Small Abdominal Aortic Aneurysms: Should We Wait?

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ABSTRACT: The proper management of small abdominal aortic aneurysms (AAAs), namely those under the threshold of 5.5 cm in diameter, has been under investigation for years. Risk of rupture for this group of AAAs is higher than the rest of the population, and specific factors have been associated with increased growth rate of small AAAs. This review aims to collect and present all available research data on the development and progress of small AAAs. Furthermore, the results of major randomized trials on proper treatment of such patients are discussed, and conclusions regarding interventional and conservative management are made.

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n abdominal aortic aneurysm (AAA) is defined as a dilatation of the aorta more than one and a half times its normal diameter at the level of the renal arteries. Therefore, an aorta of more than 2 cm in diameter is considered an ectatic aorta that should be closely followed up using ultrasound imaging. The latest guidelines recommend the repair of AAAs 5.5 cm in diameter or greater in asymptomatic patients. Patients with symptomatic aneurysms and whose aneurysms increase in diameter by 0.5 cm or greater within 6 months should also undergo repair, regardless of aneurysm diameter. However, there has been debate for years over the proper management (intervention or surveillance) of small AAAs, namely of sizes between 4 cm and 5.5 cm. This review will present all available data on the prognosis and management of small AAAs in order to produce useful conclusions.

GROWTH RATE AND RISK FOR RUPTURE

Several factors have been associated with small AAA growth rate and expansion. A large initial diameter and family history of aortic aneurysm have been identified as independent risk factors for more rapid growth of small AAAs. The growth rate of AAAs is significantly greater in women than in men as well, according to several studies. This could have implications for the frequency of follow-up and timing of repair of AAA in women. Other factors have been reported to be associated with increased AAA expansion, including large
AAA thrombus size, high AAA wall stress, elevated plasma concentration of matrix metalloproteinase-9 and presence of carotid artery disease. Collagen markers such as serum elastin peptides (SEP), plasmin-antiplasmin (PAP) complexes and interferon-gamma (IFN-gamma) have also been strongly associated with AAA development and growth.

However, there are factors negatively correlated with AAA growth such as diabetes mellitus and chronic limb ischemia. Progression of small AAA seems to be more than 60% lower in patients with diabetes. Additionally, male sex, smaller aneurysms, and large body size seem to be linked with smaller risk for rupture. This could help to identify subgroups of individuals at lower likelihood of AAA enlargement or rupture, such as diabetic large men.

Regarding growth rate of small AAAs, Bown et al concluded in a recent meta-analysis that for each 0.5-cm increase in AAA diameter, growth rates increase on average by 0.59 mm per year (95% confidence interval [CI], 0.51-0.66) and rupture rates increase by a factor of 1.91 (95% CI, 1.61-2.25). However, Powell et al found in a similar study that the pooled mean growth rate was 2.32 (95% CI, 1.95-2.70) mm/year although the heterogeneity between studies was quite high. The authors concluded that a 3.5 cm aneurysm would take a mean 6.2 years to reach the limit of 5.5 cm, whereas a 4.5 cm aneurysm would take only 2.3 years. Specifically for the diameter range 3.0 cm to 5.5 cm, rupture rates seem to range between 0 and 1.61 ruptures per 100 person years. However, even small AAAs have been associated with higher mortality compared to controls, independently from the presence of cardiovascular disease symptoms.

**OPEN REPAIR VS SURVEILLANCE**

Regarding treatment, 2 major randomized trials have compared open repair of small AAAs with a noninterventional approach. In the 1990s, the UK Small Aneurysm Trial evaluated 1,090 patients aged 60–76 years, with asymptomatic abdominal aortic aneurysms 4.0 cm to 5.5 cm in diameter. The patients were randomized to undergo early elective open surgery (n=563) or ultrasonographic surveillance (n=527). Patients were followed-up for a mean of 4.6 years, and only if the diameter of aneurysms in the surveillance group exceeded 5.5 cm, surgical repair was recommended. The 30-day operative mortality in the early-surgery group was 5.8%, which led to a survival disadvantage for these patients early in the trial. However, mortality did not differ significantly between groups at 2, 4, or even 6 years. Age, sex, or initial aneurysm size did not modify the overall hazard ratio. Therefore, the authors concluded that ultrasonographic surveillance for small AAAs is safe, with early surgery not providing a long-term survival advantage. Finally, the same cohort of patients was followed for an average of 12 years by the collaborating authors, and they found that early elective surgery did not confer any survival benefit in the fittest patients, although the least fit patients showed a survival advantage with early open repair.

The second randomized trial was the ADAM trial (Aneurysm Detection and Management Veterans Affairs Cooperative Study Group), evaluating more than 1,000 patients with small AAAs. Patients included in this study were 50–79 years old, with AAAs ranging between 4 and 5.4 cm in diameter. They were randomized either to open repair (n=569) or surveillance by ultrasonography or computed tomography.
The follow-up period ranged between 3.5 and 8 years. The rate of death from any cause was not significantly different in the 2 groups (relative risk in the immediate-repair group as compared with the surveillance group: 1.21; 95% CI, 0.95-1.54). Trends in survival did not favor immediate repair in any of the prespecified subgroups defined by age or diameter of aneurysm at entry. Although immediate open repair was followed in this study by a low total operative mortality of only 2.7%, the trial highlighted that survival is not improved by elective repair of small AAAs. Furthermore, a later analysis of results indicated that impotence was higher in the open repair group 1 year after randomization, although the same group showed an improved perception of health in the first 2 years.

**Endovascular Repair vs Surveillance**

Endovascular repair of AAAs (EVAR) is a less invasive alternative to open surgical management. The short-term technical success rate of the endovascular approach ranges up to 95%. Large randomized trials comparing EVAR with open repair have shown that short-term morbidity and mortality rates are better after endovascular repair, although long-term survival does not show any difference between the 2 methods. Two major randomized trials have been published in the last decade evaluating the potential role of EVAR in small AAA management.

In the PIVOTAL (Positive Impact of Endovascular Options for treating Aneurysms Early) trial, 728 patients (13.3% women; mean age, 71±8 years) with AAAs of 4 cm to 5 cm in diameter were randomly assigned to early EVAR (n=366 patients) or ultrasound surveillance (n=362). After a mean follow-up of 20±12 months (range, 0-41 months), the death rate was almost 4% in both groups, and the unadjusted hazard ratio for mortality in the early-EVAR group was 1.01 (95% CI, 0.49-2.07, P=.98). Aneurysm rupture and aneurysm-related death were also equivalent in both groups. Therefore, the investigators concluded that both approaches appear to be safe alternatives for patients with small AAAs, protecting the patient from rupture or aneurysm-related death for at least 3 years.

In the CAESAR (Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair) trial, 360 patients between 50 and 79 years of age, with an AAA of 4.1 cm to 5.4 cm, were randomly assigned (1:1 ratio) to receive immediate EVAR, or surveillance by ultrasound and computed tomography. Repair was also selected only after a defined threshold (diameter ≥5.5 cm, enlargement >1 cm/year, symptoms) was achieved. The main end point was all-cause mortality. Mortality and rupture rates were low and no clear advantage was shown between early or delayed EVAR strategy. The investigators concluded that within 36 months, 3 out of every 5 small aneurysms under surveillance might grow to require repair and 1 out of every 6 might lose feasibility for EVAR. Moreover, patients with small AAA under surveillance had significant impaired functional health at 6 months after assignment, although short-form 36 health-related quality of life was similar between both groups after a mean 31.8 months follow-up.

Although the results of previous trials did not show a difference between EVAR and surveillance, the results of Zarins et al are opposing. In this retrospective study, data on patients with small AAAs from the multicenter AneuRx trial treated endovascularly, were compared
with the surveillance group from the UK Small trial. Inclusion criteria were the age limit (60 years to 76 years) and the size of the aneurysm (4 cm to 5.5 cm). The authors concluded that EVAR of small AAAs significantly reduces the risk of fatal aneurysm rupture and aneurysm-related death and improves overall patient survival compared to an ultrasound surveillance strategy with selective open surgical repair. In this study, ruptures occurred in 1.6% of EVAR patients and 5.1% of patients under surveillance, although this difference was not significant. Fatal aneurysm rupture rate, adjusted for follow-up time, was 4 times higher in patients under surveillance (0.8/100 patient years) than in patients treated endovascularly (0.2/100 patient years, \( P < 0.001 \)). Elective operative mortality rate was significantly lower in the EVAR group (1.9% vs 5.9%, \( P < 0.01 \)). Finally, all-cause mortality rate was significantly higher in the surveillance group (8.3/100 vs 6.4/100 patient years, \( P = 0.02 \)). However, one should underline that this was a retrospective analysis, without a primary randomized designation of study.

In order to produce better conclusions from future studies, reports of EVAR should stratify their outcomes according to the diameter of the aneurysm. Large aneurysms need a more rigorous post-EVAR surveillance schedule than do smaller aneurysms. In a large retrospective study enrolling more than 4,000 patients treated with EVAR from the EUROSTAR database, the authors found that small AAAs show lower rupture rates, better follow-up results at 4 years and less aneurysm-related death compared to patients with AAAs larger than 5.5 cm in diameter (\( P < 0.0001 \)). In another large prospective study by Zarins et al, 923 patients undergoing EVAR were stratified into different groups according to AAA size. The authors concluded that patients with small AAAs (<5.0 cm) are more favorable candidates for EVAR and have the best long-term outcomes, with 99% freedom from AAA death at 5 years.

Finally, a pooled analysis of all four major randomized trials (UKSAT, ADAM, CAESAR and PIVOTAL) was published recently in order to shed light on proper management of small AAAs. A total of 3,314 patients were analyzed. Although early survival rates favored the surveillance group (due to 30-day operative mortality with surgery), there was no significant difference in long-term survival (adjusted hazard ratio 0.88, 95% CI, 0.75 to 1.02, mean follow-up 10 years for UKSAT; HR 1.21, 95% CI 0.95 to 1.54, mean follow-up 4.9 years for ADAM; HR 0.76, 95% CI, 0.30 to 1.93, median follow-up 32.4 months for CAESAR; HR 1.01, 95% CI, 0.49 to 2.07, mean follow-up 20 months for PIVOTAL). When analyzing the 2 trials evaluating open repair (with a maximum follow-up of 7 to 8 years), the authors found no statistically significant difference in survival between immediate open repair and surveillance (propensity score-adjusted HR 0.99; 95% CI, 0.83 to 1.18), and that this lack of treatment effect did not vary by AAA diameter (\( P = 0.39 \)) or participant age (\( P = 0.61 \)). The meta-analysis of mortality at 1 year for the endovascular trials likewise showed no significant association, compared to surveillance (risk ratio at 1 year 1.15, 95% CI, 0.60 to 2.17).

**FUTURE RECOMMENDATIONS**

Data so far indicate that a more conservative management would be more appropriate for patients with small AAAs. Surveillance intervals of several years are...
clinically acceptable for men with AAAs in the range of 3.0 cm to 4.0 cm, and AAAs <3 cm do not require a repeat scan for 5 years.\textsuperscript{30} According to Thompson et al, intervals of around 1 year are suitable for AAAs of 4.0 cm to 4.9 cm, whereas intervals of 6 months would be acceptable for AAAs of 5.0 cm to 5.4 cm.\textsuperscript{31} Research results so far show that lengthening surveillance intervals for the smallest aneurysms seems to be cost effective as well. Concerning the surveillance method, ultrasound imaging is quite reliable for follow-up, with 3D ultrasound reconstruction demonstrating lately acceptable reproducibility and good agreement with CT scanning.\textsuperscript{32}

Regarding the optimal medical treatment during the surveillance period, several drug categories have been associated with reduction of AAA growth rate. Lipid-lowering drug treatment as well as initial AAA diameter appear to be independently associated with lower AAA growth rates.\textsuperscript{33,34} Therefore, medical treatment with statins seems to offer some benefit. Mosorin et al have also found that statins slightly decrease the AAA growth rate and significantly improve freedom from aneurysm repair and rupture.\textsuperscript{35} Moreover, statins appear to be associated with attenuation of AAA growth, irrespective of other known factors influencing aneurysm growth.\textsuperscript{36} Shouten et al showed that statin users had a 1.16 mm/year lower AAA growth rate compared to non-users (95% CI 0.33-1.99 mm/year).\textsuperscript{36} However, in the largest cohort to date evaluating the effect of statins on small AAAs (n=652), no association between statins or LDL levels with AAA expansion was found.\textsuperscript{37}

In a large Cochrane database research involving more than 1,500 patients, randomized trials studying the role of medical treatment on small AAA growth and progress were evaluated.\textsuperscript{38} Quality of evidence from the collected trials was quite unclear and did not lead to solid conclusions, mainly due to the small size of the different trials. The meta-analysis included only two trials with antibiotics, showing that mainly roxithromycin has a small but significant protective role. More studies referred to the role of beta-blockers, especially propranolol. This agent showed low tolerance in the majority of the trials, although its positive effect was limited. Therefore, the initiation of such agents during surveillance period is still controversial. Furthermore, diabetes and smoking have been strongly associated with small AAAs.\textsuperscript{39} Smoking cessation should be suggested for such patients, although antihypertensive and other cardioprotective medication does not seem to affect small AAAs significantly.\textsuperscript{39} Low-dose aspirin has been associated with lower expansion rates and less need for later repair in AAAs sized above 3.5 cm.\textsuperscript{40}

In conclusion, the consensus in the literature is that small AAAs should be followed up rather than operated immediately, until recommended indication for repair is set. Surveillance programs should consider regulating specific risk factors such as smoking, as appropriate. Results so far regarding the protective role of medical regimes against small AAAs progression and rupture are still controversial. However, data so far could help define certain subgroups of patients that could be under tighter surveillance and thus recognize indicated candidates for surgical repair sooner.

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