote aneurysmal disease.²⁹ Indirect clinical evidence in support of this concept includes the fact that above-knee traumatic amputation³⁰ and chronic spinal cord injury²⁹ are associated with increased AAA risk independent of other risk factors, including cigarette smoking.

Tobacco

Tobacco smoking as a specific risk factor for AAA disease prevalence, incidence, and progression deserves special mention. The relative risk of AAA in individuals who have ever smoked is 2.5 times greater than the relative risk for coronary heart disease. AAA is more closely associated with cigarette smoking than any other tobacco-related disease except lung cancer.¹⁰ Nearly all AAA patients (>90%) relate a history of smoking; however, only about half of those continue to smoke at the time of diagnosis.¹¹ Several small studies have associated continued cigarette smoking with more rapid aneurysm expansion. Chang and associates⁹ found a significant correlation with continued smoking and aneurysm expansion. MacSweeney et al³¹ monitored 43 patients with small (median size <4.0 cm) AAAs to assess active smoking (serum cotinine levels), blood pressure, cholesterol, and triglycerides. Only active smoking was associated with a small but significant increase in growth rate. Lindholt³² evaluated and prospectively followed up 117 AAA patients; he found a positive correlation between continued smoking and the rate of expansion.³² In the UK SAT itself, smoking and initial aneurysm size were the only 2 factors positively associated with aneurysm growth, although that study did not find a dose response between self-reported smoking habits or serum cotinine levels and aneurysm growth rate.²⁷ Animal studies have confirmed accelerated aneurysm growth with smoking, although the mechanism for this effect does not appear to be related to a direct increase in matrix metalloproteinase (MMP)-9 levels.³³ When the studies are considered together, continued smoking appears to be associated with a

relatively small (15%) increase in growth rate that has important implications when compounded over several years. At the present time, smoking cessation should be considered one of the most certain approaches to decreasing the rate of aneurysm expansion.

Statins

Statin therapy reduces the progression of atherosclerosis and improves clinical outcomes in cardiovascular diseases. Although effective in reducing atherogenic lipoproteins, statins also demonstrate additional biological effects (ie, pleiotropic effects), including reduction of C-reactive protein levels, that may be relevant to the pathogenesis of AAA disease.³⁴ Several studies have found an association between the presence of AAA and total cholesterol.^{8,12} There is, however, no clear relationship between total cholesterol and AAA expansion rate.^{27,31,32} Despite the absence of a relationship between cholesterol and growth rate, there is evidence from a number of studies to suggest that statins may influence aneurysm growth rate, presumably via these pleiotropic effects. Simvastatin therapy at $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ reduces both aortic diameter and the percentage of mice with aneurysms after elastase infusion.³⁵ No changes in effect size were noted when these experiments were repeated in hypercholesterolemic apolipoprotein E-deficient mice.

MMP-9 expression is closely linked to aneurysm formation in animal models of AAA. In human AAA specimens explanted for organ culture, addition of cervistatin (0.001 to $0.1 \mu\text{m/L}$) significantly reduces tissue levels of both total and active MMP-9 in a concentration-dependent manner.³⁶ Cervistatin did not reduce the number of macrophages or neutrophils present in cultured aneurysms, which suggests that statin therapy inhibited inflammatory cell activation. In a prospective study by Evans et al,³⁷ patients were randomized to a 3-week preoperative course of simvastatin versus placebo before open aneurysm repair. MMP-9 levels in excised aneurysm tissue were decreased in the simvastatin group. In 1 observational study of 130 patients followed up for 2 years, no aneurysm expansion was observed in the 75 patients taking statins, whereas the mean aneurysm size in the group not taking statins increased from 4.5 to 5.3 cm.³⁸ Schouten et al³⁹ monitored 150 patients for a minimum of 12 months with at least 3 measurements. Aneurysm expansion rate was decreased in the patients who were taking statins (2.0 mm per year) compared with those not taking statins (3.6 mm per year).³⁹

Although these associative data are intriguing, there are many potential biases in these uncontrolled observational studies. They are reminiscent of similar analyses that suggested that β -blockers would inhibit aneurysm expansion, whereas randomized clinical trials showed propranolol to be ineffective. Because AAA, coronary artery disease, and peripheral vascular disease share common risk factors, such as tobacco use, there will be clear indications for statin use in many AAA patients related to coronary artery disease and peripheral vascular disease. The use of statins will become more common with efforts to meet the National Heart, Lung, and Blood Institute's increasingly stringent adult treatment protocol guidelines. A high prevalence of statin use among

AAA patients will make it challenging to design trials to assess the specific role of statin therapy as an inhibitor of aneurysm expansion. Such studies will be important, however, because some guidelines such as those for the Women's Health Initiative have made the leap to categorizing AAA as a peripheral vascular disease equivalent.⁴⁰ At the present time, there does not appear to be sufficient evidence to recommend that statin therapy be initiated for the diagnosis of AAA alone.

β -Blockers

Several animal studies have indicated that propranolol might have beneficial effects on aneurysmal disease on the basis of both its hemodynamic properties and its biochemical effects on matrix proteins.^{41,42} Two clinical studies used retrospective analysis to assess the impact of β -blockers in aneurysm growth rates.^{43,44} Both identified a significant inhibitory effect of β -blockers. These studies provided the underpinning for 2 multicenter randomized trials that tested propranolol in aneurysm patients. Propranolol did not inhibit aneurysm expansion in a trial reported by Lindholt et al.⁴⁵ These results were compromised by low compliance in the propranolol arm, because only 22% of patients continued the medication for 2 years. The mean growth rate was slightly (but not significantly) higher in the propranolol group. A Canadian trial that recruited 552 patients suffered similarly from compliance problems in that 42% of propranolol-treated participants discontinued the drug during the trial.⁴⁶ The growth rate in the placebo group and in the propranolol group did not differ, although there was a slight trend in favor of propranolol. Quality of life, assessed by the short-form 36-item (SF-36) questionnaire, showed that propranolol had a significant negative effect, as one would anticipate from the low compliance rate.⁴⁶

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors have been shown to both stimulate and inhibit MMPs depending on cell type or animal model.^{47,48} Losartan does not appear to have a direct effect on MMPs.⁴⁸ A number of animal experiments using different models of aneurysmal disease have suggested an important role for the angiotensin/renin axis in aneurysm development. Captopril but not losartan, an angiotensin receptor blocker, prevents aneurysm formation in the rat elastase model of AAA.⁴⁹ This model relies on infusion of elastase into the infrarenal aorta, which results in initial mechanical dilation followed by progressive enlargement. Another commonly studied aneurysm model is based on chronic infusion of angiotensin II into apolipoprotein E-deficient mice, which results initially in midaortic dilation and eventual rupture.⁵⁰ Losartan prevents aneurysm formation in this model. This effect of losartan is consistent with observations in genetically engineered mice with Marfan syndrome. Work done in these mice has suggested that the inability of mutated fibrillin to sequester transforming growth factor- β plays a role in the progression of tissue changes associated with Marfan syndrome.⁵¹ In a series of studies, transforming growth factor- β antagonism by losartan was

effective in preventing progressive matrix degradation.⁵² The reason for the discrepant effects of losartan—ineffective in the elastase aneurysm model and effective in the angiotensin and Marfan models—may relate to differences among the models. In the angiotensin infusion model, initial dissection of the upper abdominal aorta is followed by dilation. This process may have more similarities to the Marfan syndrome models, in which the thoracic aorta is affected. Clinical trials of losartan in Marfan syndrome have recently begun enrollment.⁵³

Hackam et al⁵⁴ recently published results of an analysis of a linked administrative database from Ontario, Canada analyzing ruptured (n=3379) and nonruptured (n=11 947) aortic aneurysms from 1992 to 2002. ACE inhibitor use within the prior 3 to 12 months was less frequent among those admitted for aneurysm rupture⁵³ (OR 0.82, CI 0.74 to 0.90). β -Blockers, lipid-lowering agents, and angiotensin receptor blockers showed no relationship to rupture. In a published response to that article, Lederle and Taylor⁵⁵ noted that among those patients who discontinued ACE inhibitors within the past 3 to 12 months, there was a harmful effect in favor of aneurysm rupture. The case-control study by Schouten et al and post hoc analysis of the UK aneurysm trial data did not find a relationship between ACE inhibitors and aneurysm expansion rates.^{27,39} Most patients presenting with aneurysm rupture have large, undetected aneurysms, whereas patients with known aneurysms typically undergo repair long before their rupture risk becomes significant. Thus, this information regarding ACE inhibitors and rupture risk might find its most practical application among the small number of patients deemed unfit for repair.

Macrolides

A number of antibiotics have been proposed as a treatment for AAA with varying rationales. One line of reasoning is that AAA progression is enhanced by secondary infection within the aortic wall. *Chlamydia pneumoniae* has been found in atherosclerotic plaque and the wall of AAAs.^{56,57} There was once great enthusiasm for the hypothesis that treatment of the secondary chlamydial infection could slow progression of atherosclerosis. This has been diminished by subsequent prospective randomized trials that showed no cardiovascular benefit of a year of a treatment with azithromycin in patients with stable coronary artery disease.⁵⁸ Similar negative results were found by Burkhardt et al.⁵⁹ A small study by Lindholt et al⁵⁷ suggested that serological evidence of a *C pneumoniae* infection was associated with an increased rate of aneurysm expansion. This led to a randomized clinical trial in which 43 patients received a 1-month course of roxithromycin, whereas 49 patients received placebo.⁶⁰ Patients in the treatment arm had an expansion rate at the end of the study of 1.56 mm per year compared with a rate of 2.75 mm per year in the placebo-treated group. The inhibition was greater in the first year than the second year. The study did not clarify the mechanism of effect because there was no correlation between *Chlamydia* titers and roxithromycin ability to inhibit aneurysm expansion.

Tetracyclines

The tetracycline antibiotics have been studied because of their known inhibition of MMPs. Petrinic et al⁶¹ were the first to demonstrate that doxycycline could suppress aortic wall MMP activity, elastin degradation, and aneurysm development in the elastase-induced rat model. They achieved similar results using nonantimicrobial (chemically modified) tetracyclines and nonselective hydroxamic acid derivatives as MMP inhibitors, which indicates that the aneurysm-suppressing effects of doxycycline are most likely related to its activity as an MMP inhibitor.⁶² Longo et al⁶³ characterized a second murine aneurysm model using calcium chloride applied to the abluminal surface to induce the aneurysm. In this model, doxycycline demonstrates the same dose-dependent inhibition of aneurysm expansion.⁶⁴ The plasma doxycycline levels achieved in these animal studies were in the same range as those seen in AAA patients receiving doxycycline (100 mg BID).⁶⁵ These murine studies suggest that inhibition can still be achieved at plasma levels in the 1- to 2- μ g/mL range.⁶⁴

A number of studies in patients have suggested that doxycycline can inhibit MMPs in aneurysm tissue. Curci et al⁶⁶ treated a series of patients with a 3-week course of doxycycline before open aneurysm repair. Tissue levels of MMP-9 were significantly reduced by doxycycline compared with untreated patients. Baxter et al⁶⁵ showed in a small series of 36 patients on a 6-month course of doxycycline that plasma MMP-9 levels decreased significantly compared with baseline levels. This work has been followed by a small, prospective, randomized trial of doxycycline in which 32 patients were randomized, with 17 receiving doxycycline (150 mg/d) for 3 months. Patients were followed up for 18 months.⁶⁷ *C pneumoniae* titers were assessed but found not to be affected by doxycycline treatment. The calculated growth rate at the end of the 18-month period of observation was 1.5 mm per year in the doxycycline-treated group versus 3.0 mm per year in the placebo-treated group. This difference did not achieve statistical significance, but the 6- and 12-month time periods did show a significant difference in favor of doxycycline treatment. Level B evidence (from small randomized trials) suggests that roxithromycin or doxycycline will decrease the rate of aneurysm expansion.

Considerations for Evaluating Medical Therapies

There are 3 important features of AAA that lend themselves to medical treatment: (1) Inexpensive and accurate methods for detection; (2) long period of surveillance before intervention; and (3) life expectancy of the affected population. Increased public awareness and the availability of screening will lead to increased aneurysm detection in the next decade. Ninety percent of aneurysms detected at screening are below the threshold for immediate repair, and aneurysm expansion is gradual. A reduction of the expansion rate of a 4.0-cm AAA by 50% potentially increases the time before surgical intervention is required to >10 years, which exceeds the life expectancy of many aneurysm patients. The current standard of care for these small AAAs is "watchful waiting." The provision of a relatively benign and efficacious medical therapy to these patients may reverse the diminished quality

Table. Results of Interventions on AAA Growth

Intervention	Reference(s)	Effect on AAA Growth	Level of Evidence	Class of Recommendation
Propranolol	46, 69	No inhibition	A	III
Macrolides	60	Inhibition	B	IIa
Tetracycline*	67	Inhibition	B	IIa
Statins	38, 39	Inhibition	B	IIb
ACE inhibitors	27, 39, 52, 53	No inhibition	B and C	IIb
AR blockers	48, 50	Animal data	C	IIb

*Inhibition at 6 and 12 months after 3 months of treatment.

of life associated with detection of a potentially life-threatening condition for which no immediate treatment is offered. In the format of the American College of Cardiology/American Heart Association clinical practice guidelines,⁶⁸ level A evidence (from large randomized trials) is available to indicate that observation of aneurysms in men is safe up to a size of 5.5 cm and that propranolol does not inhibit aneurysm expansion (Table).⁶⁹

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Disclosures

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