Endovascular Repair of Abdominal Aortic Aneurysms vs. Surveillance

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A. Introduction

An abdominal aortic aneurysm (AAA) is defined as an infrarenal dilatation of the aorta >2.5 cm. Their prevalence increases with age, and it is estimated that approximately 7.6% of men and 1.3% of women age 65-80 have a AAA >3cm. One of the large population based studies to estimate the risk of undiagnosed AAAs in the asymptomatic public was done through the VA[1,2] which estimated that 2.1% of men 50-79 had a AAA >4.0cm (126,196 veterans screened – 2662 AAA).

The main risk of AAAs is of rupture, with at least a 50% mortality rate. It is estimated that ruptured AAAs cause 15000 deaths per year in the US[3]. The only treatment for years to prevent rupture has been open surgical repair of the aorta. The US currently performs 50,000 of these operations per year[4]. Over the last 2 decades, there has been a lot of interest in developing a better understanding of AAAs, their natural history, their actual risk of rupture, the risks and benefits of repair, and the identification of modifiable risk factors.

Many studies have shown that current smoking is associated with an increased expansion rate and risk of rupture. In the UK Small Aneurysm trial, initial diameter, female sex, current smoking, blood pressure and lower FEV1 were all associated with increased rupture. Schewe et al showed that contrary to expectations, cholesterol, LDL, HDL, LDL/HDL, and the extent of smoking were not associated with risk of rupture[5]. Some small trials have even shown that diabetes may confer protection from the development and rupture of AAAs.

Open surgical repair of a AAA is a long surgery under general anesthesia. It requires a large incision, cross clamping the aorta. There is significant postoperative pain. The median hospital stay is 8 days, and many patients need some rehabilitation to regain their ADLs. Various patient series have reported 30 day operative mortality between 2.7% and 5.5% (2.7% is considered low). One of the best centers is Cleveland Clinic which published their 7 year experience with open repair of AAAs: 1135 patients, 30day mortality 1.2%, single postoperative complications 13%, multiple postoperative complications 4%, late complications 0.4%, 75% survival at 5 years, 49% at 10 years.[6]

The US experience was published from the NIS: (data for 16,450 intact AAAs repairs)[7]

in-hospital mortality rate 4.2%
the overall complication rate 32.4%
91.2% of patients were discharged home
the bad outcome rate 12.6%.
median length of stay 8 days
median hospital charges $28,052

Given the signicant risks and costs of surgery, an effort has been made over the last decade to try to identify more specific guidelines for which patients benefit from surgery, with the hope that some

[1] Ann Intern Med 1997 Mar 15; 126(6):441-9
[2] Arch Inteern Med 2000 May 22; 160(10):1425-30
[3] Arteriosclr Thromb Vasc Biol 1996; 16:963-70
[4] NEJM 346(19), 2002 May:484-5
[5] Clin Investig 1994 Aug;72(8):585-91
[6] J Vasc Surg 2002 Jun;35(6):1145-54
[7] J Vasc Surg 2001 Feb;33(2):304-10

patients could be spared from surgery. Several patient series were published which attempted to estimate the actual risk of rupture based on size of AAA.

300 consecutive patients[8]		187 consecutive patients[9]	
<4cm	1% rupture over 6 years	<5cm	2.5% rupture over 7 years
4.0-4.9cm	2% rupture over 6 years	≥5cm	28% rupture over 3 yrs
≥ 5.0cm	20% rupture over 6 years		

The UK Small Aneurysm Trial investigators reported a 1% annual rupture rate for their first cohort of 1090 patients with 4.0-5.5cm aneurysms, and a 2.2 % annual rupture rate for the second cohort of 1167 patients (3 year followup)[10].

The ADAM investigators reported a 0.6% rupture rate in their surveillance group of patients with AAAs 4.0-5.4cm (4.9 year followup).

The VA recently published the outcomes of 198 veterans with large AAAs (≥5.5cm) who refused surgery or were not eliglibe for surgery (1.5 year mean followup)[11]. Overall 57% died over 1.5 years. The 1 yr incidence of probable rupture was calculated for different aneursym sizes:

5.5-5.9cm	9.4% per year
6.0-6.9cm	10.2% per year
6.5-6.9cm	19.1% per year
≥7.0cm	32.5% per year

Trials such as these have been interpreted that larger aneurysms have a greater risk of rupture, and the benefit of open surgical repair of aneurysms larger than 5.5cm definitely outweighs the risks of surgery. Investigators have also sought to clarify the expansion rates of aneurysms to identify appropriate surveillance recommendations. As with risk of rupture, rate of expansion was clearly shown to depend on the initial size of the aneurysm, with larger aneurysms expanding faster. Bengtsson et al studied 155 patients with various size aneurysms over 3.4 years, and approximated that aneurysms increase each year by 6.6% of the starting diameter of that year[12].

University of Ottawa, 300 patients followed for 6 years[13]

Diameter	median rate of change
2.5-2.9cm	0.09 cm/yr
3.0-3.9cm	0.19 cm/yr
4.0-4.9cm	0.23 cm/yr
>5cm	0.30 cm/yr

Minneapolis VAMC 790 veterans followed 3.9 year, identified by USG screening[14]

3.0-3.9cm	AAAs expand 0.11 cm/yr
3.0-3.4cm	4% expanded to needing surgery within 3.9 yrs
3.5-3.9cm	14% expanded to needed surgery within 3.9 yrs

Given that it seems inevitable that many small aneurysms will go on to become large aneurysms which require surgery, several randomized prospective studies were designed to determine if there is a set

[8] Am J Surg 1991 Nov;1622(5):481-3
[9] Eur J Vasc Surg 1991 Apr;5(2):125-30
[10] Ann Surg 1999Sep;230(3):289-96
[11] JAMA 2002 Jun12;287(22):2968-72
[12] Eur J Surg 1993 Sep;159(9):46107
[13] Am J Surg 1991 Nov;162(5):481-3
[14] J Vasc Surg 2002 Apr;(35):666-71

of patients with aneurysms less than 5.5cm who would benefit from having earlier surgery, or conversely, surgery conferred no benefit over "watchful waiting".

The ADAM trial investigators recently published the 4.9 year followup on 1135 veterans with AAAs 4.0-5.4cm who were randomized to surgery or surveillance. Patients in the surveillance group who progressed to having 5.5cm aneurysms or became symptomatic were then offered open surgical repair[15].

4.0-4.4cm 27% of surveillance group went on to open surgical repair
4.5-4.9cm 53%
5.0-5.4 cm 81%
0.6% of aneurysms in the surveillance group rupturee per year
61.6% overall went on to open surgical repair

Although there was increased mortality early in the treatment arm, after 4.9 years median followup, there was no statistically significant difference in all-cause mortality (25% surgery, 22% surveillance), or AAA related mortality (3% surgery, 2.6 % surveillance) between the two groups. This was interpreted to support the idea of watchful waiting until aneurysms reach 5.5cm in size or become symptomatic.

The UK Small Aneursym Trial also recently published its 8 year followup of 1090 patients similarly randomized to surgery or surveillance[16].

	surveillance	surgery
4.0-4.4 cm	7.4% died	7.1% died
4.5-4.8 cm	7.9% died	6.7% died
4.9-5.5 cm	10.4% died	7.5% died

The mortality curves cross at 3 years (reflecting early operative mortality), and finally reached statistical significance for the surgery group at 8 years. The major criticism of this result is that a significant number of people in the surgery arm quit smoking cigarettes after their surgery compared to the surveillance arm, therefore clouding whether surgery might offer a durable benefit for smaller aneuryms.

The most exciting development in the field of AAA management however has been repair by endovascular stent. These devices are placed via catheterization (usually of the femoral artery) across infrarenal AAAs to create new lumens. As the procedure is much less invasive, it was hoped that they would have similar efficacy as open surgical repair, and decrease length of stay, operative mortality and morbidity, and increase quality of life. The devices are new and are only recently making their way into general practice, most often for difficult patients in whom surgery carries high risk. Several case series have been published on the experience with these grafts. No randomized trials have been done yet to compare endovascular repair to open repair, but the DREAM (Dutch Randomised Endovascular Aneurysm Management) trial is currently recruiting patients to answer this[17].

30 consecutive endografts, 11 month followup[18]
    23 successful
    2 no access
3 persistent endoleaks
    1 AAA expansion
    1 late rupture

[15] NEJM 2002 May 9;346:1437-44
[16] NEJM 2002 May 9;345:1445-52
[17] J Cardiovasc Surg (Torino) 2002 Jun;43(3):379-84
[18] Vasc Surg 1998 Jun; 27(6) 992-1003

263 endografts, 7.3 month followup (patients with multiple comorbidities)[19]
AAA diameter decreased ≥5mm in 32%
Diameter stayed same in 60%
Diameter increased by ≥5mm in 8.7%
1.9% 30 day mortality
12.5% major morbidity
8.4% minor morbitidy

362 consecutive endografts over 7 years[20]
1.6% died within 30days of procedure (all older, worse health)
1.4% needed early conversion
2.2% late conversion
0.8% rupture
AAA expansion >5mm 5.6%
10.7% needed catheter based treatments or limited surgical interventions for a variety of late problems, majority of which (92%) were successful
overall 8.3% failure rate

B. Hypothesis

Endovascular repair of small abdominal aortic aneurysms (AAAs) between 4.0 and 5.4 cm prolongs time to open surgical repair.

C. Methods

a. Conceptual and operational definitions

Primary outcome – open surgical repair of AAA (infrarenal dilatation of the abdominal aorta). Surgery is required when AAAs become symptomatic (embolic phenomenon, abdominal or back pain felt to be due to expansion of aneursym), expand rapidly (expansion ≥ 1.0cm over past 1 year or ≥ 0.7cm in the past six months), or reach a diameter of 5.5cm

b. Study design

Prospective, double-blinded, randomized study.

The size of the aneurysms will be determined by USG within 12 weeks of randomization. If anatomy is unclear regarding exclusion criteria, CT scans will be done. Patients who meet eligibility criteria will undergo stratified randomization for sex and initial diameter (4.0-4.4cm, 4.5-4.9cm, 5.0-5.4cm) to either a treatment arm (endovascular repair of the AAA), or surveillance arm. Both arms will undergo USG assessment of AAA diameter every 6 months. Letters will be sent to the physicans of both arms informing them that current smoking and high blood pressure are associated with increased rates of expansion as well as rupture of AAAs. Data will analyzed at 3 and 5 years.

c. Statistical analysis

The proportion of patients in the treatment arm going on to open surgical repair will be compared to the proportion of patients in the surveillance arm going on to open surgical repair using the chi square test. Multiple logistical regression analysis will be performed for the following factors: initial diameter of AAA, age, sex, BMI, SBP, DBP, MAP, cholesterol, LDL, HDL, LDL/HDL, presence of diabetes,

[19] J Vasc Surg 2002 Jun; 35(6):1123-8
[20] J Vasc Surg 2002 Jun; 35 (6):1137-44

HgA1C, extent of smoking, current smoking status, ABI, FEV1. Groups will be analyzed by intention to treat.

d. Sample size

Using chi square test, assuming 35% of surveillance group will go to surgery over 3 years and 25% of intervention group will go to surgery over 3 years, I estimate that the study will need 350 in each arm to achieve power of 80% to detect significant difference at p 0.05.

D. Subjects Selection

The CPMC abdominal imaging studies (MRIs, CTs, USGs) from 1998-2002 will be text searched for diagnosis of AAA (3.0 to 6.0cm, not described as involving the renal artery) in all patients who would be 50-65 at the time of randomization. Letters will be sent to these patients' physicians informing them of the study. Patients who are referred to the study will have an USG performed to determine the size of AAA (4.0-5.4 cm eligible) and approximate anatomy.

Patients will be considered ineligible if their AAA is symptomatic (embolic phenomenon, abdominal or back pain felt to be due to expansion of aneursym), the etiology of aneursymal dilatation is inflammatory, the patient has ectasia of entire aorta, the patient has undergone previous aortic surgery, the patient has evidence of rupture of the aneurysm, the patient is known to have expansion of the aneurysm ≥ 1.0cm over past 1 year or ≥ 0.7cm in the past six months, the aneurysm is suprarenal or juxtarenal aortic aneurysm (defined by an anticipated need for reimplantation of a main renal artery), the patient has a known thoracic aortic aneurysm of 4.0 cm or more, the patient has probable need for aortic surgery within six months other than repair of the AAA, the patient has severe heart, lung or liver disease (J Vasc Surg 1994;20:296-303), the patient has a serum creatinine ≥ 2.5mg/dL, the patient has a history of major surgical procedure or angioplasty within the previous 3 months, the patient is not expected to survive more than 5 years, the patient is severely debilitated, or the patient is unable to give informed consent.

It is expected that men will outnumber women in this study by as least 3:1 as has been the case in all other studies. This is unfortunate because it has been shown that female sex is associated with a 3 fold risk of rupture of AAAs, however subgroup analysis will be done for each gender at the conclusion of the study. Minorities should be well represented in the study given the catchment area for CPMC.

E. Miscellaneous

Several studies have shown in the last decade that modifiable risks for AAA expansion rate and rupture rate are current cigarette smoking and elevated blood pressure. There is speculation that the late increased survival of the surgery arm of the ADAM trial at 7years may be due to significant smoking cessation observed in the surgery group. Nonmodifiable risks for AAA expansion rate and rupture rate include female sex and initial diameter of AAA. FEV1 may be associated with increased risk. Factors that were studied but found not to be associated with increased risk include ABI, BMI, cholesterol, LDL, HDL, LDL/HDL, extent of smoking, and age. FEV1 may be associated with increased risk. Diabetes may confer protection from AAA rupture. For this reason, a letter will be sent to all physicians of patients found to have AAAs in the CPMC database informing them of this. An additional letter will be sent to all physicians of patients enrolling in the study requesting that they attempt to control their patients blood pressures (SBP<130, DP<90), and discuss smoking cessation if applicable at all office visits, or refer the patient to a smoking cessation clinic. All parameters will be documented and reported in Table 1 format.