clinical practice

# Small Abdominal Aortic Aneurysms

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 68-year-old man with a 50-year history of smoking presented with amaurosis fugax and was found to have an incidental infrarenal aortic dilatation, with a maximal diameter of 3.2 cm. After five years of routine follow-up, the aortic diameter has increased to 4.8 cm. What is the appropriate follow-up for and management of this case?**

## the clinical problem

In the absence of symptoms related to an aneurysm, the threat that the aneurysm will rupture is the major consideration. Only 10 to 15 percent of patients survive the rupture of an abdominal aortic aneurysm; a minority reach the hospital alive, and of these, only about half survive the emergency surgical repair.[1] But overall, few patients with aneurysms die from a ruptured aneurysm; most (approximately 66 percent) will die from another cardiovascular cause.

Ultrasonographic screening studies show that about 5 percent of men older than 65 years of age have an occult small aneurysm (3 to 6 cm in diameter).[2] The risk of rupture of small aneurysms is low, but the natural history of an untreated aneurysm is one of continued expansion.[3] When the diameter of the aneurysm exceeds 5.5 cm, the risk of rupture increases markedly (Fig. 1), and all vascular surgeons would recommend repair of aneurysms larger than 6 cm, provided that the patient was fit for surgery.[4] Aneurysms this large (Fig. 2) account for less than 10 percent of aneurysms detected by screening.[5] What recommendations should be made for those with smaller aneurysms?

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### epidemiology

The prevalence of abdominal aortic aneurysms among men is about three times that among women, and women younger than 55 years of age rarely have such aneurysms. The age-related increase in the diameter of the infrarenal aorta in men (median diameter, 1.75 cm at 25 years of age and 2.25 cm at 55 years of age) is more marked than that in women.[6] After 55 years of age, the median diameter remains constant, but the distribution becomes skewed toward larger diameters: 6 percent of men have an aortic diameter of more than 2.9 cm by 65 years of age.[6] Thereafter, the prevalence of aneurysms (as indicated by an aortic diameter of 3 cm or larger) among men increases by about 6 percent per decade. Clinically relevant aneurysms (at least 4 cm in diameter) are found in about 1 percent of men 55 to 64 years of age, and the prevalence increases by 2 to 4 percent per decade thereafter.[6,7]

Smoking is the strongest independent risk factor[7]: 90 percent of patients with aneurysms have smoked. As compared with persons who have never smoked, the incidence of aneurysm is increased by a factor of six among those who have smoked for more than 40 years and by a factor of seven among those who have smoked more than 20 cigarettes per day.[8] After smoking cessation, the risk of development of an aneurysm declines each year by approximately 1/30 of the original risk.[8]

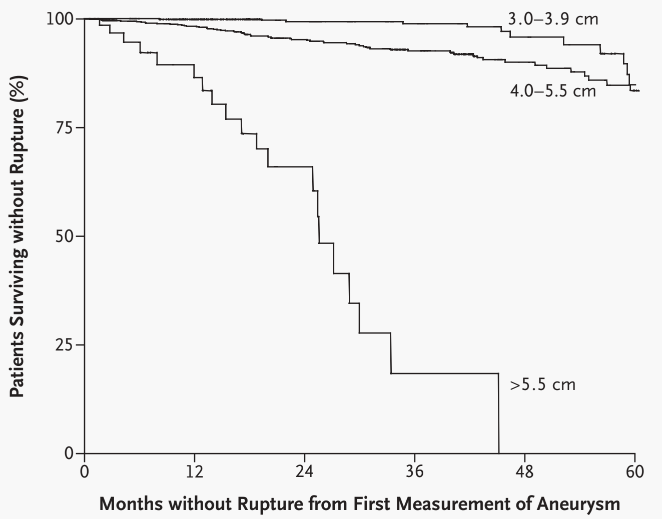


**Figure 1. Risk of Rupture of Aneurysm According to the First Measured Aortic Diameter.**

The analysis is based on information from 1792 men and 465 women with abdominal aortic aneurysms.

#### PATHOGENESIS

Atherosclerosis has been considered to be a cause of abdominal aortic aneurysms, since studies show a positive relation between aneurysm and other cardiovascular disease and related markers, ranging from a history of previous carotid or coronary artery disease to the measured ankle–brachial pressure index.[9,10] Selective screening for aneurysms in patients with intermittent claudication nearly doubles the yield of screening in the general population, whereas screening of cohorts of patients with hyperlipidemia or hypertension often does not.[11] Screening of siblings (older than 50 years of age) of patients with aneurysms revealed an occult aneurysm (3.3 to 6.5 cm) in 29 percent of brothers and 6 percent of sisters.[12]

Abdominal aortic aneurysm is a familial disorder, possibly genetic (polygenic) in origin.[13] Monogenic disorders associated with an increased risk of aortic aneurysm — including the fibrillin-1 defect (Marfan's syndrome) and abnormal type III procollagen (Ehlers–Danlos syndrome type IV) — are rare. Proteolysis and inflammation are the biologic mechanisms driving the expansion of aneurysms.[14] Evidence from studies in mice and humans indicates that metalloproteases have an important role in the formation of aneurysms, particularly the macrophage-associated enzyme MMP-9.[15] Currently, there is no strong evidence linking variation in protease or protease-inhibitor genes with the likelihood of the development of an aneurysm, but a debate has started over whether functional gene polymorphisms can predict the outcome.[16] Patients with an aortic aneurysm who had an interleukin-6 genotype associated with high plasma interleukin-6 concentrations had three-year overall mortality that was twice that among patients without this genotype.[17] The 4G/5G polymorphism in the plasminogen-activator inhibitor type 1 (*PAI-1*) gene promoter alters plasma PAI-1 levels and hence fibrinolysis. Patients with the *PAI-1* 5G5G genotype, which is associated with the lowest plasma PAI-1 levels in vivo, had lower operative mortality after elective aneurysm repair than patients with other *PAI-1* genotypes (0 percent vs. 8 percent).[18]

## STRATEGIES AND EVIDENCE

#### SURGICAL INTERVENTION

Two large randomized trials have addressed the issue of whether elective surgical repair of small abdominal aortic aneurysms saves lives. Patients with asymptomatic aneurysms (diameter, 4.0 to 5.5 cm) were randomly assigned to either early elective (open) surgery or a period of surveillance for rapid expansion and the development of symptoms, with a protocol recommending surgery when the diameter exceeded 5.5 cm. The United Kingdom Small Aneurysm Trial, in which ultrasonographic surveillance was used, showed that the cumulative 6-year survival rate was 64 percent in both treatment groups, the risk of aneurysm rupture was 1 percent per year, and the 30-day operative mortality among patients who underwent elective repair was 5.6 percent.[19,20] The Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study, in which surveillance was primarily conducted by computed tomography (CT), showed a six-year cumulative survival rate of 74 percent in each treatment group, rates of rupture of 0.6 percent per year, and operative mortality of 2.7 percent.[21] The absolute differences between the two trials probably relate to the different populations studied. The United Kingdom trial included a substantial proportion of women (17 percent). Patients in the ADAM study cohort were more fit, with better lung and renal function and more favorable lipid profiles.[22] Both studies demonstrated that elective surgery for small aneurysms does not improve six-year survival.

Longer-term follow-up, to 9 years, in patients in

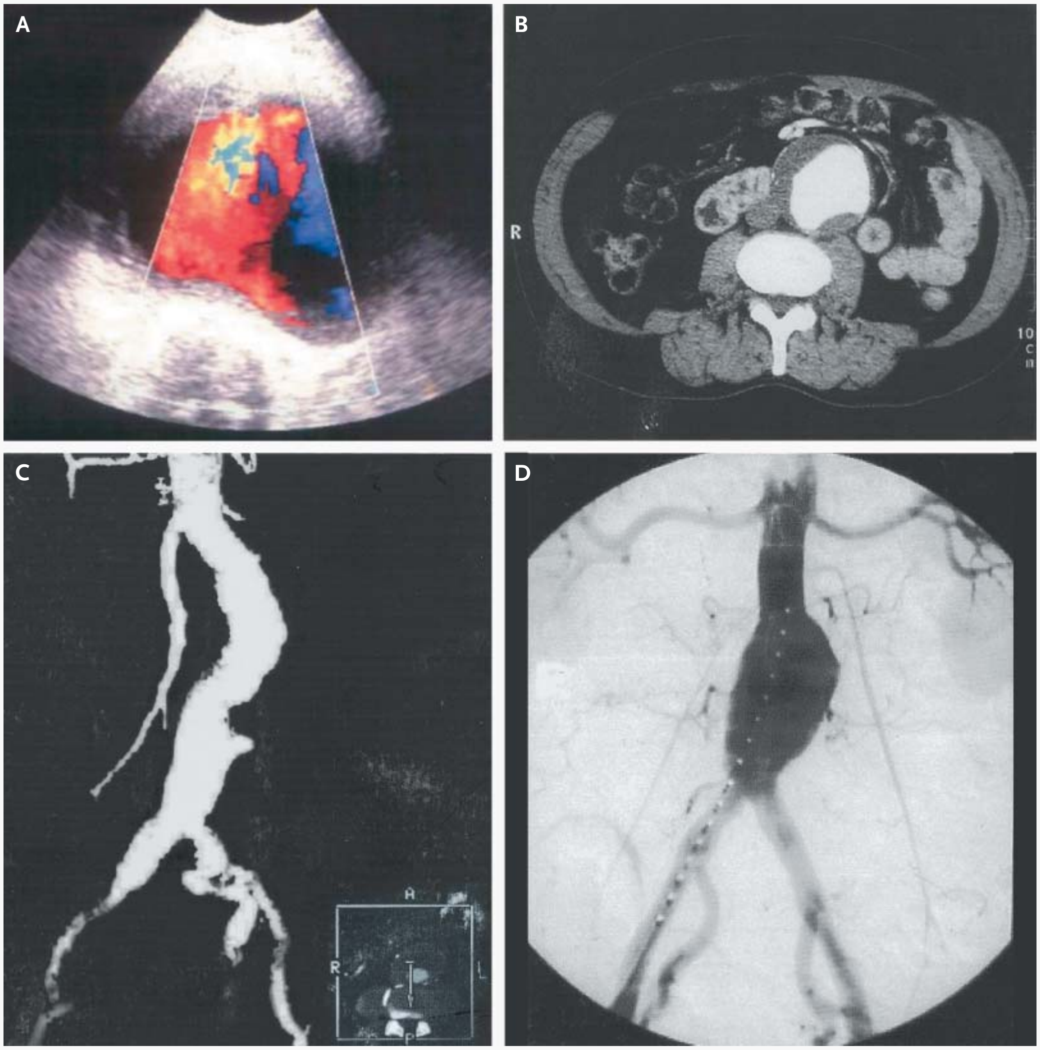


**Figure 2. An Abdominal Aortic Aneurysm.**
Panel A is a duplex ultrasonographic image, with the central sector showing the color flow. Panel B is a planar computed tomographic (CT) image, Panel C a CT angiographic image, and Panel D a fluoroscopic image obtained during endovascular repair.

the United Kingdom trial showed no significant difference in the mean survival between the surgery group and the surveillance group (6.7 years and 6.5 years, respectively).[22] However, there was a marginal late benefit in overall survival in the surgery group ($P=0.05$). This is not a finding that supports a change in practice, since the results were largely attributable to changes in lifestyle, including smoking cessation prompted by surgery.[23] The higher costs of treatment associated with a policy of early surgery[22] reinforce the preference for ultrasonographic surveillance for men with small aneurysms, particularly in places where there is tax-funded health care.

The results of both trials may inform decisions about the timing of surgery, since about three quarters of the patients in the surveillance group eventually underwent surgery. Neither trial provided clear evidence that the 30-day mortality from elective surgery increased with age. Biologic age, as reflected by measures of lung, cardiac, and renal function, appears to be more important.[1,20,24] There is no robust, prospectively validated method for selecting patients who have low operative risk. Although almost half the early deaths that occur after elective aneurysm repair are attributed to cardiac causes, preoperative cardiac testing may not identify those patients who are at the highest risk.[25] Instead, patients with poor lung and renal function have the highest risk of death after elective open surgical repair[1,20,24-26]: for patients with a serum creatinine concentration of more than 1.2 mg per deciliter (104 μmol per liter) and a forced expiratory volume in one second of less than 2.0 liters, the risk of death could exceed 10 percent. Preoperative physiotherapy should be recommended, since it improves outcome after major abdominal surgery.[27] Even with low operative mortality, the ADAM study failed to show a survival benefit associated with a policy of early surgery.

In men, surgery can safely be delayed until the aneurysm exceeds 5.5 cm in diameter, because the risk of rupture is low. The risk of rupture is negligible for aneurysms with a diameter of less than 4 cm, but the risk increases with increasing diameter (Fig. 1). However, the risk of rupture is four times as high among women as among men.[22] The fact that aneurysms rupture at smaller diameters in women may simply reflect the tendency for the normal diameter of the aorta to be smaller in women than in men, with a fixed diameter representing a greater dilatation as a proportion of the original diameter.[6] For women, the threshold diameter of 5.5 cm for aneurysm repair is probably too high, but trial data do not permit the specification of a lower threshold.

### SMOKING CESSATION AND MEDICAL THERAPY

The therapeutic goal is to prevent small aneurysms from reaching a size at which the risk of rupture is high. Data from population screening show wide variability in the rates of expansion of aneurysms, but growth appears to be exponential. One study reported growth rates of 2.0, 3.4, and 6.4 mm per year for aneurysms that began at 3.0 to 3.9 cm, 4.0 to 4.9 cm, and 5.0 to 5.9 cm, respectively.[3] Effective medical therapy must reduce the rate of expansion by more than 50 percent in order to keep a 4-cm aneurysm from reaching the 5.5-cm threshold within five years.

Smoking, the only consistent risk factor for expansion of aneurysms, increases the growth rate by 20 to 25 percent.[3,8,28-30] Data from 1743 patients followed prospectively showed that aneurysms expanded significantly more rapidly (by a mean of 0.29 cm per year) in current smokers than in former smokers (mean, 0.25 cm per year). Blood pressure and cholesterol levels did not predict the rate of expansion, and the rate was slower in patients with diabetes than in those without diabetes.[30] The risk of rupture and the risk of death due to rupture are higher among current smokers than among former smokers and patients who never smoked — by as much as a factor of 14 for smokers of hand-rolled cigarettes.[1,31]

There is a dearth of information about the treatment of hypertension and hyperlipidemia in patients with aneurysms and conflicting evidence about how these and other cardiovascular risk factors relate to the progression of disease.[32,33] Propranolol does not reduce the growth rate of small aneurysms and impairs quality of life.[34] Statins have both lipid-lowering and antiinflammatory actions, but none of the trials of statins have evaluated aortic diameter. Antioxidant vitamin supplementation (with alpha-tocopherol, beta carotene, or both) does not reduce the incidence of aneurysm or rupture.[35] Doxycycline, an antibiotic that is effective against *Chlamydia pneumoniae* and an inhibitor of metalloproteases, awaits evaluation in a large randomized trial assessing its efficacy in slowing the expansion of aneurysms.[36] The results of a small trial suggest that a short course of roxithromycin reduces expansion for 12 months,[37] but more data are needed. For patients with aneurysms, modification of cardiovascular risk factors is more likely to prolong life in ways other than by slowing the expansion of aneurysms.

### SCREENING AND SURVEILLANCE

Abdominal aortic aneurysms are not always asymptomatic, and tenderness on aortic palpation, back pain, abdominal pain, and intermittent claudication can all be aneurysm-related symptoms. Abdominal palpation has neither the sensitivity nor the specificity of ultrasonography in screening for aneurysm.[38] Evidence from two studies suggests that one-time ultrasonographic screening of men, at the age of 65 years, is sufficient to identify nearly all those who are at risk.[39,40] Twelve years after screening, no subject with an initial aortic diameter of less than 2.6 cm had had aneurysm repair or rupture, and all survivors had an aortic diameter of less than 4 cm.[39] Recently, a trial involving 67,800 men in the United Kingdom demonstrated that screening halves the rate of aneurysm-related death within four years but does not reduce overall mortality and does reduce quality of life (principally patients' perceptions of their own health).[41] Without a medical therapy that limits the growth of aneurysms, population-screening programs may not be cost effective.[42]

Screening and surveillance programs must be rigorous and have stringent quality control. Ultrasonographic monitoring of previously diagnosed aneurysms is reliable, safe, noninvasive, and relatively inexpensive.[42] There has been no formal evaluation of the benefits of screening persons with a history of smoking or a family history of aneurysms. Evidence concerning the appropriate interval between screenings comes from the analysis of the previous diameter of the aneurysm, the rate of growth, and rates of rupture (Table 1). If women were considered for surgery when their aneurysms reached a diameter of 5 cm, screening intervals of 12 months could be recommended for aneurysms with diameters of 3.0 to 4.4 cm, and intervals of 6 months for aneurysms with diameters of 4.5 to 5.5 cm. On this basis, approximately 5 percent of patients would be considered for surgery at each surveillance visit.

## AREAS OF UNCERTAINTY

### ENDOVASCULAR REPAIR

Conventional open repair of aneurysms with replacement with a Dacron (polyester) graft is a major surgical procedure. The expectation that endovascular repair, first described in 1985,[44] poses less operative risk than conventional repair remains unproved. Endovascular repair requires radiologic and surgical skills. Under local or general anesthesia, a stent–graft system is introduced through the femoral artery, and either self-expanding or balloon-expanding stents are used to trap a Dacron prosthesis, with the proximal end precisely below the lower renal artery. The common devices are bifurcated and modular and incorporate stents in the wall to facilitate distal iliac fixation. Some devices use hooks and barbs to secure better fixation and prevent device migration.

"Endoleaks" — leaks from fabric tears or between modular systems that permit continued perfusion and expansion of the aneurysmal sac — can lead to rupture. In 2001, the Food and Drug Administration issued a public health notification following reports of adverse events related to the integrity of devices and vascular damage that occurred with two approved products, and these products were withdrawn from the market. In 2002, the Medical Devices Agency of the United Kingdom issued similar alerts about three additional devices. To assess problems in the future, close surveillance of devices used for endovascular repair of aneurysms is recommended, usually with repeated CT scanning one and three months after repair and annually thereafter. The effect of increased exposure to radiation from CT surveillance is unknown. Although ultrasonography is useful in the measurement of the diameter of the sac, endoleaks (which complicate 10 to 20 percent of repairs) are often missed; magnetic res-

**Table 1. Recommended Intervals for Surveillance for Small Aneurysms.**

| Criterion for Surveillance Interval | Context | Study | Base-Line Diameter of Aneurysm<br>*cm* | Recommended Interval between Screenings<br>*mo* |
|---|---|---|---|---|
| Survival without rupture following last ultrasonographic screening | Cohort of 181 patients with abdominal aortic aneurysms in Rochester, N.Y. | Reed et al.[43] | 3.0–3.9<br>4.0–5.0 | 12<br>6 |
| <1% Probability of expanding to a diameter ≥6 cm* | 1017 Patients in population-screening studies in the United Kingdom | Vardulaki et al.[3] | 3.0<br>3.5<br>4.0<br>4.5<br>5.0 | 24<br>24<br>12<br>12<br>3 |
| <1% Probability of expanding to a diameter ≥5.5 cm | 1090 Patients in the United Kingdom with small aneurysms | United Kingdom Small Aneurysm Trial[19] | 3.5<br>4.0<br>4.5<br>5.0 | 24<br>12<br>12<br>6 |

* In the case of an aneurysm with a diameter of 5.0 cm, the 1 percent threshold was exceeded.

onance imaging takes longer, is more expensive, and cannot be used for stainless-steel–based devices.[45,46]

There is, at present, no evidence that the risk of rupture of an aneurysm is reduced after endovascular repair; the reported risk of rupture is 1 percent per year[47] — similar to that for patients who have not undergone surgery and are followed in surveillance programs.[19,21] The majority of reports on endovascular repair have thus far been from single-center, nonrandomized studies.[48] Such studies are subject to bias and exclude patients who are considered to be poor candidates for endovascular repair, usually because the neck of the aneurysm is unsuitable for the fixation of a graft (although increasing experience and technological advances should improve the generalizability of this procedure). Randomized trials comparing open surgical repair with endovascular repair are under way.

### PATIENTS' PREFERENCES AND TIMING OF SURGERY

Patients' preferences for treatment, including the potential timing of any corrective procedure, should be considered. The awareness that one may have to undergo major surgery in the future may impair one's quality of life. In the United Kingdom Small Aneurysm Trial,[23] there were only small differences in the quality of life (as evaluated by a short questionnaire) at one year between those assigned to early surgery and those assigned to ultrasonographic surveillance. However, survivors of early elective surgery perceived their health to be better than did patients in the surveillance group.[23] Hospitalization for surgery may promote smoking cessation, with associated improvements in health and survival.[22] The potential for medical therapy to slow or arrest the growth of an aneurysm could also influence the preferences of patients in the future.

## GUIDELINES

There are no formal guidelines for the screening or management of small abdominal aortic aneurysms.

## SUMMARY AND RECOMMENDATIONS

In the case of a patient with a small abdominal aortic aneurysm, such as the case described in the vignette, the first step is to counsel the patient to stop smoking and to recommend nicotine replacement, bupropion, or both, as necessary. Hyperlipidemia and hypertension should be adequately treated, although there are no data to indicate that the expansion of aneurysms is slowed by such therapy. Because data from two large trials did not indicate that early elective surgery improves survival, the patient should undergo regular surveillance, with repeated ultrasonographic screening at six-month intervals. The aneurysm is likely to reach 5.5 cm in diameter in about two years, during which time endovascular technology will most likely have improved further and medical therapy may be on the horizon. When the diameter of the aneurysm exceeds 5.5 cm, surgery (or possibly endovascular repair, depending on the results of ongoing clinical trials) would be appropriate, following assessment of lung, renal, and cardiac function.


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