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# The Evidence for Management of Abdominal Aortic Aneurysms: Lessons Learned from Randomised Controlled Trials

Reza Mofidi<sup>1</sup> and Stuart A. Suttie<sup>2</sup>

<sup>1</sup>*James Cook University Hospital, Middlesbrough*

<sup>2</sup>*University of Dundee, Dundee,  
United Kingdom*

## 1. Introduction

Abdominal aortic aneurysm (AAA) is a common life threatening condition in the western world. In England and Wales alone, over 2500 patients present to hospital with rupture of AAA annually, of whom over two thirds die of their condition<sup>1</sup>. The best treatment for AAA is elective repair of pre-symptomatic abdominal aortic aneurysms. Such a therapeutic strategy depends on effective identification of patients with AAA and the subgroup of patients in whom there is a real risk of aneurysm rupture. As the vast majority of patients with AAAs are asymptomatic, timely identification of AAA may be achieved through targeted screening of the at risk populations. Over the last two decades longitudinal studies of patients with smaller AAAs have provided insights into the timing of AAA repair and the need for and frequency of ultrasound surveillance if an expectant management strategy is followed. This chapter discusses the available evidence for screening for AAA as well as all the other measures which have helped to optimise therapeutic strategies in the management of patients with AAA throughout the patients' journey from the initial diagnosis to the eventual repair of AAA.

## 2. Targeted screening for AAA

In the past 40 years with the advent and generalised use of abdominal ultrasonography there has been an accurate, cheap and non invasive tool for the diagnosis of abdominal aortic aneurysms. Abdominal ultrasonography has been found to be an accurate and reproducible modality in measuring the dimensions of AAA. This has led to the concept of its use for screening of at risk populations. In the last 20 years there have been four population based randomised controlled trials which have assessed the value of targeted screening in reducing mortality from abdominal aortic aneurysms in the unselected elderly male population<sup>2-5</sup>. These trials which have been undertaken in Chichester (England)<sup>2</sup>, England (MASS trial)<sup>3</sup>, Viborg County (Denmark)<sup>4</sup> and the city of Perth and suburbs (Western Australia)<sup>5</sup> have together recruited over 120,000 subjects. All of these studies have reported on long term (over 10 years) follow up. Using the predefined criteria set by the US Preventative Screening Task Force USPSTF<sup>6</sup> the MASS trial has been classified as good with

the other three trials classified as fair i.e. not meeting all the criteria but judged to have no fatal flaws<sup>7</sup>.

The Chichester trial was the first to assess the value of screening for AAA in the at risk population. It was also unique as it included women as well as men. It identified all men and women aged between 65 and 80 years of age from 9 general practices in the catchment area of St Richard's hospital in Chichester between 1988 and 1991<sup>2,8,9</sup>. The subjects were randomised to undergo a single screening ultrasound (US) or a control group who were followed up. AAA rupture rates, aneurysm related mortality, and overall mortality was compared between the two groups. Upon identification of AAA the therapeutic strategy for AAAs with maximum diameters between 30-44mm was once yearly surveillance US, AAAs between 44 and 59mm underwent 3 monthly ultrasound scans, whilst aneurysms greater than 60mm in diameter were considered for repair<sup>2,8,9</sup>. Overall 6040 men were randomised, the authors reported a significant reduction in aneurysm related mortality which has been maintained over 15 years. However, to date this study has demonstrated no difference in the all cause mortality between the two groups. The Chichester trial has been criticized for its relative small size, a relatively high aneurysm diameter threshold for repair and including 75-80 year old patients in whom the benefits of screening are marginal. In addition 27-percent of subjects who were invited for screening refused to participate thereby diluting the benefits of screening. Despite these criticisms the Chichester study remains a land mark as it demonstrated the feasibility of US screening for AAA and its potential value and remains a blue print for other aneurysm screening studies. This study identified a low but none the less troubling rate of AAA rupture in patients who had a non aneurysmal aorta on the first screening study<sup>2</sup>. A population based screening study in Gloucester demonstrated that 2.2-percent of men aged 65-73 years have a maximal aortic diameter of 2.5 to 2.9 mm and suggested that this group of patients should undergo repeat US scanning at 5 yearly intervals<sup>10</sup>.

The second RCT to study the value of population based screening for AAA was carried out in Viborg County of Denmark. In 1994 all men aged between 65 and 74 were randomised to either undergo a single screening US or the control group. In all 12639 patients were randomised<sup>4,11,12</sup>. This study reported a 66-percent reduction in the aneurysm related mortality which has been maintained over 14-years. In addition they reported a 2-percent reduction in overall mortality after long term follow-up which did not reach significance<sup>4</sup>.

The Western Australia population based screening was a study of similar design. It randomised 41000 men between the ages of 65 and 85 years to a single US screening and a control groups. They reported no difference in aneurysm outcomes in the full study population but when the analysis was restricted to 65-74 year old men they reported a significant reduction in aneurysm related mortality after 5 years of follow-up<sup>5</sup>. Long term follow-up results of this study have not been published as a separate publication to date, however in a reply to a correspondence by Lederle, Norman and Lindholt did report a surprisingly high, 3-percent reduction in overall mortality in the restricted (65-74 year old) patient population after 10 years of follow-up from the Western Australia trial which was statistically significant<sup>13</sup>.

The MASS trial which was a population based screening RCT for men aged between 65 and 74 years of age included 4 screening centres in the United Kingdom. This study randomised 67770 patients again to single screening ultrasound or a control group and was designed to study cost effectiveness of screening in addition to reductions aneurysm related and overall mortality<sup>3,14,15</sup>. This study reported a 48-percent relative risk reduction in aneurysm related

mortality as a result of screening. This benefit was present at 4 years <sup>14</sup> and was maintained at 10 years (Figure-1)<sup>3</sup>. There was a reduced AAA rupture rate in the patients who were invited for screening. Most of these ruptures occurred in patients who were excluded from the potential benefits of screening, such as patients who refused or did not attend screening, patients who were lost to follow-up and those who either refused or deemed not fit for surgery<sup>3</sup>. The MASS trial also reported a small rate of AAA rupture in patients who did not have an AAA on the screening scan, this rate was reported as 3 per 10,000 person years after 10 years of follow up<sup>3</sup>.

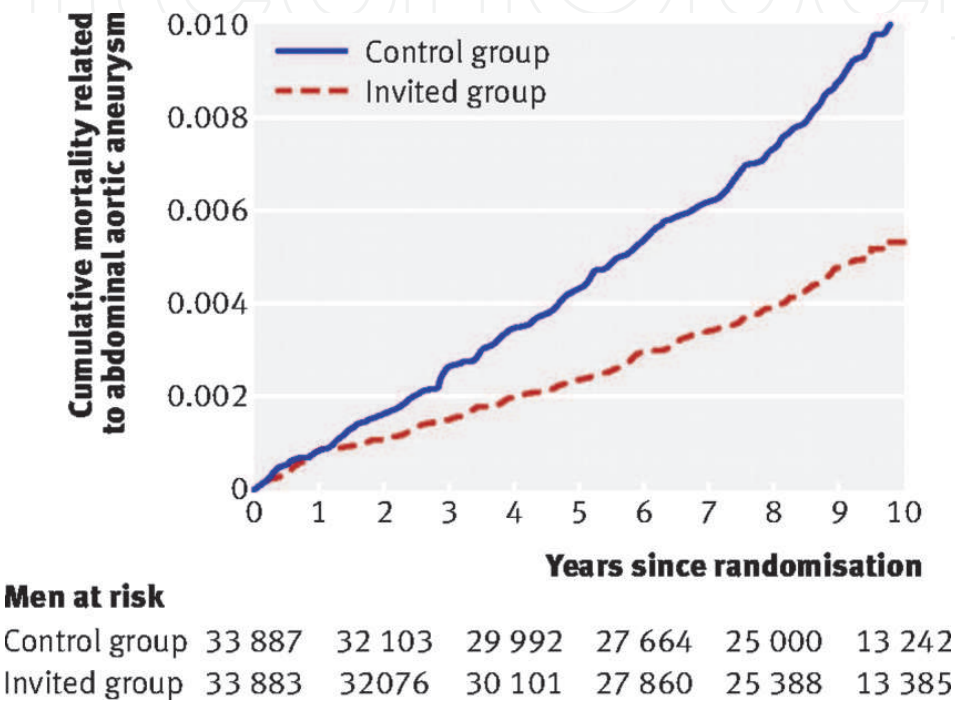


Fig. 1. Cumulative deaths related to abdominal aortic aneurysm, by time since randomisation (MASS Trial)<sup>3</sup>. From: Thompson SG, Ashton HA, Gao L, Scott RA and Multicentre Aneurysm Screening Study Group, Screening men for abdominal aortic aneurysm: 10 year mortality and cost effectiveness results from the randomised Multicentre Aneurysm Screening Study, BMJ 2009; 338: b2307.

In addition to the above RCTs a number of systematic reviews and meta-analyses have attempted to assess the value of population based screening in the medium and long term. Cosford and Leng in a Cochrane systematic review reported that there was significant evidence of reduction in aneurysm related mortality from AAA in men aged 65 to 80 years who undergo population based ultrasound screening, but no significant reduction in all cause mortality<sup>16</sup>. This review was based on the 3-5 year follow up data from the above RCTs. Subsequent to this Norman and Lindholt published a meta-analysis which showed that population based AAA screening after 7-15 years of follow up resulted in a reduction of both AAA and all cause mortality<sup>17</sup>. Their findings were contested as the reported 3-percent all cause mortality reduction was larger than what was expected by an approximately 50-percent reduction in aneurysm related mortality, bearing in mind that the mortality from AAA in the patient population is reported to be between 1.1 to 3-percent<sup>18</sup>.

Takagi et al. conducted a further meta-analysis of US screening in the male population over the age of 65years using long term 10 to 15 year follow up data from the RCTs. They reported an absolute risk reduction in aneurysm related mortality of 4 per 1000 subjects screened (Figure-2). They also revealed a strong trend towards a significant reduction in all cause mortality<sup>7</sup>. The latter finding was surprising for the reasons mentioned already. The authors hypothesized that screening may coincide with the asymptomatic at risk population for cardiovascular disease coming in contact with health care professionals and becoming aware of smoking risk, their blood pressure etc. The resultant reduction in cardiovascular risk factors may be in part responsible for additional reduction in all cause mortality. Such a hypothesis opens the door to the possibility of risk factor alteration and institution of secondary prevention measures such as commencement of anti-platelet agents and statin therapy during screening programmes thereby increasing the value of the screening<sup>7</sup>.

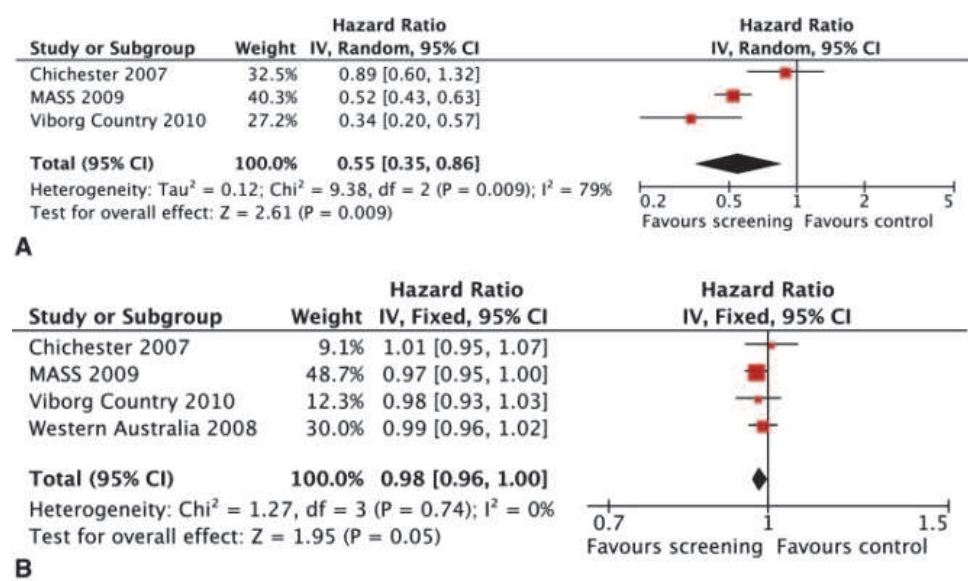


Fig. 2. Forrest Plot of illustrating the reduction in aneurysm related mortality (A) and the trend towards a reduction in overall mortality (B) as a result of population based screening of men between the ages of 65 and 80 years after 10 years of follow up<sup>7</sup>.

From: Takagi H, Goto SN, Matsui M, Manabe H, Umemoto T. A further meta-analysis of population-based screening for abdominal aortic aneurysm. J Vasc Surg. 2010; 52(4):1103-8.

Cost effectiveness of a population based screening programme is calculated by measuring the costs of ultrasound screening as well as the extra procedures and surveillance that is required for the screen identified AAA and subtracting them from the costs of treating ruptured AAA. It is expressed in cost per life year gained. As the survival advantage in terms of life year gained continues to increase with time, the cost effectiveness of screening continues to improve. A comprehensive analysis of costs of screening was performed by the MASS trial participants. They calculated the cost per life year gained to be £41,000 after 4 years<sup>14</sup>, £14,000 after 7 years <sup>15</sup>and £7600 after 10 years<sup>3</sup>. Using the estimated life span of men aged 65 years the cost per life year gained is estimated to be in the region of £2300, which is well below the guideline figure of £25,000 which is considered acceptable for the adaptation of new medical technologies and interventions in the National Health Service of the United Kingdom<sup>19</sup>. Lindholt *et al.* also performed a comprehensive cost analysis of population based AAA screening using data obtained from the Viborg trial. They reported cost per Quality



Adjusted Life Year (QALY) gained as a result of screening to be €179 albeit with relatively wide 95% confidence intervals (€-4083 to €4682)<sup>4</sup>. Both of these values for costs of screening are much lower than the cost analysis carried out by the USPSTF using primarily economic modelling in 2003 and suggest that population based AAA screening in men is more cost effective than the initial assessments suggested<sup>20</sup>.

The role of screening for AAA in women remains controversial. To date there is no evidence that screening for AAA in an unselected population of women is associated with a reduction even in aneurysm-related mortality. Scott and colleagues conducted the only RCT (Chichester trial) which studied the value of screening in women over the age of 65 in an unselected population (n=9342)<sup>21</sup>. They reported the prevalence of AAA in women to be 1.3 percent, with other authors reporting a similar rate of 0.7–1.3 percent in unselected populations<sup>22–24</sup>. Scott *et al.* did not demonstrate a difference in rupture rates between the women randomized to screening and control populations of women at 5- and 10-year follow-up<sup>21</sup>. They concluded that screening for women was neither clinically indicated nor economically viable<sup>21</sup>. This study was limited by high rate of non attendance of women for AAA screening which ranged between 27 and 42-percent depending on patients age. They screened an unselected population of women without consideration of risk factors for aneurysm disease and fitness for repair; consequently a large proportion of women who were found to have an AAA did not undergo aneurysm repair<sup>25</sup>. The UK Small Aneurysm Trial revealed that female sex was an independent risk factor for AAA rupture; the rupture rate in women was three times higher than that in men, despite a smaller initial AP diameter. Furthermore, mean AP diameter preceding rupture was significantly lower in women than men<sup>26</sup>. A number of other authors have reported a higher growth and rupture rate of AAA in women<sup>27–33</sup>. A Finnish community-based follow-up study reported that the aortic diameter was less than 5.5 cm in 24 per cent of women with a ruptured AAA, compared with only 5 per cent of men<sup>21</sup>. In light of these findings the 6 cm cut off value for repair of AAA in Chichester trial may have been too large to prevent aneurysm rupture in a proportion of screened women thereby reducing the value of screening in women.

For screening to be effective in reducing aneurysm-related mortality in women, it will need to be limited to high-risk women who are fit to undergo aneurysm repair<sup>22</sup>. There is increasing evidence that women with atherosclerotic disease are at significantly higher risk of developing AAA. Derubertis and colleagues<sup>22</sup> reported that the prevalence of AAA in women with multiple (more than three) atherosclerotic risk factors was 6.4 per cent. When these findings are considered in conjunction with the increased growth rates of AAA<sup>26</sup> and higher aneurysm rupture rate in women, screening in women with multiple risk factors for AAA may become clinically and economically viable<sup>34–36</sup>.

### 3. Optimum therapeutic strategy for small AAAs

Abdominal aortic aneurysms are treated in order to prevent rupture and the associated mortality. Aneurysm treatment has its own associated morbidity and mortality. Open surgical repair is an invasive procedure which is tolerated poorly by the subgroup of patients with multiple medical co-morbidities. Even endovascular repair cannot be accomplished without an obligatory complication rate as a result of the initial deployment of the stent graft, in addition to which a proportion of patients require secondary procedures necessary to address complications such as endoleaks, device migration and stent thrombosis requiring long term close surveillance<sup>37</sup>. A small proportion of patients

who have undergone endovascular repair (EVAR) succumb to rupture. Therefore the natural history of the AAA needs to be balanced against the risk associated with treatment. Aneurysm diameter is one variable which has been consistently associated with the risk of rupture and has therefore been used to stratify patients into risk categories which decides whether US based surveillance or intervention is required to repair the aneurysm. In patients who are entered into surveillance programmes the maximum diameter of the aneurysm is used to decide on the frequency of scanning. In case of aneurysms greater than 5.5 cm there is consensus that risk of rupture mandates repair if the patient is fit to undergo the procedure. In the case of aneurysms less than 4.0 cm in diameter, most clinicians agree on a watchful waiting approach. The evidence for the optimum therapeutic strategy in the mid-sized aortic aneurysms (maximum diameter between 4.0 to 5.5 cm in diameter) has been strengthened by a number of randomised controlled trials in the last 20 years which have consolidated the modern management of AAA<sup>26,38-41</sup>.

The UK small aneurysm trial (UKSAT) was a multicentre RCT which randomised 1090 patients, who were diagnosed as having an AAA with maximum AP diameter of 4.0 to 5.5cm and were deemed fit to undergo an open repair of AAA to either immediate open repair or 3 monthly ultrasound surveillance. They reported the rupture rate of these AAA in the surveillance group to be in the 1-percent per year. They did not find any significant difference in aneurysm related or all cause mortality between the two groups after a follow up period of 7 years (Figure-3)<sup>26</sup>. During the follow up period over two thirds of patients who were randomised to surveillance had undergone repair of their aneurysms based on clinical grounds.<sup>26</sup> Long term follow up data from the small aneurysm trial has confirmed the initial findings of the UKSAT<sup>38</sup>.

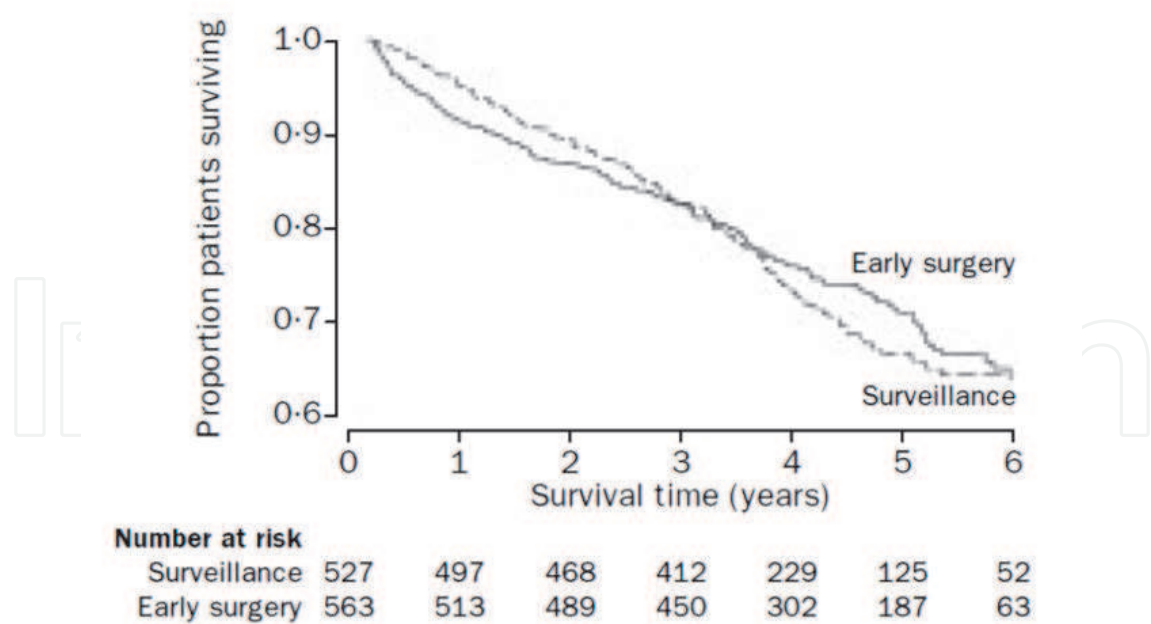


Fig. 3. Kaplan-Meier survival curves comparing survival of patients with small abdominal aortic aneurysms randomised to ultrasound surveillance and early surgery from UK small aneurysm trial<sup>26</sup>. From: United Kingdom Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. Lancet 1998;352: 1649-55.

A number of years after the publication of the UKSAT, the Veterans Affairs Cooperative Study group published the Aneurysm Detection and Management ADAM study<sup>39</sup>. This study involved screening of 126,196 veterans aged between 50 and 79 years of age for AAA with a single abdominal US. Those with AAA measuring 4.0 to 5.4 cm in diameter were offered entry to the trial. In all, 1136 subjects were randomly assigned to undergo early elective repair or ultrasound surveillance. Annualized rupture rate in the surveillance arm of the study was 0.6-percent, with no difference in aneurysm related and overall mortality between the two arms of the study <sup>39</sup>. In this study as in UKSAT the majority of patients in the surveillance arm of the study had undergone elective repair after 8 years of follow up based on clinical grounds (symptomatic aneurysm, growth to greater than 5.5cm in diameter or rapid expansion by greater than 1 cm per year) <sup>39</sup>. Completion of these two landmark trials which utilised open elective repair coincided with the advent and generalised use of endovascular repair as a primary modality treatment of AAA. This resulted in some authors questioning the validity of these landmark trials in the era of endovascular repair and suggested that as endovascular repair can be performed with significantly lower peri-procedural morbidity and mortality a policy of surveillance for smaller AAAs should be examined against endovascular repair.

To date two randomised controlled trials (PIVOTAL<sup>40</sup> and CAESAR<sup>41</sup>) have been conducted to compare early endovascular repair of small AAAs with ultrasound surveillance. The prerequisite for both studies was that the patients which were randomised had AAAs which were anatomically suitable for endovascular repair.

The PIVOTAL trial which was published in 2010, randomised 728 patients with AAAs measuring 40 to 50 mm in diameter to ultrasound based surveillance or early endovascular repair<sup>40</sup>. The mean duration of follow up was 20 months (+/-12 months) they found no difference in all cause or aneurysm related mortality between the two groups <sup>40</sup>. At the end of the relatively short follow up duration almost one third of patients who were in the surveillance group had undergone an aneurysm repair based on clinical grounds<sup>40</sup>. The other study of a similar design was the CAESAR trial which randomised 360 patients with AAAs measuring between 40 and 54 mm to early endovascular repair or a watchful waiting strategy. <sup>41</sup> After 54 months of follow up there was no significant difference in rupture rates, aneurysm related and overall mortality between the two groups (Figure-4). This study revealed that the probability of the patients in the surveillance arm of the study requiring delayed repair based on clinical grounds during the duration of follow up was 60-percent<sup>41</sup>. In addition they reported that 16.4-percent of aneurysms which upon entry into the trial were suitable for endovascular repair will be no longer suitable for EVAR after 36 months<sup>41</sup>.

A constant finding in these trials has been that a significant proportion of AAAs under ultrasonographic surveillance come to require repair within the duration of the study<sup>26,39</sup>. This, taken together with the low but present annual risk of rupture has lead to differing interpretations of the results of these trials with some authors still advocating in favour of early repair of small AAA using the justification that a policy of early EVAR is as safe as a policy of US Surveillance<sup>42</sup>. To date there is no objective data to recommend either open or endovascular repair of smaller AAAs over a policy of watchful waiting and US surveillance. A policy of early EVAR is associated with a risk of early and delayed complications and a need for secondary procedures, thus mandating the need for close surveillance in patients who undergo early EVAR. It is therefore unlikely that there will be an economic justification for early endovascular repair.



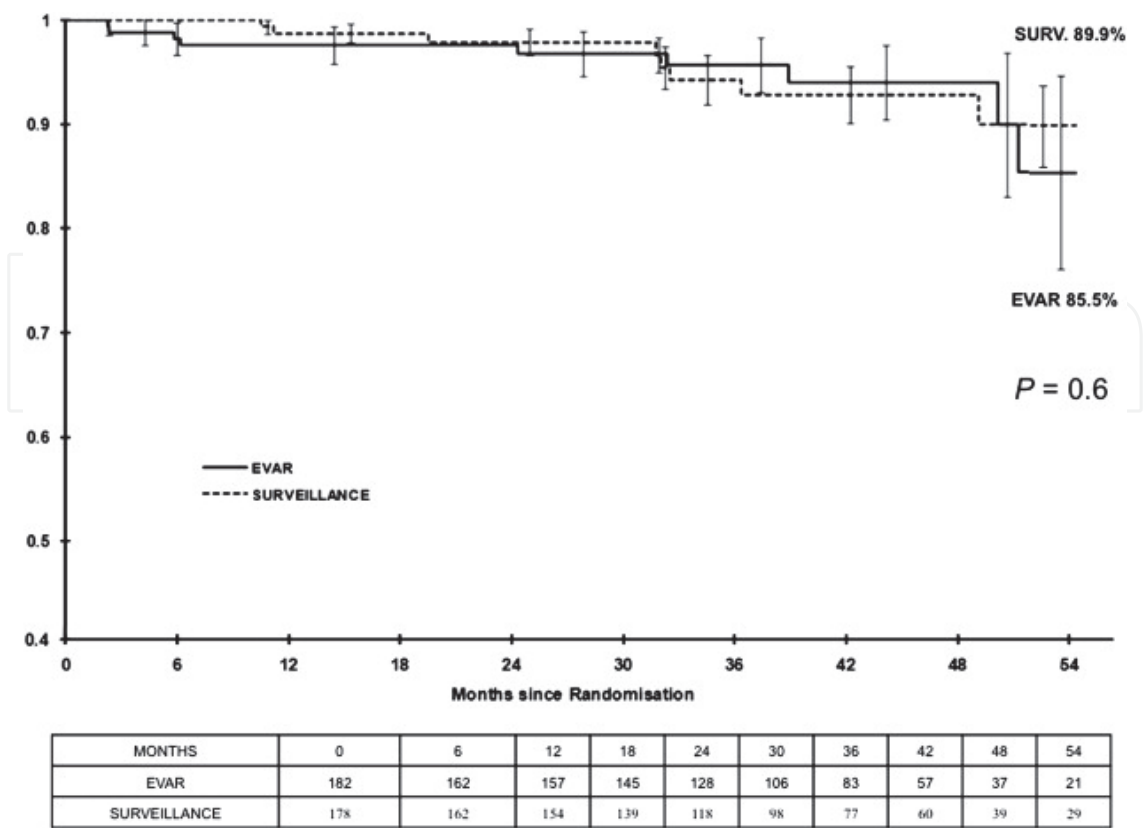


Fig. 4. Kaplan–Meier estimates of survival at 54 months from time of randomisation in EVAR versus Surveillance groups.  $P = 0.6$ . Numbers at risk are shown. CAESAR trial<sup>41</sup>. From: Cao P; DeRango P, Verzini F, Parlani G et al. Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR) trial: results of a randomised controlled trial. *Eur J Vasc Endovasc Surg.* 2011; 41(1): 13-25.

4. Open versus endovascular repair of AAA

Ever since its inception, EVAR has offered the promise of reducing the perioperative morbidity and mortality which has been associated with open elective repair. By the end of last century, data from EVAR registries such as RETA <sup>43</sup>and EUROSTAR <sup>44</sup> suggested that endovascular repair, although safe was associated with an immediate complication rate in addition to events such as endoleak and device migration which mandate lifelong surveillance and in a group of patients re-intervention. As with any new or emerging technology or intervention the case for primacy of EVAR over open repair in terms of perioperative mortality rate, post operative complications and cost effectiveness needs to be made using good quality evidence. A number of trials with a similar design have been commissioned in order to compare the outcomes following EVAR and open repair of AAA in patients who are anatomically suitable to undergo endovascular repair and fit to undergo open repair. These include the Dutch Randomised Endovascular Aneurysm Management (DREAM) <sup>45,46</sup>trial, EVAR-1 Trial (United Kingdom) <sup>47</sup>, ACE trial (France) <sup>48</sup> and Open Versus Endovascular Repair (OVER) of abdominal aortic aneurysms trial (United States)<sup>49</sup>. The DREAM trial which was the first to report its results enrolled 351 patients between November 2000 and December 2003 from 24 centres in the Netherlands and 4 centres in Belgium. This study focused on short term combined mortality and morbidity outcomes<sup>45</sup>. It

reported a significantly lower operative mortality and severe complication rates in the EVAR group compared to the patients who had been randomised to open repair. At 2 years follow up aneurysm related mortality following EVAR was still significantly lower than open repair (2.1% versus 5.7%) however after 2 years of follow up there was no significant difference in the overall survival rates or freedom from moderate to severe complications between the two groups. The conclusions drawn from this trial was that there was a significant reduction in early morbidity and mortality following EVAR compared to open aneurysm repair but this difference is not sustained past 2 years<sup>45,46</sup>.

EVAR-1 trial was a multicentre RCT which was conducted in 37 hospitals in the UK. It randomised 1252 patients with large AAA to either open or endovascular repair. Unlike the DREAM trial, EVAR-1 was designed to perform a comparison of long term survival, graft durability, quality of life and hospital costs associated with open repair and EVAR in addition to comparing short term mortality and morbidity between the two groups<sup>47</sup>. They reported a significantly lower in perioperative morbidity and mortality following EVAR. Four years after randomisation, all cause mortality was similar between the two groups, although there was a persistent reduction in aneurysm related mortality in the EVAR group,(Figure-5)<sup>47</sup>. After 12 months there was no difference in quality of life scores between the two groups with a greater number of complications and re-interventions at 4 years in the EVAR arm of the study. The hospital costs of EVAR were 25-percent higher than open repair<sup>47</sup>.

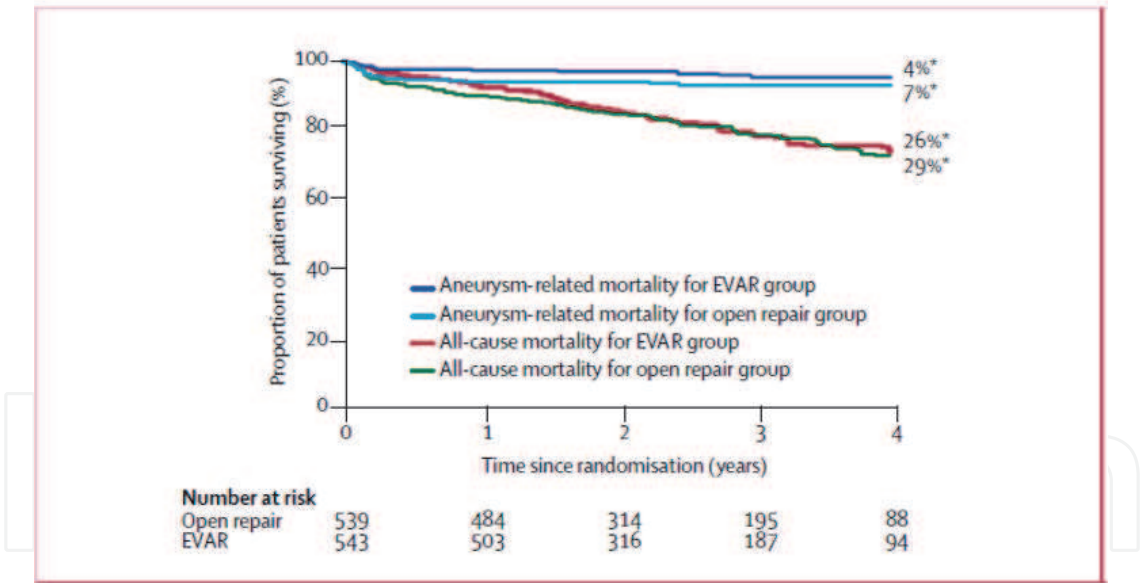


Fig. 5. EVAR-1 Kaplan-Meier survival curves comparing aneurysm related and overall mortality between patients who have been randomised to open elective and endovascular (EVAR) repair of AAA (EVAR-1 trial)<sup>47</sup>. From: EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 2005; 365(9478): 2179-86.

The OVER trial is a RCT which included 42 Veterans Affairs medical centres in the United States. It randomised 881 patients who had AAA with a greater than 50 mm in maximal diameter, an iliac aneurysm greater than 30mm in diameter or rapid sac expansion, to elective open repair or EVAR. The preliminary results from this study indicated that the

EVAR group had significantly lower 30-day mortality as well as all cause mortality<sup>49</sup>. After a mean follow up of 1.8 years the complication rate was not significantly different between the two groups nor was the secondary reintervention rate. As in the DREAM trial, the reintervention following EVAR was mainly due to a device related complications whereas the commonest reason for reintervention following open repair was for incisional hernia<sup>46,49</sup>. Early results from the ACE trial suggest similar early mortality benefit following endovascular repair which is lost after medium term follow up<sup>48</sup>.

Some subgroups of patients such as those who have significant co-morbidities such as cardiovascular or respiratory disease, octogenarians and women with AAA, require an individualised approach and revised criteria for the management of AAA. From its inception EVAR has provided the promise of repairing AAA in patients in whom open repair poses a high risk. Therefore armed with the knowledge that smaller AAAs are best managed by a policy of watchful waiting, EVAR appeared to be an ideal modality for the management of patients with larger AAAs which are anatomically suitable for endovascular repair, have a reasonable predicted longevity but are unfit to undergo open repair. The EVAR-2 trial was designed to answer this question. EVAR-2 trial was a randomised controlled trial of 338 patients who had an AAA with a maximum diameter of greater than 5.5cm and their aneurysm morphology was anatomically suitable for EVAR, but were medically unsuitable to undergo open repair. Primary endpoint was all-cause mortality, with secondary endpoints of aneurysm-related mortality, health-related quality of life, postoperative complications, and hospital costs<sup>50</sup>.

The 30-day operative mortality in the EVAR group was 9.0-percent and the no intervention group had an annual rupture rate of 9.0-percent per year. Aneurysm related mortality in the patient population was 13-percent and all cause mortality after 4 years of follow up was 64-percent <sup>50</sup>.

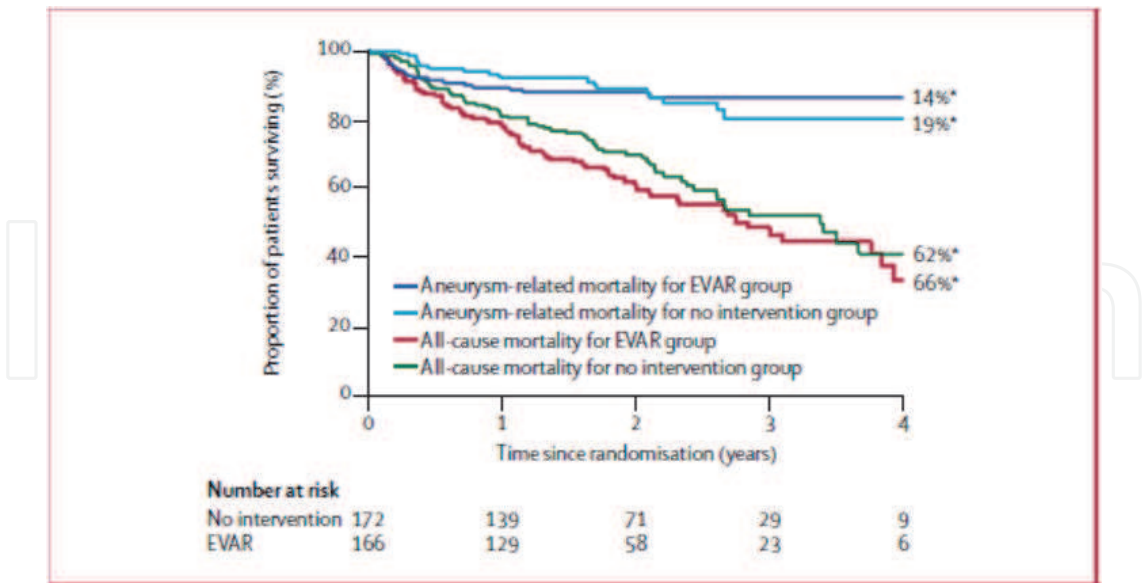


Fig. 6. Kaplan-Meier curves comparing aneurysm related and overall mortality between patients who have been randomised to EVAR and no intervention group (EVAR-2 trial)<sup>50</sup>. From: EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005; 365(9478): 2187–92.

There was no significant difference in all-cause mortality between the EVAR group and the no intervention group (hazard ratio 1.21, 95% CI 0.87–1.69). There was no difference in aneurysm-related mortality (Figure-6) <sup>50</sup>. A policy of early endovascular repair was significantly more expensive than expectant management and was associated with a higher complication and reintervention rate. There was no difference in quality of life scores between the two arms of the study<sup>50</sup>. Therefore the conclusion drawn by the authors was that this population of patients are best served by conservative treatment. Clearly the design of such a study provides one difficulty and that is the definition of not fit for open AAA repair is subject to clinical opinion and may be related to factors that do not affect patient's longevity. The other group of patients are those with one organ morbidity such as respiratory disease or border line medical fitness, who have a large AAA and favourable anatomy for endovascular repair. Therefore clinical judgement is exercised in the application of results of EVAR-2 trial.

## 5. Medical treatment of patients with AAA

In addition to risk of growth and rupture, patients with AAA are at risk from other cardiovascular events by the virtue of their age, medical co-morbidities and male preponderance of AAA. Medical management of patients with known AAA follows two parallel but different aims, reducing cardiovascular event rates perioperatively and during follow up in addition to aneurysm specific therapy which is aimed at slowing aneurysm growth and reducing the risk of rupture<sup>51-53</sup>.

Hyperlipidaemia, a known modifiable risk factor in the development of cardio-vascular disease, can be treated with the use of drugs such as the statins (3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors). Patients with AAA are known to be at high risk of cardio-vascular disease as well as increased risk of cardio-vascular complications following AAA repair <sup>54</sup>. Statin therapy has been associated with improved survival due to decreased risk of cardio-vascular complications, in both open and endovascular repair <sup>54-58</sup>. Although the primary mechanism of statins is in reducing low density lipoproteins and total cholesterol levels along with increasing levels of high density lipoproteins, other protective non lipid mechanism may be at work. These so called pleiotropic effects describe a diversity of cellular events which have an effect on several components of the arterial wall, including: endothelial cells; smooth muscle cells; platelet function, monocytes and macrophages, which together help to modify the inflammatory process in the vessel wall. Statins have been shown to be beneficial in the secondary prevention of coronary heart disease even in those patients with normal lipid profiles<sup>59-60</sup>.

Matrix Metallo Proteinase-9 (MMP-9) expression is closely linked to aneurysm formation in animal models. In vitro experiments have shown that addition of Cerivstatins to human organ cultures from AAA reduces tissue levels of both total and active MMP-9 in a concentration dependent manner. Evans et al reported significantly reduced MMP-9 levels in excised tissue obtained from the aneurysm sac at the time of the aneurysm repair in patients who had been started on statins 3-weeks preoperatively compared with controls<sup>59</sup>. Schouten et al monitored 150 patients with small AAAs for 12 months and reported a reduction in the aneurysm expansion rate in patients receiving statin therapy<sup>60</sup>. In an observational study of 130 patients under surveillance, Sukhija reported no aneurysm expansion in 75 patients who were on statin therapy over a 2 year follow up period<sup>61</sup>. Schlosser et al in an analysis of the results of a large observational cohort study which



involved 5057 patients with vascular disease (Second Manifestation of ARterial disease (SMART) study) and included 230 patients with small AAA revealed an independent association between statin therapy and reduced aneurysm growth rate. This reduced growth and rupture rates were independent of serum lipid values<sup>62,63</sup>.

Over the years there has been some interest in  $\beta$ -blockers, both to slow the growth rate of AAA and to reduce perioperative morbidity from cardiovascular events. The benefit was postulated partly due to their haemodynamic properties and partly due to the effect of  $\beta$ -blockers on matrix proteins. In a trial reported by Lindholt and colleagues the use of Propranolol did not reduce the rate of expansion of AAA, admittedly in the treatment arm of the study the compliance was poor with only 22-percent continuing on Propranolol by 2-years<sup>64</sup>. Another trial which was carried out in Canada came to a similar conclusion owing to poor patient compliance in the treatment arm of the study<sup>65</sup>.

In the last 15 years there has been significant interest in using peri-operative  $\beta$ -blockade as a means of increasing myocardial oxygen delivery thereby reducing the risk of perioperative myocardial infarction and death. Mangano et al randomised 200 patients who were undergoing major elective non-cardiac surgery to either receive Atenolol or placebo. This was started before the induction of anaesthesia. Patients with evidence of congestive cardiac failure, systolic blood pressure of less than 100mmHg or pulse rate of less than 55 beats /minute, 3<sup>rd</sup> degree heart block or broncho-spasm were excluded. This treatment was continued for 6 months postoperatively. They reported a significant reduction in cardiovascular event rate and death from cardiac causes<sup>66</sup>.

Poldermans and colleagues performed a similar study in patients undergoing elective aneurysm or infrainguinal arterial reconstruction. They screened 1351 patients for cardiac disease using Dobutamine stress testing, 173 patients had a positive test of whom 59 were randomised to receive Bisoprolol and 53 placebo<sup>67</sup>. They also reported a significant reduction in non fatal cardiac events as well as cardiac death. In these patients  $\beta$ -blockade was started at least a week in advance of the operation and they were screened for bradycardia and hypotension preoperatively<sup>67</sup>.

POISE was a large international randomised controlled trial of the use of extended release Metoprolol in patients undergoing non-cardiac surgery, the study randomised 8351 patients to either receive Metoprolol or placebo which was started 2-4 hrs before surgery and continued for 30 days. They reported a significantly reduced risk of myocardial infarction in the Metoprolol group but at the expense of higher mortality and stroke rate in the treatment arm of the study<sup>68</sup>. Similarly, Yang et al randomised such patients undergoing major vascular surgery, not already  $\beta$ -blocked, to dose adjusted Metoprolol or placebo 2 hours prior to surgery and until discharge or maximum of 5 post-operative days, and found no protective effects of  $\beta$ -blockade in terms of 30 day myocardial infarction and death rates<sup>69</sup>.  $\beta$ -blockade did result in significantly more episodes of bradycardia and hypotension. In light of these findings the American Heart Association guidelines regarding perioperative  $\beta$ -blocker therapy in patients undergoing non cardiac surgery have been altered to be more cautious and circumspective (Table-)<sup>70</sup>.

In a large observational study, Hackham et al have shown that the use of Angiotensin Converting Enzyme Inhibitor (ACE<sub>I</sub>) therapy taken 3-12 months prior to data analysis significantly reduced the risk of rupture from AAA, independently of blood pressure<sup>71</sup>. This data was obtained from a large administrative database of 3379 patients with ruptured and 11947 with non ruptured AAA. Other anti-hypertensive medications had no such effect<sup>71</sup>. Interestingly, patients who had stopped ACE<sub>I</sub> therapy prior to admission were more likely

to present with ruptured AAA<sup>71</sup>. The effect of ACE<sub>i</sub> on expansion of AAA is still equivocal, with some studies demonstrating no protective effect of ACE<sub>i</sub> therapy<sup>72-73</sup>. Thompson et al in a recent observational study of 1269 patients with small AAA who were followed up for a mean of 3.4 years, reported a significant reduction in aneurysm growth rate as a result of ACE inhibitor therapy<sup>72</sup>. The follow up data from UK small aneurysm trial does not support the above finding<sup>74</sup>.

Infection with Chlamydiae pneumonia has been postulated as a risk factor for AAA expansion, as the organism has been isolated from atherosclerotic plaque and the walls of AAA<sup>75,76</sup>. Three small trials have aimed to elucidate the effect of the antibiotics Doxycycline and Roxithromycin in AAA growth, two of which have shown reduced aortic expansion associated with treatment<sup>77,78</sup>, whilst another one by Baxter and colleagues showed no effect of doxycycline on aortic diameter<sup>79</sup>. These three trials were limited by their small numbers. In addition administration of Doxycycline has been shown to suppress MMP-9 in both human and animal studies<sup>79-81</sup>, suggesting that the reduction in aneurysm expansion rate with administration Doxycycline may be mediated through a mechanism which is independent from treatment of Chlamydiae pneumoniae infection.

To date there is no conclusive evidence that any medical therapy is associated with a reduction in aneurysm growth or risk of rupture. However diagnosis of AAA provides a forum for instituting appropriate secondary prevention therapies, which will reduce morbidity and mortality in the peri-operative period as well reduce long term cardiovascular risk. There is some evidence that instituting some of these treatments such as statin therapy, ACE inhibitors may well have an effect on aneurysm growth and rupture rates.

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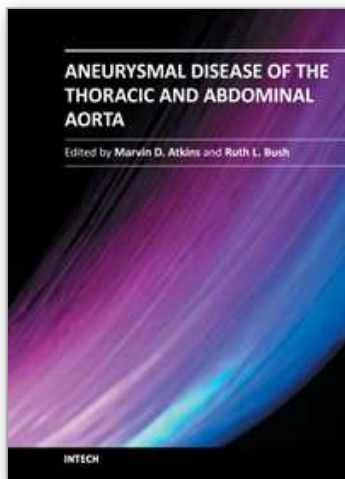


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## **Aneurysmal Disease of the Thoracic and Abdominal Aorta**

Edited by Dr. Ruth Bush

ISBN 978-953-307-578-5

Hard cover, 226 pages

**Publisher** InTech

**Published online** 16, December, 2011

**Published in print edition** December, 2011

The first successful open surgical repair of an abdominal aortic aneurysm was in 1951 by Dubost and represented a tremendous milestone in the care of this challenging disease. The introduction of endovascular repair in 1991 by Parodi furthered the care of these patients by allowing for lower morbidity and mortality rates and also, enabling surgeons to extend surgical treatment to patients traditionally deemed too high of a surgical risk. This new book on Aortic Disease covers many interesting and vital topics necessary for both the practicing surgeon as well as a student of vascular disease. The book starts with background information on the evolution of aortic management from traditional open surgical repair to modern endovascular therapies. There is also a chapter covering the data supporting current treatment modalities and how these data have supported modern management. Also, the use of endovascular means for care of the challenging situation of ruptured aneurysms is discussed. In addition to management of abdominal aneurysm, there is a chapter on treatment of aneurysms of the ascending aorta. Along with surgical treatment, one must also understand the molecular basis for how blood vessels remodel and thus, the role of cathepsins in aortic disease is elucidated. Lastly, chapters discussing the perioperative management of radiation exposure and ultrasound-guided nerve blocks as well as the need for high-quality postoperative nutrition will lend well to a full understanding of how to management patients from presentation to hospital discharge. We hope you enjoy this book, its variety of topics, and gain a fuller knowledge of Aneurysmal Disease of the Thoracic and Abdominal Aorta.

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Reza Mofidi and Stuart A. Suttie (2011). The Evidence for Management of Abdominal Aortic Aneurysms: Lessons Learned from Randomised Controlled Trials, Aneurysmal Disease of the Thoracic and Abdominal Aorta, Dr. Ruth Bush (Ed.), ISBN: 978-953-307-578-5, InTech, Available from:  
<http://www.intechopen.com/books/aneurysmal-disease-of-the-thoracic-and-abdominal-aorta/the-evidence-for-management-of-abdominal-aortic-aneurysms-lessons-learned-from-randomised-controlled>

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