This is the accepted version of a chapter which will appear in the 3rd edition of *Mechanisms in Vascular Disease*

Abdominal aortic aneurysm pathology, and progress towards a medical therapy

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Abstract

Abdominal aortic aneurysm (AAA) is an important cause of mortality in the older adults due to aortic rupture. Surgical repair (either by endovascular or open surgery) is the only treatment for AAA, however, large randomized controlled trials suggest that elective repair of small (<55mm) AAAs does not reduce all-cause mortality. Most AAAs detected through screening programs or incidental imaging are too small to warrant immediate surgical repair. Such patients are managed conservatively with repeated imaging to monitor AAA diameter, however, 60-70% of AAAs managed in this way eventually grow to a size warranting elective surgery. Discovery of a drug therapy which effectively slows the growth of small AAAs has significant potential to improve patient welfare and reduce the number of individuals requiring elective surgery. This chapter reviews the current understanding of AAA pathogenesis gained through assessment of rodent models and clinical samples. Previous AAA drug trials are also discussed. Finally, the challenges in developing AAA drugs are outlined.

Introduction

An aneurysm is frequently defined as an abnormal, focal dilatation within an artery which causes vessel diameter to exceed 1.5 times the expected size, and in some cases has a natural history of progressive enlargement and eventual rupture (1, 2). The infra-renal aorta is the most common site of aneurysm formation in humans (3). An infra-renal aortic diameter of ≥30mm is usually used to diagnose an abdominal aortic aneurysm (AAA), although other definitions have been suggested, for example those based on normalizing aortic diameter to body surface area (2-5). AAA is

usually asymptomatic, but can be readily diagnosed through the use of imaging such as ultrasound or computed tomography. There are, however, no currently available medications which effectively slow AAA growth and open surgical or endovascular aneurysm repair (EVAR) are the only treatments for AAA (4). Four large randomised controlled trials and subsequent meta-analyses have demonstrated that elective repair of asymptomatic AAAs with diameters smaller than 55mm (regardless of method used) does not improve patient survival (6-10). Importantly, most asymptomatic AAAs detected through population screening, or incidental imaging are smaller than 55mm and current guidelines recommend that such patients should be treated conservatively through cardiovascular risk management, and regular imaging assessments to monitor AAA growth (11). Surgery is only recommended when AAA diameter exceeds 54mm in men, 50mm in women, or if the AAA becomes symptomatic (11). Conservative management of small asymptomatic AAA has been associated with reduced health-related quality of life (detailed in (12, 13)). Moreover the majority of AAAs managed in this way expand to a size where surgical repair is required (8, 14). For example, ~65% of patients with AAAs measuring 40-55mm within the conservative arm of the United Kingdom (UK) Small Aneurysm Trial had undergone surgical repair within 5 years of recruitment (6). Due to the absence of an effective treatment for small asymptomatic AAAs there is significant interest in identifying non-surgical therapies capable of slowing the growth of small AAAs, and this is reflected by an increase in the number of drug trials conducted over the last decade. The aim of the current chapter is to summarise how results from epidemiological studies and laboratory studies have contributed to current understanding of AAA pathophysiology. In addition this chapter includes a discussion

of current and past clinical trials examining potential medical therapies to limit small AAA growth.

AAA epidemiology

Findings from a recent study suggest that the global death rates attributable to AAA rose by 12% in the 20 years between 1990 and 2010 to 2.8/100,000 (15). The highest rates of death attributable to AAA were observed in higher income countries, with Australasia, Western Europe and North America having the highest mortality rates of 8.38/100,000, 7.68/100,000, 6.11/100,000 and respectively (15, 16). Reports from screening studies and epidemiological studies in a number of developed countries in contrast suggest that AAA prevalence is declining. The national screening programmes run in the UK and Sweden have reported that the prevalence of AAA is markedly lower than anticipated (observed prevalence of approximately 2.0% in 65 year old men, compared to 5-7% found in earlier studies) (17-20). Moreover, reductions in the rates of hospitalisation and death attributable to AAA have been reported for a range of countries including Australia, New Zealand, and England and Wales (20-22). Reasons for the falling AAA prevalence remain incompletely understood, although several independent studies have linked this to a decrease in smoking rates (22, 23). Whatever the reasons, the potential negative impact of declining AAA prevalence on the financial viability of screening programmes has been raised (20). Some (not all) clinical trials have shown that ultrasound screening programmes in men aged ≥65 years reduces AAA-related mortality by limiting deaths due to AAA rupture (24, 25). A meta-analysis has suggested that screening focusing solely on older men with a history of smoking (making up 69% of the assessed population), would account for 89% of the reduction

in AAA-mortality expected from a screening programme including all men aged 64-75 years (24). Following from this, the US Preventative Services taskforce has suggested that screening be restricted to individuals considered to be at high risk (e.g. persons with a history of smoking, and/or family history of AAA), in an attempt to improve cost-effectiveness (26). In contrast, AAA screening in the UK and Sweden is offered to all males in the year of their 65th birthday, and it has been suggested that this may not be financially viable in the light of falling AAA incidence (27). Final findings from an Australian clinical trial demonstrated that a AAA screening program of all men aged >65 years is unlikely to be effective within Australia (28), but there is more support for such a program in New Zealand (29). Of note, Māori people are hospitalised for AAA repair at a significantly earlier age than those of European ancestry (difference of 8 years of age at presentation between these two populations), and Māori women have increased risk of developing AAA than their European counterparts (relative risk 1.56 [95% confidence intervals 1.37-1.79]) (30). Thus, any AAA screening program in New Zealand would need to be tailored in order to appropriately meet the needs of specific high-risk groups.

Risk factors identified from epidemiological studies

The precise initiating factors for AAA development remain unclear, however, epidemiological studies have consistently associated male sex, old age, Anglo-European race, tobacco smoking, family history and prior diagnosis of atherosclerosis-associated cardiovascular disease with increased risks of being diagnosed with an AAA (12, 31). Smoking has been shown to be the strongest

modifiable risk factor for AAA (32). Approximately 20% of AAA patients report having a family member who has also received an AAA diagnosis (12), highlighting the importance of inherited factors in AAA pathogenesis (detailed below). Individuals with a first-degree relative affected by AAA are at ~2-fold higher risk of developing AAA, when compared to those with no family history of AAA (33, 34).

AAA pathogenesis

Current understanding of AAA pathogenesis is built upon evidence provided by epidemiological studies, clinical data and samples collected from AAA patients, and pre-clinical models that mimic features of the human disease. Collectively, these data suggest that AAA is a multifactorial disease which is caused by a combination of environmental, genetic, molecular and biological factors. A range of animal models for AAA have been described, however those in mice have been most widely reported, most likely due to their well-characterised genomes and the relatively low cost of small compared to large animal research (detailed in (35-37) and Table 1). AAA is most commonly induced in rodents through subcutaneous delivery of angiotensin-II (dyslipidaemic strains are more susceptible to AAA induction), infusion into the aortic lumen of elastase, adventitial application of calcium phosphate or chloride to the infra-renal aorta, or transplant of decellularised aortic xenografts (35, 36). Several modifications to these established models aiming to incorporate known clinical risk factors including smoking, dyslipidaemia and hypertension have been suggested as a means to more closely mimic the human disease (see (35, 38)). Animal models have been used to investigate the pathophysiology of AAA and to test potential therapeutic interventions. This chapter includes a discussion of the key

mechanisms implicated in AAA pathogenesis, incorporating findings from the study of patients and rodent models.

Tissue samples

Examination of aortic biopsies recovered from patients demonstrates that AAA leads to pathological changes to all layers of the aortic wall (Figure 1 and discussed in detail in (4)). This is in contrast to atherothrombosis which appears to involved less marked changes in the media and adventitia (4). AAA samples recovered from patients and animal models demonstrate marked inflammation, which involves cells involved in the innate (notably mast cells, macrophages, neutrophils and dendritic cells), and adaptive (e.g. B and T cells) immune response (38). Chronic inflammation has been implicated in the destruction of the aortic extracellular matrix owing to the secretion of matrix degrading enzymes (particularly matrix metalloproteinases), oxygen-derived free radicals and pro-inflammatory cytokines from activated immune cells. This in turn is believed to induce an inflammatory phenotype in the vascular smooth muscle cells within the aortic wall with subsequent apoptosis (39). Microarray and bioinformatic analyses have demonstrated that the gene signatures of AAA biopsies recovered from both patients and angiotensin-II infused mice are significantly enriched for pro-inflammatory molecules, inflammatory cell markers and proteinases (40-43). Interventional studies in rodent models have also provided data supporting a pathological role for inflammation in AAA development and progression (detailed in (38)). For example, depletion of B, T or mast cells has been reported to limit AAA severity in some, but not all commonly employed mouse models. In contrast, mice deficient in T-regulatory cells develop more severe AAAs than

controls, whereas increasing T-regulatory cell numbers is reported to reduce AAA pathology (38). Most AAAs have areas of calcification, although the role of calcification in AAA pathogenesis is controversial (4).

The degree to which atherosclerosis contributes to AAA pathogenesis remains controversial. Atherosclerosis is a common co-morbidity in AAA patients, and traditional theories have suggested that AAA is simply an end-stage manifestation of atherosclerosis arising from dysregulated positive remodelling in response to arterial stenosis, or loss of vascular smooth muscle cells from the tunica media as a consequence of intimal thickening (discussed in detail in (38)). Other observational evidence suggests that atherosclerosis and AAA may in fact be distinct diseases. Diabetes, a major risk factor for atherosclerotic disease appears to be inversely associated with AAA diagnosis and AAA growth (44, 45). More recently, genetic studies have identified specific risk alleles for AAA, some of which do not appear to be a risk factor for atherosclerosis-associated cardiovascular disease (see (33, 46, 47)). Furthermore, recent meta-analyses have suggested that AAA growth rates may be slower in patients with concurrent lower limb occlusive disease (48-50). The mechanisms underpinning this association remain unclear, with some studies suggesting that localised haemodynamic perturbations resulting from distal arterial occlusion may slow AAA growth (see Dua and Dalman 2010 for further reading (51)). The UK Small Aneurysm Trial investigators reported that lower ankle-brachial pressure indices were associated with slower AAA growth, although this relationship was not independent of potential confounders (52). Other studies have reported that athero-occlusive disease within the carotid and coronary arteries may be associated

with slower AAA growth, albeit to a lesser extent than lower-limb atherothrombosis and with considerable inter-study heterogeneity (49, 53).

Most AAA patients have a large non-occlusive thrombus within the aneurysmal sac (54). Owing to close contact with the arterial bloodstream, the AAA intra-luminal thrombus is continually remodelled and its size is closely correlated with AAA sac size (4). Early investigations suggested that the thrombus may play a protective role by shielding the aortic wall from high-pressure blood flow and reducing AAA wall stresses (4, 55). This is refuted by data suggesting that the thrombus contributes to aortic hypoxia, and acts as a secondary site of accumulation of activated platelets and leukocytes which release wall degrading proteases and cytokines, thereby contributing to AAA pathogenesis (54, 56). Studies have reported that mice receiving aspirin, clopidogrel or clotting factor Xa and IIa inhibitors develop less severe AAAs than controls in response to angiotensin-II (35, 57-59). Interpretation of these findings is however complicated by the fact that the angiotensin-II infused model more closely mimics human aortic dissection than AAA. Until recently, few animal models have convincingly replicated the intra-luminal thrombosis seen in AAA patients (although thrombosis has been reported in the xenograft and elastase models), which has made it difficult to elucidate the extent to which this process contributes to AAA pathogenesis (36, 38). This limitation may have been overcome through a new method of inducing AAAs, involving peri-adventitial elastase application, followed by ongoing oral administration of 3-aminoproprionitrile (BAPN) to inhibit collagen cross-linking (60). Reported data suggest that mice treated in this way develop extremely large infra-renal AAAs with marked intraluminal thrombus formation (60).

Blood samples

Analysis of blood samples have suggested that the pathological processes occurring within the AAA wall are reflected in the systemic circulation of patients and experimental animals. A large body of evidence suggests that serum concentrations of a range of pro-inflammatory cytokines, extracellular matrix degrading proteases and extracellular matrix components are significantly higher in AAA patients than controls (see (61-64) for comprehensive reviews). Similarly, chronic turnover of the intra-luminal thrombus is reflected by significantly elevated concentrations of fibrinogen, D-dimer and thrombin-antithrombin III complex in venous blood samples collected from AAA patients compared to non-aneurysmal controls (65). Other studies have highlighted differences in the circulating concentrations of non-protein molecules including small non-coding RNAs and novel lipids in AAA patients compared to non-aneurysmal controls (2, 66). Collectively, these observations have led to the hypothesis that detection of differentially expressed molecules may provide a blood test for AAA, however, to date none of the suggested markers have shown sufficient specificity and sensitivity for clinical use (61-63). Clinically the availability of a blood marker which identified small AAAs most likely to progress would be particularly valuable. While a large number of markers associated with AAA growth have been identified very few have been consistently reported in more than one study (D-dimer is one example; see a previous review for a detailed discussion (64)).

Insight provided by genetic studies

There is evidence for a strong genetic predisposition for AAA (4, 38). AAA heritability is estimated to be >0.7 (i.e. genetic components may explain over 70% of

the risk of developing AAA) (12, 33). Despite this, the genetic loci driving AAA susceptibility are poorly characterised and genome-wide association studies (GWAS), have suggested multiple single nucleotide polymorphisms (SNPs) which may influence the risk of developing AAA. Jones and colleagues recently conducted a meta-analysis, combining data from six independent GWAS, providing a total population of 4,972 AAA cases and 99,858 controls (33). Meta-analysis and subsequent assessment in an independent validation cohort confirmed the association of five previously reported SNPs with AAA diagnosis, and identified a further 4 novel risk loci which were suggested to be specific to AAA (Table 2). AAA-associated SNPs were predicted to influence a range of molecular processes including inflammation, lipid metabolism, gene transcription and protease activity, however network analyses suggested a central role for matrix metalloproteinase-9 in driving these effects (12, 33). It should, however, be noted that the loci identified in this and other analyses have relatively small effect sizes, with each SNP suggested to individually influence AAA risk by no more than ~20% (33). Thus, it seems unlikely that these SNPs alone would fully explain the high degree of heritability seen for AAA. Additional research has suggested that epigenetic modifications may also contribute to AAA risk. Unlike SNPs which are a direct alteration of the encoding nucleotide sequence, epigenetic factors alter gene function through chemical modification or post-transcriptional silencing, which are not reflected by changes to the DNA code (detailed in (2, 34)). These include micro-RNAs (which are a class of small non-coding RNA which have been shown to regulate gene expression at the post-translational level), histone modifications (post-translational modifications to histone proteins which can impact gene expression by altering chromatin structure), and DNA methylation and hydroxylation (which can affect promoter function and

impact on transcription). Studies in animal models and patients have suggested the importance of multiple epigenetic changes in AAA pathogenesis (discussed in (2, 34, 67)). Drugs capable of reversing epigenetic changes have been developed, but are primarily being assessed for their ability to treat cancer. Despite this, the potential cardiovascular benefits for these agents has been suggested, although much of the literature has focused on atherosclerotic disease, with little consideration of AAA (see (68) and (69) for recent reviews).

AAA pathogenesis: Factors contributing to AAA rupture

AAA rupture is thought to occur when the arterial wall becomes too weak to withstand the mechanical pressures exerted by the arterial blood flow (70). To date, the most accepted indicator of rupture risk is AAA diameter; a recent meta-analysis has suggested the annual risk of rupture is 3.5% for AAAs measuring 55-60 mm, 4.1% for 61-70mm AAAs, and 6.3% for those above 70mm (71). It is, however, well documented that some small AAAs can rupture and some large AAAs remain stable suggesting that infra-renal aortic diameter alone does not fully explain a patient's rupture risk (3, 72). There is interest in utilising imaging approaches to characterise the biomechanical forces exerted upon the AAA wall as a means to provide a more specific indication of AAA rupture risk. Several recent studies have demonstrated that calculated wall shear stress is significantly higher in ruptured AAAs when compared to intact AAA controls (70). Known risk factors for AAA rupture, including complex arterial geometry, current smoking and small body habitus, are also reported to unfavourably influence the biomechanical parameters of the AAA by increasing wall stress, or reducing aortic wall strength (73, 74). It should be noted,

however, that experimental biomechanical models are underpinned by assumptions, regarding aortic wall thickness and variations in blood pressure, which limit their current clinical utility, and focus on more patient-specific models is warranted to improve translational potential (72, 75).

Meta-analysis of individual patient data has highlighted that current smoking (compared to those who have quit, or never smoked), female sex and increased mean arterial blood pressure and pulse pressure are associated with significantly higher risk of AAA rupture after adjusting for AAA diameter (adjusted hazards ratios [95% confidence intervals] 2.02 [1.33-3.06]; 3.76 [2.58-5.47]; 1.32 [1.11-1.56] and 1.11 [1.02-1.22] respectively; Hazards ratios for blood pressure parameters relate to an increase of 10mmHg) (45). The same analysis identified a significant inverse relationship between body mass index (BMI) and AAA rupture (hazards ratio [95% confidence interval] 0.93 [0.88-0.99] per kg/m^2 after adjusting for AAA diameter). The authors did not demonstrate any relationship between commonly prescribed cardiovascular drugs and reduced rupture incidence (45), suggesting that better understanding of the cellular processes underpinning AAA rupture is needed to identify potential therapeutic targets.

Identifying the molecular pathways leading towards rupture might provide a basis for the development of drugs capable of limiting AAA rupture. It is rarely ethically appropriate to use AAA rupture as an outcome measure for clinical studies, as most patients undergo corrective surgery once their AAA approaches 55mm (50 mm in women) or becomes symptomatic to minimise the risk of rupture (45). Study of AAA rupture in animal models may have relevance for drug development. Aortic rupture is

a common outcome in the angiotensin II rodent model, and has also been reported in the xenograft and elastase models (36, 38). Moran and colleagues, for example, previously reported that mice receiving a kinin B2 receptor agonist showed significantly higher rupture rates in response to angiotensin-II infusion, compared to controls (39). This effect was abrogated following neutrophil depletion, suggesting a pathological role for neutrophils activated through the kinin B2 receptor in accelerating aortic wall destruction (39). More recently, Fashandi and colleagues have described a model which was reported to increase the rate of AAA ruptures and may permit research specifically investigating AAA rupture, however, further validation of this is required (76).

Discovering effective medications for AAA: Current progress in clinical trials.

As detailed in the sections above, epidemiological and biochemical findings implicate multiple factors including hypertension, inflammation, extracellular matrix remodelling and thrombosis in AAA pathogenesis and complications. A logical hypothesis is therefore that an effective therapeutic will inhibit one or more of these processes, and this is reflected in the design of previous and current clinical trials seeking to identify novel drugs to treat small AAAs. Often, the selection of drug to test was informed by findings from epidemiological association studies, and/or results from basic science experiments utilising human tissues, cell lines or animal models of AAA. To date, relatively few trials have been conducted in this field, possibly owing to practical challenges in study design such as slow AAA growth rate resulting in small effect sizes, difficulties in reproducibly measuring AAA size and loss of patients due to requirements for surgical repair (16, 77). Many of the published trials have

assessed potential off-label benefits of already approved medications (so-called 'drug repurposing'), which, if successful can help bypass long and expensive routes to translation associated with *de novo* drug development. On the other hand, this may further complicate trial design as many potential participants may need to be excluded if they are prescribed similar medications as part of their standard care, thereby limiting feasible study sample sizes. Moreover, inter-study heterogeneity in the outcome measures used and the methods used to assess them can complicate direct comparison, subsequent meta-analysis and overall generalisation (78). The remainder of this chapter focused on the reported outcomes from completed randomised controlled trials, the design of ongoing trials, and the insight these have provided into AAA pathophysiology. Examples of clinical trials with reported outcomes, and those currently in progress are provided in Tables 3 and 4 respectively.

Trials assessing anti-hypertensive medications

Early research suggested that AAA severity was significantly less in experimental animals receiving the beta-blocker propranolol compared to controls, associated with an increase in the cross-linkage of collagen and elastin fibres within the aortic extracellular matrix (79-82). These observations were supported by retrospective clinical data which suggested that AAA growth was slower in patients prescribed propranolol, compared to those who were not (83). Several randomised controlled trials have investigated the difference in growth rate of small AAAs in patients allocated propranolol and those receiving placebo (84-87). These studies independently demonstrated no benefit of the drug on AAA growth (see (78) for a

meta-analysis), and reported high rates of adverse events which greatly reduced patient adherence with the trial medication (see Table 3). This was particularly noted in one trial which was terminated due to slow recruitment and high dropout rates (85). Collectively this suggests that propranolol is unlikely to be an effective or practical therapeutic for AAA.

A significant body of evidence from studies conducted in experimental animals and patient populations suggests a pathological role for the renin-angiotensin system in AAA (see (38, 87, 88) for dedicated reviews on this topic). Angiotensin converting enzyme (ACE) has been suggested as a potential therapeutic target for AAA. Bicknell and colleagues recently reported the outcomes of the AARDVARK study, a 3-armed randomised controlled trial which monitored AAA growth over 2 years in groups of patients randomised to receive either perindopril arginine (10mg/day), amlodipine (5m/day) or placebo (89). The three-way design was utilised to test the hypothesis that ACE inhibition may confer therapeutic benefits to AAA, independently of reductions in blood pressure, evidenced by significant reductions in AAA growth in patients receiving perindopril compared to amlodipine. The AARDVARK trial was planned as a pilot study, reflected by relatively small sample sizes in each treatment arm (Table 3), however, presented power calculations suggested that the investigators were adequately powered to detect a 20% difference in AAA growth between the perindopril and amlodipine groups. Study authors reported good patient retention (attrition rate of 4%), and adherence to medication as evidenced by pill counting (>80% for all treatment groups at each timepoint assessed). Systolic blood pressure in patients receiving placebo remained stable during follow-up, but dropped significantly from baseline in those receiving

perindopril or amlodipine for 12 months (mean [standard deviation] difference from baseline -9.5 [13.1] and -6.7 [12] mmHg, respectively, both p<0.001). Despite this, no difference in AAA growth rates was observed between any of the groups. Sensitivity analyses accounting for factors known to influence AAA growth did not change these results (89).

Trials assessing anti-inflammatory agents

Two anti-inflammatory agents have been tested as potential AAA therapeutics. The tetracycline drug, doxycycline, has attracted interest based on a reported ability to suppress inflammation and proteolysis, with potential to preserve the aortic extracellular matrix (detailed in (87, 90)). Studies utilising a range of pre-clinical models (predominantly angiotensin-II, and elastase-infused mice) have independently reported that animals receiving doxycycline develop less severe AAAs than controls (see (91, 92) for examples). Infra-renal aortic biopsies collected from patients randomised to receive doxycycline for 2 weeks prior to open AAA repair showed significantly lower concentrations of CD8+ T-cells, neutrophils and pro-inflammatory markers, than those allocated to placebo (93). These encouraging observations were further supported by a series of pilot clinical studies suggesting that the drug was generally well tolerated and adhered to, and that patients allocated to doxycycline exhibited slower AAA growth rates (94, 95). The Pharmacological Aneurysm Stabilisation Trial (PHAST) was the first large-scale study to directly assess the potential benefits of doxycycline and randomised 286 patients with AAAs measuring 35-50mm to receive active drug (doxycycline 100 mg/day, n=144) or placebo (n=142) for 18 months (96). The authors hypothesised that patients

receiving doxycycline would experience a 50% reduction in AAA growth rate. Presented sample size calculations indicated that the trial was designed to detect this difference with at least 80% power. The study was, however, terminated prematurely following an efficacy interim analysis (conducted after collecting ~75% of anticipated data), which demonstrated no benefit for the drug. Of interest, AAA growth rates were statistically significantly higher in patients receiving doxycycline compared to controls, although the difference between groups was not considered to be clinically relevant (estimated increase in AAA diameter compared to controls: 0.8mm [95% confidence intervals 0.18-1.42] over 18 months, p=0.012, and no increased requirement for AAA repair) (96). The reasons behind this unexpected result remain unclear, and further investigation is ongoing (96).

Mast cells emerged as a potential therapeutic target owing to their presence within aortic biopsies recovered from AAA patients, the demonstrated ability for mast cell secretions to degrade the aortic extracellular matrix (e.g. chymase), and observations that genetic deletion of mast cells, or mast-cell chymase protected against AAA formation in rodent models (97, 98). Building from this, the recent Anti-inflammatory ORal Treatment of AAA (AORTA) trial recruited patients with medium-sized AAAs (infra-renal aortic diameter 39-49mm), to determine the therapeutic potential of the mast cell inhibitor pemirolast (99). The AORTA trial adopted a multi-arm design in which patients were allocated to placebo (n=84), or one of three pemirolast regimes (10, 25 or 40 mg twice daily, n=80, 78 and 84 per group respectively), aimed to identify a dose which effectively slowed AAA growth over a 12 month follow-up period. The primary outcome for this study was the change in AAA diameter from baseline as assessed by standardised ultrasound imaging. The

investigators reported that there was no statistically significant difference in medication compliance, adverse events or drop-out rates between the groups suggesting that the drug was well tolerated. Despite this, there was no significant difference in AAA growth rates between the groups in both intention to treat, and per protocol analyses (99).

Trials assessing dyslipidaemic drugs

The recently published FenofibrAte in the ManagemEnt of abdominal aortic aneurysm-2 (FAME-2) trial assessed the potential for the peroxisome proliferator activated receptor-α ligand fenofibrate to favourably modify AAA pathology following observations within a mouse model that fenofibrate limited AAA severity (100, 101). Mice receiving fenofibrate had significantly lower aortic concentrations of a number of pro-inflammatory proteins including osteopontin than controls, suggesting that fenofibrate was able to blunt aortic inflammation and extracellular matrix remodelling (100-102). Building from this, the FAME-2 study was a double-blind placebo controlled randomised trial to determine whether patients receiving 145mg/day fenofibrate for 6 months would exhibit similar reductions in AAA pathology (102). Primary outcome measures for FAME-2 were changes in serum osteopontin and kallistatin between the groups (103). One-hundred and 40 patients with small AAAs were recruited to FAME-2 (n=70 per treatment arm) in order to fulfil sample size requirements, 3 of whom (~2%) were lost to follow-up. Overall adherence to the trial medication regime was reported as 85%, with no statistically significant differences between the groups (81.4% and 88.6% for those allocated fenofibrate or placebo respectively, p=0.237). Patients allocated fenofibrate demonstrated a significant

reduction in serum triglyceride concentrations after taking the drug for 3 weeks, which persisted for the remainder of the trial, suggesting that an effective therapeutic dose was administered. Despite this, circulating concentrations of osteopontin, kallistatin and other AAA-associated proteins were similar between groups leading the authors to conclude that the drug provided no direct impact on AAA pathophysiology. An important limitation raised by the authors was the fact that peripheral blood samples were examined, and the possibility that fenofibrate may have exerted beneficial effects within the aortic wall could not be dismissed (102). To overcome this limitation, the same group of researchers are currently completing a related clinical trial (FAME), in which patients are allocated to a short course of fenofibrate or placebo prior to scheduled open surgical repair of large AAAs (104). Aortic biopsies collected during surgery will be examined to determine the effect of fenofibrate on AAA pathophysiology, as assessed by the extent of arterial inflammation (such as the number of infiltrating macrophages), and osteopontin concentrations (104).

The FAME study follows a similar design to that of a previously reported small trial assessing the potential benefit of short term statin use in reducing markers of aortic wall proteolysis (55). This study recruited 40 patients who were randomised in a 1:1 ratio to receive either atorvastatin or placebo in the 4 weeks leading to scheduled open AAA repair. The primary outcome measure for the study was the concentration of matrix metalloproteinase-9, and no significant difference for this marker was observed between groups following treatment (median [interquartile range]: 2.29 [1.55-9.79] and 2.70 [1.85-4.46] ng/mg tissue in patients receiving atorvastatin or placebo, respectively; p=0.285) (55). Whilst these data suggest that atorvastatin had

no impact on aortic wall markers, it is difficult to generalise findings from this study as the sample size may have been too small to detect subtle differences between groups. Recruitment for this trial appeared problematic as a large number of potential participants were excluded since they were already receiving a statin, however the researchers were able to fulfil *a priori* sample size calculations. In addition no data regarding adherence to trial medication were presented, and it is therefore difficult to determine whether compliance may have affected the reported outcomes. Of note, a recent meta-analysis has suggested that statins may provide some protection against AAA growth and subsequent rupture although this hypothesis is based on observational data only (105). Current management guidelines recommend that AAA patients should receive statin therapy to reduce the risk of myocardial infarction, stroke or vascular death, rather than limit AAA growth (106).

Current trials

Table 4 details the design of some contemporary trials assessing potential therapies for AAA. At the time of writing, two of these studies have been terminated. One assessing subcutaneous infusion of canakinumab, a monoclonal antibody against interleukin-1 beta was abandoned owing to a lack of efficacy, whilst another comparing the efficacy of aliskerin and amlodipine could not complete owing to a reported inability to recruit sufficient patients (data reported from https://clinicaltrials.gov, accessed 15/10/2018). As with past studies, the ongoing trials are focused on agents aimed to limit inflammation, hypertension or thrombosis. Independent studies investigating the therapeutic effects of doxycycline (at a higher

dose than the previous PHAST trial) and ticagrelor have reported that recruitment is completed, and results are eagerly anticipated (107).

More recently an increasing body of data has suggested that the slower AAA growth observed in patients with diabetes may not be solely attributed to the presence of diabetes, but may also be due to the drugs used to treat diabetes (108). Several independent centres have reported that the prescription of metformin is associated with slower AAA growth, and rates of rupture or surgical repair, whereas this trend is not robust for other commonly prescribed diabetes drugs (109-113). Interpreting these findings is complicated by the fact that all included patients receiving metformin also had diabetes. Thus the degree of protective effect (if any) exerted solely by metformin is difficult to quantify, however, experimental data suggest that non-diabetic rodents receiving metformin appear to be more resistant to AAA formation and subsequent growth, than those receiving control interventions (113, 114). Collectively, this body of evidence has provided stimulus for interventional trials assessing the potential effects of metformin on AAA outcomes in patients who do not have diabetes (115). At the time of writing, one small randomised controlled trial aiming to assess the effects of 12 months of metformin prescription on AAA growth has been announced, and outcomes of this trial are eagerly anticipated (see https://clinicaltrials.gov/ct2/show/NCT03507413).

Interpreting findings from clinical trials

None of the completed clinical trials to date have demonstrated a clinical benefit for any assessed medications, and this likely arises due to multiple factors. Firstly, many

potential therapeutics have been selected based on promising results from investigations conducted in rodent models. Thus the possibility that the lack of translation may be due to inherent biological differences between rodents and humans must be considered. Of note, mice appear naturally resistant to cardiovascular disease owing to key differences in lipoprotein metabolism meaning that significant genetic and/or surgical manipulations are often required to predispose them to AAA formation (35). In addition, AAA development in rodent models is an acute process, but occurs over decades in humans meaning that chronic pathology cannot be easily simulated. Rodent models usually do not include human AAA risk factors such as old age and widespread atherosclerosis which are known to be important in human populations. Haemodynamics observed within the AAA sac of commonly used rodent models have also been shown to differ from those experienced by patients (116, 117). The design of rodent model experiments may also have contributed to the lack of translation as many previous studies have investigated the ability of potential therapeutics to block AAA formation, as opposed to limiting progression of established AAAs which is more representative of the clinical situation (36). Moreover, animal-based studies have not traditionally followed the same rigorous processes required of clinical studies such as presentation of sample size calculations, randomisation of subjects, blinding of assessors to group allocations and detailed statistical reporting, potentially increasing the scope for interpretation bias (118). This limitation is, however, not restricted to AAA research and can be broadly extended across the biological sciences. In recognition of this limitation, the UK-based National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), has proposed a series of experimental and reporting standards, the ARRIVE guidelines, to improve the transparency of *in*

vivo experiments (118). There is growing acceptance of the ARRIVE guidelines within the scientific literature, revealed by an increasing number of journals requesting evidence of compliance as part of the publishing process, aiming to improve the translational potential of findings from pre-clinical models.

In questioning the current lack of success in identifying an effective AAA therapy, the design and conduct of contemporary clinical trials must also be examined. The difference in AAA growth between treatment groups has been the most commonly employed outcome measure for the trials reported to date. Whilst an objective measure of AAA progression, AAA growth is typically slow (trials reporting an average of 1-3 mm/year), and variable between patients. Hypothesised reductions in AAA growth rate attributable to pharmaceutical intervention are therefore extremely subtle, and are potentially within the limits of error for many abdominal imaging techniques (38). This can be partly overcome through the establishment of highly reproducible protocols for AAA size measurement, however large sample sizes and long follow-up periods are also required to improve analytical sensitivity. Despite this, many reported and currently ongoing studies have relatively small sample sizes, and follow-up periods are typically less than 2 years (see Tables 2 and 3). This likely reflects the practical constraints associated with recruiting, and following AAA patients within small catchment areas. Lessons from the past therefore suggest that multi-centre and multi-national trials involving centres with harmonised outcome assessment approaches may be needed to definitively assess therapies into the future (discussed in (77)).

Conclusion

Although AAA prevalence has decreased over the past decade, AAA remains an important cause of mortality in older adults. Surgical repair is currently the only means to treat AAA, however, surgery is costly, associated with peri-operative risks, and has limited long-term durability. Most AAAs identified in high-income countries are below the recommended size threshold for elective surgery but subsequently reach this size during surveillance. Effective AAA drugs would improve patient care and may provide a more cost-effective management. Past clinical trials have not identified any drugs which convincingly limit AAA growth. Challenges in discovering effective AAA drugs include poorly designed pre-clinical studies and clinical trials, difficulties in modelling human AAA in pre-clinical studies and lack of interest from the pharmaceutical industry in drug development in this field. To overcome these hurdles, it is likely that an international collaborative approach will be necessary to ensure that future randomized controlled trials have sufficiently large sample sizes to reliably detect a clinically meaningful outcome.

Learning points

- Important risk factors for AAA include male sex, advanced age, prior or current smoking and a positive family history. Diabetes appears to be negatively associated with AAA diagnosis and growth, however, the exact reasons for this are unclear;
- Elective surgery is the only means to treat AAA but is associated with significant peri-operative morbidity and mortality, and concerns regarding the durability of repair;

- Elective surgery does not improve survival in patients with small (<55mm) AAAs. Patients with small AAAs are managed conservatively through repeated imaging which confers no therapeutic benefit and is associated with decreased health-related quality of life;
- A medical therapy which effectively slows the growth of small AAAs may improve patient care and a large body of work to identify promising drug leads has been conducted;
- To date, no randomized controlled trial has delivered an effective medical therapy for small AAAs. This may relate to difficulties in translating findings from commonly used laboratory models to the patient, in addition to weaknesses in the design of previous trials.

Recommended reading

Detailed discussion on AAA pathogenesis and current medical management approaches can be found in references (12, 38).

A detailed overview of the similarities and differences between AAA and atherosclerosis is found in references (46, 47).

Reference (36) provides a recent systematic review detailing the characteristics of available animal models for AAA research.

An overview of insight into AAA pathology provided by clinical trials is provided by reference (16). *This is supported by recommendations for the standardisation of the design of AAA clinical trials to improve translational potential made in reference* (77).

The current Society for Vascular Surgery guidelines for AAA patient management are provided in reference (11).

Figure legends

Figure 1. Schematic diagram illustrating AAA pathophysiology. Schematic cross section of the aorta that shows normal wall architecture on the left side comprising a mono-layer of endothelial cells, organised layers of vascular smooth muscle cells and elastin filaments within the tunica media, and fibroblasts within the tunica adventitia. This is contrasted by the right-hand side of the figure showing pathological changes typically found in AAA samples. These include intraluminal thrombus, and aortic wall inflammatory cells including macrophages, T-cells and B-cells, and vascular smooth muscle cell senescence and apoptosis.

This is the accepted version of a chapter which will appear in the 3rd edition of *Mechanisms in Vascular Disease*

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Table 1 – Examples and characteristics of commonly utilised rodent models in AAA research (modified from (36, 38))

Model	Similarities to human AAA	Key differences to human AAA	Pros and Coons
Angiotensin II infusion	• Marked aortic inflammation, angiogenesis and proteolysis; • Aortic rupture commonly reported; • Males more susceptible to AAA formation;	• AAA develops predominantly within the supra-renal aorta; • Aortic dilation arises secondary to aortic dissection and intra-mural hematoma;	✓ Subcutaneous implant of angiotensin-II releasing pump is simple and relatively no ✓ Dyslipidaemic mouse strains often develop comorbid atherosclerosis, similar to pa × Significant inter- and intra-strain heterogeneity in response to angiotensin-II; × Models aortic dissection rather than AAA;
Angiotensin II infusion and BAPN feeding*	• Indications of significantly higher inflammatory signalling than standard angiotensin-II model; • AAA rupture occurs in ~80% animals.	• Limited extracellular matrix degeneration, loss of vascular smooth muscle cells and aortic inflammation;	✓ Subcutaneous implant of angiotensin-II releasing pump is simple and relatively no ✓ Reportedly higher incidence of aortic dilatation than traditional angiotensin-II mod × Model may not be suitable to study efficacy of potential drug therapies;
Elastase perfusion (luminal)	• Transmural inflammation elastic fibre destruction and angiogenesis; • Males more susceptible to AAA formation;	• Limited intraluminal thrombosis; • AAA rupture uncommon;	✓ Does not require transgenic strains; ✓ Can be performed in any rodent species; ✓ Generally good inter-animal reproducibility; × Technically challenging surgical procedure; × Limited evidence of longer term progressive aortic expansion;
Calcium chloride or phosphate (adventitial)	• Aortic calcification, inflammation, angiogenesis and proteolysis;	• No intraluminal thrombus formation; • No AAA rupture;	✓ Does not require transgenic strains; ✓ Can be performed in any rodent species; ✓ Generally good inter-animal reproducibility; × Severity of aortic dilatation limited; × Limited evidence of longer term progressive aortic expansion;
Xenograft	• Transmural inflammation, intraluminal thrombus formation and elastic fibre destruction; • Aortic rupture reported after modification of the model;	• Implanted xenographs are decellularised, thus AAA formation involves extracellular matrix alone.	✓ Does not require transgenic strains; × Highly challenging surgical procedure; × Complete loss of cells within the transplanted aorta not representative of human A
Elastase (adventitial) and BAPN feeding*	• Medial elastin fragmentation, medial thinning, influx of T cells to the aorta and matrix metallo-proteases; • Marked intraluminal thrombus formation; • Progressive AAA dilatation over time (reported up to 100 days post-surgery); • AAA rupture reported;	• No evidence AAA propensity is greater in older mice;	✓ Does not require transgenic strains; ✓ Appears to be suitable to study longer term effects of drugs on AAA growth; × Currently not widely studied.

* Note, these are newly described models and require further validation and characterisation (detailed in references (60, 76))

Table 2: Single nucleotide polymorphisms showing significant associations with AAA presence following meta-analysis of GWAS data (adapted from (12, 33))

SNP	Chromosome	Closest gene(s)	Predicted biological function	Minor allele	Major allele	Minor Allele frequency	Odds ratio (95% CI)
rs602633	1	PSRC1 CELSR2 SORT1	Mitosis (PSRC1), plasma membrane associated protein (CELSR2), and lipid metabolism (SORT1)	T	G*	0.199	0.88 (0.84-0.92)
rs4129267	1	IL6R	Inflammation	T	C*	0.370	0.88 (0.85-0.91)
rs10795061[γ]	1	SMYD2	Gene regulation	T*	C	0.337	1.13 (1.09-1.17)
rs10757274	9	CDKN2B-S1/ANRIL	Unknown	A	G*	0.462	0.81 (0.78-0.83)
rs10985349	9	DAB2IP	Tumour suppressor	T*	C	0.195	1.17 (1.12-1.23)
rs9316871[γ]	13	LINC00540	Unknown	A	G*	0.201	0.87 (0.84-0.91)
rs6511720	19	LDLR	Lipid metabolism	T	G*	0.096	0.80 (0.76-0.85)
rs3827066[γ]	20	PCIF1, ZNF335, MMP9	Gene regulation (PCIF1 and ZNF335), and protease activity (MMP9)	T*	C	0.179	1.22 (1.17-1.28)
rs2836411[γ]	21	ERG	Gene regulation	T*	C	0.369	1.11 (1.07-1.15)

* Denotes effect allele – shown odds ratios refer the risk of having an AAA for carriers of the effect allele, compared to those with the non-effect allele. 95% CI: 95% confidence intervals. [γ] SNPs suggested to be specific to AAA. SNP: Single nucleotide polymorphism; PSRC1: Proline and serine rich coiled-coil 1; CELSR2: Cadherin EGF LAG seven-pass G-type receptor 2; SORT1: Sortilin 1; IL6R: Interleukin 6 receptor; SMYD2: SET and MYND domain-containing 2; CDKN2B-S1/ANRIL: CDKN2B antisense RNA1, also known as ANRIL; DAB2IP: DAB2 interacting protein;

LINC00540: Long intergenic non-protein coding RNA 540; LDLR: low-density lipoprotein receptor; PCIF1: Pancreatic and duodenal homeobox 1 C-terminal inhibiting factor 1; ZNF335: Zinc finger protein 335; MMP9: Matrix metalloproteinase 9; ERG: v-ets avian erythroblastosis virus E26 oncogene homologue.

Table 3 – Examples of previous trials assessing medications for AAA (modified from (38))

Trial title and relevant references	Interventions	Duration	No. participants	Effect on AAA growth	Other outcomes and observations
Trials assessing anti-hypertensive agents					
Propanolol for small AAAs (84)	Propanolol (80-120 mg bid) vs placebo	30 months	548	No difference between treatment groups (**primary outcome measure**)	High rates of withdrawal in both medication and placebo groups (39% vs 21%, respectively)
Propanolol (Viborg study) (85)	Propanolol (40 mg bid) vs placebo	24 months	54	No difference between treatment groups (**primary outcome measure**) growth	Trial stopped owing to high drop-out rate (60%) in the propranolol group
Propanolol (Cambridge study) (86)	Propanolol (40 mg/day) vs placebo	Not specified	477	No difference between treatment groups (**primary outcome measure**)	Poor adherence to medication in group receiving propranolol
The AARDVARK trial (89)	Perindopril arginine (10mg/ day) vs amlodipine (5mg/day) vs placebo	24 months	227	No difference between treatment groups (**primary outcome measure**)	No differences in requirement for surgical AAA repair between groups.
Trials assessing anti-inflammatory agents					
The PHAST study (96)	Doxycycline (100 mg/day) vs placebo	18 months	286	More rapid AAA growth in patients receiving doxycycline (**primary outcome measure**)	Trial stopped following interim analysis (75% of data collected), showing futility of medication.
The AORTA trial (99)	Pemirolast (mast cell inhibitor at 10, 25 or 40 mg bid) vs placebo	12 months	326	No difference between treatment groups (**primary outcome measure**)	No difference in adverse event rates between groups. No difference in circulating inflammatory biomarker profiles between treatment arms.
Trials assessing anti-hyperlipidaemic agents					
Statin use in AAA repair (55)	Atorvastatin (80 mg/day) vs placebo	4 weeks	40	Not assessed	No significant inter-group differences in the expression of matrix metalloprotease-9

					(**primary outcome measure**), other matrix metalloproteases or their endogenous inhibitors in aortic wall biopsies taken during open surgical repair.
The FAME-2 trial (102)	Fenofibrate (145 mg/day) vs placebo	24 weeks	140	No difference between treatment groups	No difference in serum concentrations of osteopontin or kallistatin between the groups (**primary outcome measures**)

Table 4 – Examples of current clinical trials assessing potential medications for AAA

Trial and related references[α]	Phase	Interventions	Duration	Target sample size	Primary outcome measure	Recruitment status[β]
Trials assessing anti-hypertensive agents						
ACTRN12611000931976: The TEDY study (119)	4	Telmisartan (40mg/day) vs placebo	24 months	300	AAA growth as assessed by infra-renal aortic volume on CTA.	Active, not recruiting
NCT01904981: The BASE trial	4	Altenolol (50mg/day) vs valsartan (80mg/daily)	Not specified	400	AAA growth (imaging modality not specified)	Unknown
NCT01425242: The PISA study	N/A	Aliskerin (150 mg/day) vs amlodipine (5mg/day)	12 months	NR (actual recruitment: 3)	Change in AAA wall inflammation (assessed by FDG-uptake assessed via PET-CT)	Terminated (insufficient patient recruitment).
Trials assessing anti-inflammatory agents						
NCT02225756: The ACA4 trial	2	Cyclosporine A (2 treatment groups at non-specified doses) vs placebo	Not specified (indicated as a 'short course')	360	AAA growth as assessed via CTA	Unknown
NCT01756833: The N-TA^3CT study	2	Doxycycline (100mg bid) vs placebo	24 months	258	AAA growth assessed by maximum transverse diameter via CTA.	Active, not recruiting
NCT02007252: ACZ885 for the treatment of AAA	2	Canakinumab (50 mg/month) vs placebo*	12 months	NR (actual recruitment: 65)	AAA growth assessed via ultrasound	Terminated (lack of efficacy following interim analysis)
Trials assessing anti-platelet agents						

NCT02070653: The TicAAA study.	2	Ticagrelor (90mg/bid) vs identical placebo	12 months	NR (actual recruitment: 145)	AAA growth as assessed by infra-renal aortic volume on MRI.	Completed**
Trials assessing diuretic agents						
NCT02345590: Eplenerone in the management of AAA.	4	Epleronone (25 mg/day) vs placebo	12 months	172	Maximum AAA orthogonal diameter (imaging modality not specified)	Recruiting
Trials assessing anti-glycaemic agents						
NCT03507413: The MetAAA study	2	Metformin (2000 mg/day) vs placebo	12 months	170	AAA growth as assessed via CTA	Not yet recruiting
Trials assessing anti-lipidaemic agents						
ACTRN12612001226897: The FAME trial (104)	4	Fenofibrate (145 mg/day) vs placebo	At least 2 weeks prior to open AAA repair	42	Aortic wall macrophage number (biopsies collected at open surgery); Serum and aortic osteopontin concentrations	Active, not recruiting

*Based on a search for interventional trials for small abdominal aortic aneurysm. Trials assessing ruptured AAA or peri-operative medications are not included here (see https://clinicaltrials.gov/ct2/results?cond=abdominal+aortic+aneurysm&Search=Apply&age_v=&gndr=&type=Intr&rslt= , and http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=abdominal+aortic+aneurysms&isBasic=True accessed October 2018).

$^{\alpha}$ Registration number of trial; $^{\beta}$ Based on information presented on the clinical trials database as of October 2018; ** Included as current trials as outcome data have not yet been reported; NR: not reported.

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Figure