# Role of medical intervention in slowing the growth of small abdominal aortic aneurysms

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## ABSTRACT

Abdominal aortic aneurysm is a common—but preventable—cause of death in elderly men; 4% of men at the age of 65 years have an aorta >3 cm in diameter. Continued expansion runs the risk of aneurysm rupture, a condition that is fatal in all but 15% of individuals. A national screening programme has commenced that aims to reduce the number of deaths from aneurysm rupture by 50%. The programme will detect a large number of men with a small aneurysm who are not in imminent danger of rupture, but who will join a regular ultrasound programme of surveillance. If the aneurysm expansion rate could be reduced, fewer men would be at risk of aneurysm rupture, and fewer would need elective aneurysm repair. A considerable amount is known about the pathophysiology of aneurysm growth. Exploring pharmacological means to delay or reduce aneurysm growth could make a considerable contribution to any screening programme. A number of case control studies have suggested that some antihypertensive drugs, non-steroidal anti-inflammatory drugs, antibiotics, and statins may reduce aneurysm growth rates. Data from controlled studies have provided less secure conclusions. Use of these medications, together with lifestyle modification such as stopping smoking, could become standard advice to men with a small aortic aneurysm. Further studies of novel agents and larger controlled trials of existing drugs are warranted.

Recent population screening has demonstrated that abdominal aortic aneurysms (AAA) are common in elderly men.[1] The main complication of AAA is rupture. This is, however, a relatively infrequent occurrence (<1% per annum) while the maximal diameter of the aneurysm remains <5.5 cm.[2] Larger aneurysms carry an increasing risk of rupture, which is often a fatal event.[3 4] Current practice is that prophylactic repair is offered to patients with an AAA >5.5 cm, in order to prevent rupture. The mortality rates of elective repair are variable depending on the institution and technique used; however, estimates from recent audit studies in the UK suggest they may reach 7% in unselected populations.[5] The risk of repair, therefore, exceeds the risk of rupture in small aneurysms.

In the absence of a screening programme, most AAA are detected by routine examination or investigation of a patient for an unrelated pathology. Relatively few present with symptoms or acute rupture. Population screening has been demonstrated to reduce aneurysm related mortality[1] and may potentially elongate the asymptomatic phase of the disease by detecting AAA at an earlier stage. This latent interval could be targeted for non-invasive intervention that may slow down the rate of aneurysm growth and delay, or even negate the need for operative repair.

In order to manage growth of small AAA effectively using non-invasive medical interventions, it is important to have realistic goals of their therapeutic effect. The mean growth rate of small AAA is 0.26 cm per year, although this increases with aneurysm diameter.[6] If a medical intervention can reduce growth rate by at least 50% then the time taken for a 4.0 cm aneurysm to reach 5.5 cm would increase from approximately 5 years to over 10 years.[7] Consequently intervention could be delayed by 5 years in a patient with a small AAA. Therefore, reduction of growth rate by at least 50% would constitute an effective therapeutic goal for potential medical intervention.

This article briefly reviews the pathophysiology of AAA development and growth, and relates this to potential therapeutic interventions that may reduce growth rates and so delay rupture or the need for repair. The evidence for these interventions is discussed.

## PATHOPHYSIOLOGY OF AAA GROWTH

If the pathological processes underlying the development of degenerative aneurysms are understood, then their manipulation by drugs or the avoidance of damaging agents might prove protective.

The evidence for these pathological processes is derived from a combination of the examination of human aortic material obtained from autopsy and surgical repair procedures, as well as several well established animal models of AAA growth. There appear to be three important and interrelated processes in AAA growth: chronic inflammation, remodelling of extracellular matrix proteins (elastin and collagen), and depletion of vascular smooth muscle cells (VSMC).[8]

Chronic inflammatory processes are evident throughout the aortic wall with inflammatory cells found most commonly in the tunica media and adventitia of AAA.[9–12] The majority of infiltrates contain invading monocytes and macrophages, plasma cells, B cells, and T cells.[10 11] The infiltrates are also abundant with pro-inflammatory cytokines such as prostaglandin E2 (PGE2) and interleukin 6 (IL6).[13] Furthermore, concentrations of circulating cytokines, such as interferon γ, have been associated with AAA expansion and rupture.[14] Many factors may initiate the inflammatory response. For example, atherosclerosis may extend into the tunica media or breakdown products from the extracellular matrix may initiate local chemokine production. Alternatively, a local immunological or even autoimmunological response may occur, triggering chronic inflammation.

Interestingly, anti-inflammatory cytokines are also found within tissue from AAA, indicating that the inflammatory reaction is a balance of both detrimental and reparative processes. Therefore, in order to target inflammation pharmacologically, it is important to consider whether pro-inflammatory mechanisms can be blocked and anti-inflammatory mechanisms enhanced, as well as possibly targeting the mechanisms that initiate inflammation. Finally, inflammatory infiltrates also contain reactive oxygen species and nitrogen derived free radicals, suggesting oxidative stress may contribute to the pathogenesis, and offer another route for intervention.[15]

Some authors have suggested that the inflammatory response in AAA is caused (or initiated) by underlying bacterial infection. Chlamydia DNA or protein has been isolated from the aortic wall of patients with an AAA.[16–19] Furthermore, the presence of antibodies against *Chlamydia pneumoniae* in the serum of patients with AAA has been associated with both more rapid aneurysm expansion and the need for surgical intervention.[20 21] This is another potential site for intervention, although Chlamydia could simply be an innocent bystander in aortic tissue.

Remodelling of extracellular matrix proteins primarily involves structural failure of elastin in the media, with compensatory collagenous fibrosis in both tunica media and adventitia. Considering that elastin and collagen are both very stable proteins, the remodelling process must require increased degradation by elastases and collagenases. Research has identified that matrix metalloproteases (MMPs) are likely candidates for this role as they are produced abundantly in inflammatory processes, and in particular within tissue from AAA.[22] Specific candidates include MMP-2, MMP-7, MMP-9, and MMP-12. Many small animal studies have illustrated the importance of MMPs in aneurysm formation and growth.[23] Therefore another potential pharmacological target is to control MMP activity to maintain the structure of the extracellular matrix proteins.

The counterbalance for MMPs are tissue inhibitors of metalloproteinases (TIMP). These act to provide homeostasis in protein turnover, by reducing the degradation of tissue proteins. Theoretically, enhancing the activity of TIMP could be another pathway to protect aortic tissue by controlling the damaging effects of MMPs. Little is known currently about their potential role in preventing aortic expansion.

As previously noted, increased collagen deposition can initially compensate for elastin degradation by withstanding increased tensile strength and thus preventing rupture.[23] Physiological production of extracellular matrix proteins can occur from VSMC. When under strain, for example within an aneurysm, VSMC can proliferate and produce more extracellular matrix proteins, especially collagen. Therefore depletion of VSMC may be an overlooked cause of aneurysm growth, as insufficient collagen deposition occurs to prevent rupture. The exact mechanism of depletion is unknown, however, if VSMC proliferation could be encouraged pharmacologically then this may reduce the growth rate of AAA.

Recent advances in experimental research and genetic studies have enabled examination of large numbers of subjects with an AAA to seek genetic determinants that might increase or decrease growth rates. Several studies have identified haplotypes with increased AAA growth rates, but this research is in its infancy, and large population studies will be required before definitive answers are available.[24]

## POTENTIAL INTERVENTIONS

### Smoking cessation

AAA are seven times more likely to develop in smokers than non-smokers.[25] Indeed, this propensity for the development of AAA is retained in ex-smokers and most closely linked with duration of smoking as opposed to quantity.[25] When specifically considering growth rates of aneurysms, several studies have identified a correlation between active smoking and increased rate of expansion.[26–29] Furthermore, in the Small Aneurysm Trial, the risk of AAA rupture was higher in those who continued to smoke than in those who had stopped.[30] The exact mechanism by which smoking affects aneurysm development and growth has not yet been delineated. However, evidence from a mouse model suggests it is not related to activation of the remodelling process driven by matrix metalloproteinases.[31] Regardless, there appears to be sufficient evidence that smoking cessation may slow aneurysm growth and reduce the risk of rupture.

### Antihypertensive drugs

#### β-blockers

Hypertension is commonly regarded as a significant risk factor for the development of degenerative aneurysms. Unsurprisingly, therefore, a great deal of interest has surrounded the potential role of antihypertensive agents in reducing blood pressure and limiting aneurysm growth. The most commonly studied drugs are β-blockers. Evidence for the concept that controlling blood pressure affects aneurysm expansion is not yet convincing, though aneurysm growth was demonstrated to be significantly attenuated by propranolol treatment in a hypertensive animal model.[32] Yet results from clinical studies vary. A mixture of prospective and retrospective cohort studies have demonstrated a fairly consistent tendency towards reduced aneurysm growth rate with β-blocker use.[28 33–36] However, in only two of these studies did this difference reach significance.[28 36] Nonetheless, pooled data from these studies, from a meta-analysis by Guessous and colleagues, did suggest a significantly attenuated growth rate with β-blockers.[37] These results are, however, not borne out by three small randomised controlled trials that demonstrated no significant protective effect from propranolol.[38–40] Of note, low compliance in these studies may question the validity of their conclusions; one study reported a 42% withdrawal rate due to side effects of the drug.

#### Angiotensin converting enzyme inhibitors

The role of angiotensin converting enzyme (ACE) in vascular remodelling is well documented.[41] Indeed, elevated values of angiotensin II have been isolated in human aneurysm tissue.[42] Furthermore, various ACE and angiotensin II receptor polymorphisms have been associated with AAA development in cohort studies.[43–46] In a rodent model of AAA formation produced by elastase infusion, the inhibitory effects of ACE inhibitors were clearly demonstrated.[47 48] These effects appear to occur independently of angiotensin II receptor 1 and 2 functions. Although the exact mechanism by which ACE inhibitors restrict aneurysm growth is yet to be fully elucidated, activation of circulating leucocytes appears to play an important role.[41]

As yet there are no controlled clinical trials concerning ACE inhibitors and aneurysm growth. A population based case–control study examined 15326 patients over the age of 65 who were admitted with either non-ruptured or ruptured AAA over a 10 year interval. Analysis of their drug history revealed that patients taking an ACE inhibitor were significantly less likely to have a ruptured AAA.[49] In the same study, there was no significant effect seen with β-blockers, angiotensin receptor blockers, calcium channel blockers or thiazide diuretics.

### Statins

In humans, statins are commonly and effectively used to decrease low density lipoprotein (LDL) cholesterol concentrations. More importantly perhaps, statins have been found to have significant pleiotropic effects.[50] These include a reduction in pro-inflammatory mediators, such as IL6, as well as inhibition of MMPs.[51] Theoretically, this could reduce the inflammatory process and help stabilise the extracellular matrix composition of AAA. Again, using the elastase infusion model of aneurysm formation, simvastatin has been demonstrated to reduce the rate of aortic dilatation and aneurysm development.[52 53] In both studies this was associated with reduced levels of MMP-9 expression in the aortic wall.

A retrospective study, analysing ultrasound monitoring of AAA diameter over 3 years in 150 patients, suggested that the use of statins was associated with significantly reduced growth of small AAA.[54] In a second study of similar size, statins appeared to have a small but non-significant effect on reducing AAA growth.[55] Statin use was, however, correlated significantly with a reduced need for aneurysm repair and aneurysm rupture. Again no controlled clinical data exist, and it is unlikely that any prospective studies will ever be justified since it is now recommended that all subjects with an AAA should be taking a statin for its cardiovascular protective effects.

### Antibiotics

The putative use of antibiotics in reducing the rate of AAA growth is based on both their antimicrobial and anti-inflammatory effects.

#### Doxycycline

Tetracycline based antibiotics, such as doxycycline, have been found to inhibit MMPs and experimental AAA formation in various rodent and murine models.[56 57] A small scale, randomised, placebo controlled pilot study subsequently demonstrated that doxycycline at safe serum concentrations significantly reduced the growth of small AAA and was well tolerated in patients.[58] Treatment was for 3 months and follow-up restricted to 18 months. Although, in the placebo group, more rapid expansion was associated with higher titres of *Clostridium pneumoniae*, doxycycline treatment had no affect on these levels. In support, a phase II prospective study has shown that, after an initial 6 months of doxycycline administration, small asymptomatic AAA did not increase in diameter.[59] No long term data are yet available.

#### Roxithromycin

The effect of this macrolide antibiotic on AAA expansion has been investigated in a small randomised clinical trial.[60] Ninety-two patients recruited from a screened population were randomised to 28 days of either roxithromycin or placebo. In the subsequent 12 months of ultrasound surveillance, a significant 44% reduction in aneurysm expansion was seen; however, this difference tailed off over the next 5 months of surveillance.

#### Non-steroidal anti-inflammatory drugs

Inflammation is a well recognised part of the pathogenesis of aneurysms. Elevated concentrations of PGE2 and cyclooxygenase 2 (COX2) have been isolated in human aortic tissue compared with normal controls.[61] Indomethacin has also been demonstrated to prevent elastase induced AAA in rats.[62] This action appears to be mediated by inhibition of COX2 and consequent reduction in concentrations of PGE2 and MMP-9 in the aortic wall.[63]

In a small case–control study, patients who regularly took indomethacin had an almost 50% reduction in AAA growth rate compared to patients who never used a non-steroidal anti-inflammatory drug (NSAID).[64] The same authors analysed biopsy material from human AAA and found a high expression of PGE2, which was directly linked to decreased proliferation of VSMC. Larger, randomised studies are again required to elucidate further the possible beneficial effect of these drugs.

## CONCLUSIONS

Much of the positive data regarding medical intervention and aneurysm expansion is from retrospective analysis of case–controlled cohorts. These results are, therefore, vulnerable to bias. Although a number of controlled trials have been undertaken, they are small and follow-up is limited. In addition, the period of treatment is often surprisingly short. Remodelling of the vascular wall during aneurysm development is clearly a complex process representing chronic injury. It is difficult to conceive how, as in the case of the antibiotics discussed above, a short course of only a few weeks could affect AAA expansion over the next 10 years. Furthermore, many of the other proposed therapeutic agents are commonly used in arteriopaths for their general cardiovascular benefit. This compromises their further investigation, since placebo comparison is no longer ethical.

Results from animal models and examination of explanted human tissue suggests that MMP-9 might act as a common pathway in an inflammatory, remodelling process that results in aneurysm expansion. Indeed, MMP-9 concentrations are affected by many of the agents described above. Future research should concentrate on other mediators of this inflammatory cascade. A number of other agents exist that have currently only been tested on human tissue samples or small animal models of AAA. Vitamin E, an antioxidant, has been shown to block induction of AAA in mice, suggesting that inhibition of oxidative stress in aneurysm tissue may be a possible target

### Main messages

- The new NHS aortic aneurysm screening programme will identify a large number of men with a small aneurysm.
- Slowing the growth of these small aneurysms will reduce the risk of rupture, delay the need for elective interventions, and reduce the cost of the programme.
- Although a number of medications show promise (ACE inhibitors, doxycyclin, NSAIDs), large controlled trials are needed before they can be adopted as standard.

### Current research questions

- More research is needed about the growth rates and their variation in small abdominal aortic aneurysms.
- A number of existing agents that showed promise in case–control studies need to be tested in large controlled trials.
- Using what is known about the causes of aortic aneurysm, new agents should be sought that influence aneurysm progression.

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for reducing AAA growth.[65] In addition, it has been shown that inhibition of c-Jun N-terminal kinase (JNK), an enzyme highly activated in aneurysm tissue, not only prevented development of AAA in mice, but even caused a reduction in the diameter of established AAA.[66]

In the UK a National Screening Programme is currently being rolled out for men over the age of 65 years (http://aaa.screening.nhs.uk/ accessed 14 October 2009). This will identify a large number of men with small AAA. The potential cost saving in slowing growth and delaying AAA repair could be very large if the rate of surgical intervention could be reduced. Currently a small number of treatments hold promise (ACE inhibitors, doxycycline, NSAIDs), and no doubt others will emerge.[67] These could be administered along with advice about smoking cessation and statin therapy plus aspirin for their cardioprotective effects, and become standard advice for men with a small AAA. Evidence does, however, need to be supported by large controlled trials with satisfactory follow-up that includes operative intervention as an end point, not just rate of expansion.

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## Multiple choice questions (true (T)/false (F))

### 1. Population screening for AAA in men has been shown to:

A. Reduce aneurysm related mortality
B. Reduce all cause mortality
C. Reduce ruptured AAA by 20%
D. Reduce ruptured AAA by 50%
E. Reduce ruptured AAA by 90%

### 2. The following are associated with increased rate of AAA expansion:

A. Obesity
B. Increasing age
C. Female sex
D. Hypertension
E. Smoking

### 3. There is good level I evidence that the following drugs are associated with a reduced rate of AAA expansion:

A. β-blockers
B. Angiotensin inhibitors
C. Antibiotics
D. Statins
E. Non-steroidal drugs

*See page X for answers*

## APPENDIX

**Answers to the questions on *Role of medical intervention in slowing the growth of small abdominal aortic aneurysms* by D G Cooper, J A King, J J Earnshaw, on page xx.**

1. A (T); B (F); C (F); D (T); E (F)
2. A (F); B (F); C (F); D (T); E (T)
3. A (F); B (F); C (F); D (F); E (F)

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## Notes