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EDUCATIONAL ARTICLE

Medical Management of Abdominal Aortic Aneurysm

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Medical management of patients with abdominal aortic aneurysm (AAA) is required for several different reasons. Since these patients have an increased risk of cardiovascular death therapy to reduce cardiovascular events is essential. Treatment is in line with the medical management of coronary artery disease including smoking cessation, statins and anti-platelet therapy. Some of these therapies also will slow aneurysm growth. Currently there is no proven focused therapy that reduces aneurysm growth, but the emerging strategies are discussed. Medical management also is required to reduce peri-operative risks and stabilise endovascular aneurysm repair. Whilst some of the therapies targeting cardiovascular risk reduction may be helpful, other emerging strategies are discussed.

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Introduction

Randomised trials have suggested that screening for abdominal aortic aneurysm (AAA) in at risk populations can reduce related mortality.^{1,2} The principal group likely to benefit are middle aged and elderly male smokers.³ The introduction of ultrasound screening will add to the number of AAA already identified by incidental imaging, in particular those of small diameter.^{4,5} In the Aneurysm Detection And Management study (ADAM) and a Dutch primary care screening programme >90% of the small AAAs identified measured a maximum diameter of <55 mm.^{4,5} The management of these small AAAs is usually conservative. However, the identification of an AAA also has implications for mortality and morbidity secondary to associated atherosclerosis.^{6,7} Patients with AAA

are at increased risk of cardiovascular events.^{6,7} Women with AAA may be at particularly high risk, their death rate being twice that of the age-sex matched population, even after successful AAA repair.⁸ The medical management of patients with AAA needs to be tailored to address these aspects, in addition to monitoring AAA progression in order to decide about open or endoluminal repair, but evidence from randomised trials is limited (Fig. 1).

Strategies for Cardiovascular Risk Reduction

There have been no randomised trials of cardiovascular risk reduction in patients with AAA, so that current recommendations mostly derive from risk reduction trials in patients with other cardiovascular disease and observational studies (often retrospective) of patients with AAA. The most important modifiable risk factor for AAA in those with screen-detected AAA is cigarette smoking.⁹ Population studies indicate that smoking is associated with a relative risk of 5 for the presence of AAA. Smoking is associated with a marked increased risk of morbidity and mortality from a large range of other conditions, including ischaemic heart disease, stroke, lung cancer and

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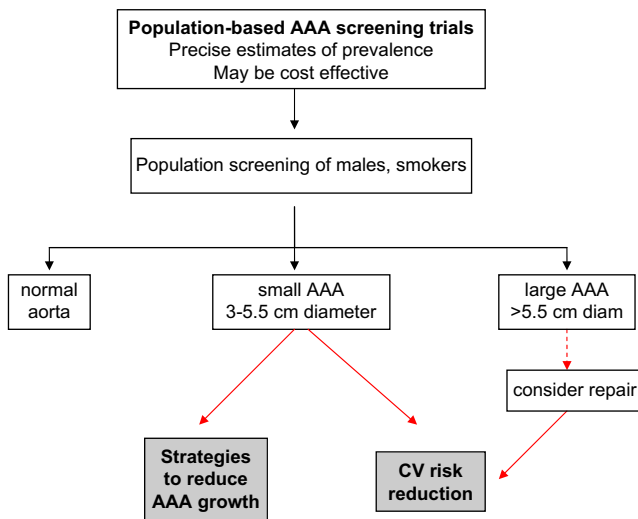


Fig. 1. Pathways for medical management indicated by solid red arrows. Interrupted red arrow indicates a pathway where medical management remains to be clarified in large randomised trials.

emphysema.¹⁰ Nicotine replacement therapy and counselling have been demonstrated to improve the rate of smoking cessation significantly and newer treatments include bupropion and varenline.¹¹ Smoking cessation trials are problematical, often of small size with limited follow-up. However, smoking cessation programmes are likely to have an important accessory role for patients with AAA.

Dyslipidaemia and hypertension are less powerful risk factors for AAA. The control of lipids and blood pressure in patients with AAA is important in reducing mortality in this group. The use of statins has been associated with an improved survival after AAA repair, with a more than 3-fold reduction in risk of cardiovascular death associated with statin usage, HR 0.3 [95%CI 0.2–0.6] $p < 0.001$ in a retrospective single centre series and a similar risk reduction in the EUROSTAR registry.^{12,13} Since patients with AAA have an increased risk of cardiovascular events and death, the results of the Heart Protection study would suggest that all AAA patients should receive statin therapy, irrespective of serum cholesterol concentration.¹⁴ The preferred first line drug for the treatment of hypertension in most of these older patients is an angiotensin converting enzyme (ACE) inhibitor.¹⁵ All these issues have been dealt with in depth in previous reviews in this series.^{16,17} Of greater worry is the problem that a number of studies indicate that management of lipids and blood pressure is often sub-optimal in patients with AAA by comparison to those presenting with coronary artery symptoms.¹⁸ Lloyd GM *et al.* have shown that patients visiting

a vascular surgery outpatient clinic before or after AAA repair are being sub-optimally treated with regard to current guidelines.¹⁹ Specifically, only 41% with an indication for statin treatment have actually received this therapy, and many others have not had a recent plasma lipid measurement. Similar results have been demonstrated for other pharmacological interventions including anti-platelet agents, ACE inhibitors and beta blockers. There is increasing awareness that the intraluminal thrombus may have a role in AAA progression,²⁰ but the likely benefit of anti-platelet therapy on AAA progression has not been investigated prospectively. Nevertheless anti-platelet therapy should be an important aspect of general cardiovascular risk reduction in the patient with AAA. Aspirin, in low doses (75 mg daily) remains the drug of choice for most patients, with clopidogrel being reserved for the aspirin intolerant. Most of these recommendations are exemplified in case study 1.

The development of specialist vascular physicians and appropriate risk reduction clinics are important mechanisms to improve management of these patients. A number of non-modifiable risks for AAA, including male gender, age and genotype impact on the development and outcome of AAA and with improved understanding of these it is hoped that in the future risk modification programs can be directed in a more individual way.

Peri-operative Medical Therapy for Those Undergoing AAA Repair

Medical therapy to reduce cardiovascular risk is particularly critical around the time of operative intervention to repair AAA when the mortality for endoluminal and open surgery are approximately 2 and 5% respectively.²¹ The main cause of mortality is perioperative cardiac events. In most centres patients are stratified based on cardiac history with those at high risk for cardiac events undergoing further imaging (see earlier review in this series). β -Blockers have been shown to improve peri-operative cardiac morbidity and mortality by 10-fold following major vascular surgery in the 10% of patients at highest cardiac risk.²² However, similar benefit was not observed in those at lower risk.²³ Another small randomised trial in vascular surgical patients indicated that statin therapy reduced the combined endpoint of cardiac events and mortality and this view is supported by larger non-randomised cohort studies of patients undergoing AAA repair; these and other studies of peri-operative statin use have been included in a recent systematic review.²⁴ In patients taking statins, the incidence of myocardial infarction or stroke within 30 days of surgery was only 3.7%

compared with 11% in those not taking statins, adjusted hazard ratio 0.24 [95% CI 0.11–0.54]. Larger randomised trials are required to definitely show a benefit of perioperative statin use.²⁴ Case study 2 discusses the peri-operative medical management of AAA.

Ruptured AAA

It might be considered that medical management has no place in this condition. However, pre-operative resuscitation guidelines should address the issue of hypotensive haemostasis.^{25,26} There is evidence from haemorrhagic trauma that mortality is reduced if pre-operative fluid resuscitation is limited to maintaining blood pressure at below normal levels. With a practice of hypotensive haemostasis, some have demonstrated excellent results for endovascular repair of ruptured AAA, with 30-day operative mortality reported to be as low as 11%.²⁷ Although, the selection of good prognosis patients for this approach may partially explain the favourable outcomes.

Strategies to Reduce AAA Growth

It is likely that therapies aimed at reducing cardiovascular events in patients with AAA will also slow aneurysm growth. Smoking has been associated with AAA progression in a number of studies.²⁸ Associations between hypertension and dyslipidaemia with AAA growth have been difficult to assess due to varying definitions of these conditions, concurrent treatment and study power.²⁹ Pathological studies of end stage human biopsies and those performed in animal models have demonstrated the importance of inflammation, proteolysis and vascular smooth muscle cell loss in AAA.³⁰ The development of specific drug therapy targeted at AAA growth has engendered relative little interest from pharmaceutical companies. Given the cost, uncertainty and delay involved in developing medication from first principles most investigators have studied drugs in present use. The only large randomised controlled trial investigating drug therapy for AAA assessed the β blocker propranolol.³¹ Due to side effects 42% of patients discontinued treatment and by intention to treat analysis therapy did not reduce AAA growth rate and significantly impaired quality of life.³¹ There are several smaller randomised trials of antibiotics, with AAA growth rate as the primary outcome measure. Animal, *in vitro* and limited clinical studies provides some evidence to support the value of a number of presently utilised other medications discussed below.

Antibiotics and MMP inhibitors

The antibiotic groups of tetracyclines and macrolides have been shown to decrease the activity of MMPs in cell and explant culture. Macrolides are also used in the treatment of *Chlamydia Pneumoniae*, an infection that has been associated with various atherosclerotic conditions including AAA. Doxycycline, a tetracycline, and the macrolide, roxithromycin, have shown some promise to decrease the expansion of aneurysms in small randomised controlled trials.^{32–34} However, sample sizes and follow-up were limited in these studies. Much larger randomised trials with long-term, standardised patient follow up will be necessary before these treatments can be evaluated properly. Perhaps it is pertinent to consider why drugs with greater selectivity for MMPs have not been used to target reduction of AAA growth, if MMPs have such a pivotal role in the pathogenesis of AAA. Selective inhibitors of MMPs have been developed, particularly with a view to preventing metastasis in cancer, but problems with drug design, lability and toxicity have frustrated progress of this new class of drug.³⁵

Statins

This class of drug inhibits 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase. The primary action, pleiotropic effects and benefit in reducing cardiovascular events have been described in detail in an earlier review in this series.¹⁶ As a result of their proven benefit in reducing cardiovascular events in patients with atherosclerosis statins are being increasingly used in patients with AAA. A number of the pleiotropic effects of statins also would be expected to reduce AAA progression. No randomised clinical trial of statins has focused on cardiovascular events in patients with AAA. However, two recent ultrasonographic surveillance studies of small AAAs have reported the association of statin use with an almost 50% reduction in AAA growth.^{36,37} Unfortunately it is impossible to know whether this association simply reflects another factor linked with statin indication or the effect of the medication itself. The increasing awareness that patients with peripheral artery disease benefit from statins means it is unlikely that a sufficiently powered randomised trial can now examine the benefit of this medication for AAA. To exemplify, a small randomised trial, closed prematurely because of difficulties in identifying patients not taking statins.³⁸ Even with low recruitment this trial showed that simvastatin reduces by 40% matrix

metalloproteinase-9 (MMP-9) concentration in the AAA wall.³⁸ The MMPs are considered to be pivotal enzymes in the progression of AAA and in cell culture studies and animal models statins have been demonstrated to favourably modify proteolytic enzyme balance through reductions in MMP 1, 2, 3 and 9 and promotion of TIMP-1 and decrease proinflammatory cytokines (TNF- α , IL-1 β and IL-6), whilst simvastatin has been demonstrated to reduce aortic dilatation in elastase induced AAA mouse and rat models associated with inhibition of inflammation and MMP-9.

Angiotensin Converting Enzyme (ACE) inhibitors

Angiotensin II has a multitude of effects that have been linked to progression of atherosclerosis and AAA development in addition to hypertension.¹⁷ Recently the association of concurrent medication with admission for AAA was examined retrospectively in an enormous Canadian database.³⁹ The investigators reported an association between ACE inhibitor use and protection from ruptured AAA. However, given the range of medications and risk factors that have to be allowed for in this type of analysis it is impossible to be sure this is a definitive association and not simply a result of multiple statistical analyses.⁴⁰

Improving the Durability of Endovascular Repair

The main cause of failure following endovascular repair of AAA is failure to adequately exclude the weakened aortic wall from the circulation associated with continued aortic expansion. Approximately 20% of patients require re-intervention for this problem within 4 years of the primary procedure.⁴¹ At present there are no recognised drug therapies which have been demonstrated to improve durability of EVAR. Since the main causes of failure to completely exclude the aneurysm are anatomical unsuitability for EVAR and graft failure it might be considered that medical therapy has a small part to play in improving outcome. However, strategies that inhibit aortic destruction may be particularly helpful in this group in which partial off-loading of the pressure on the aortic wall already has occurred. In a recent prospective study of patients undergoing endovascular AAA repair it was noted that post-operative plasma concentrations of MMP-3 and -9 were predictive of endoleak, suggesting that therapies targeting aortic weakening may be useful in this group of patients.⁴²

Studies Identifying Novel Targets for AAA Therapy

Animal studies have identified a range of other medication strategies which have been demonstrated to reduce AAA development mostly targeting oxidative stress, proteolysis and inflammation.²⁹ Most of these investigations have focused on attempts to reduce development or slow progression of aneurysms in animals receiving the medication of interest. A recent study reported the use of a c-Jun N-terminal kinase inhibitor to induce regression of AAA in mice which already had established aneurysms.⁴³ The investigators supported this work with studies suggesting the importance of c-Jun N-terminal kinase in AAA development. Whether medications of this type targeting pathology peculiar to AAA can be developed for human use with an appropriate safety profile depends on a number of factors in particular whether pharmaceutical companies are willing to invest the substantial funds required.

Issues to Address in Randomised Clinical Trials of AAA

Natural history studies of small AAA have identified a number of findings which significantly impact on the development of a randomised controlled trial. Firstly, changes in maximal aortic diameter are slow. Mean aortic diameter increases are reported to be between 1 and 3 mm/year in ultrasound surveillance studies.^{28,44–47} These changes are within the inter-observer measurement error reported for ultrasound.²⁸ The primary factor demonstrated to influence growth rates is initial aortic diameter and therefore it is tempting to limit an AAA medication trial to patients with aneurysms of over 40 mm in maximum diameter. However, conservative estimates of intervention rates for 40–54 mm AAAs are 40% at 3 years based on two trials.^{48,49} Intervention rates for these size aneurysms are likely higher in most centres since many clinicians intervene at aortic diameters <55 mm. Thus future trials of small AAA management are best focused in patients with initial aortic diameter under 45 mm. Trials of these size aneurysms require long follow-up and accurate aortic imaging in order to assess medication value. In this regard entry and exit CT with aortic volume and maximum orthogonal aortic diameter is likely to be valuable. The calculation of mean aortic diameter changes for a treatment and control group is complex, particularly when a threshold diameter for intervention is included.²⁵ In addition growth is neither regular nor linear and complex statistical modelling is necessary to produce unbiased estimates of AAA growth.

Future Directions: Local versus Systemic Therapy and Biomarker Directed Therapy

Since AAA often is a focal condition it would be attractive to have a locally applicable medical therapy rather than systemic treatment which may have effects on many other organs. The combination of a locally applied therapy with other interventions such as endoluminal grafting or stenting would be a possible means of reducing the requirement for re-intervention. These issues are beginning to be investigated in experimental models of AAA. Since natural history studies of small AAAs have emphasised that growth is variable both between and within patients over time,²⁸ there is a need to develop biomarkers to identify patients requiring targeted therapy to minimise AAA growth. A large number of serum tests and genetic markers are presently being investigated as biomarkers to predict AAA behaviour, however, at present these markers have generally not been found to have sufficient accuracy in modelling AAA behaviour.²⁹ The application of proteomic and genomic techniques to large multicentre cohorts of AAA patients is expected to advance the development of such biomarkers.

Case study 1

Mr X is a 68 year old man identified to have a 4.1 cm AAA in a screening program. The patient admits to being a smoker for the last 40 years. On examination he is noted to have a blood pressure of 180/90 mm Hg. What are the priorities in the medical management of this patient?

The principal priority is to reduce the risk of cardiovascular events since the risk of AAA rupture is low:⁶

1. Control of blood pressure: Strong consideration should be given to Angiotensin Converting enzyme inhibitors given the suggestive evidence for their benefit in reducing AAA growth and their recommended first line use in hypertension.^{15,39}
2. Statins: Good evidence supports the value of this medication in this patient group even in the absence of hypercholesterolaemia.^{12–14,16}
3. Smoking cessation: Medication and counseling to help quit smoking is valuable.¹¹
4. Anti-platelet medication: Aspirin or clopidogrel are of proven benefit in reducing cardiovascular events.
5. AAA surveillance: The above measures may slow AAA expansion, but ultrasound surveillance at yearly intervals is required.

Case study 2

Mr Y is a 70 year old man in which incidental imaging has identified a 6.5 cm AAA. The patient has a history of hypertension, previous myocardial infarction, and chronic emphysema. A decision is made to proceed to endovascular AAA repair. What are the priorities in the medical management of this patient?

The principal priority is to reduce the risk of peri-operative events:

1. Cardiovascular events: Strong consideration should be given to the peri-operative use of β blockers, to titrate the pulse rate down to less than 70 bpm pre-operatively, given the level 1 evidence of reduction in cardiac events with this approach.²² Continued statin use and ACE inhibitors may also be helpful.²⁴
2. Optimisation of respiratory status is likely to be valuable, incorporating chest physiotherapy and bronchodilators. Consideration of the use of regional or local anaesthetic may be appropriate depending on the severity of respiratory impairment.

Following discharge the principal priorities are maintaining management of cardiovascular risk and surveillance of the endoluminal repair.

Conclusions

AAA remains one of the very few common cardiovascular disorders without randomised trials addressing the issue of risk reduction and no formal guidelines for medical therapy. Application of treatments to reduce cardiovascular risk in line with accepted guidelines for coronary artery disease is needed now. Whilst some of these treatments also may have beneficial effects to slow aneurysm expansion, there remains an urgent need for more targeted therapy to reduce AAA growth, although the studies needed to validate any such novel treatments will be complex and require prolonged patient follow up.

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