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Diagnosis and monitoring of abdominal aortic aneurysm: Current status and future prospects

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Abstract

Abdominal aortic aneurysm (AAA) remains an important cause of morbidity and mortality in elderly men, and prevalence is predicted to increase in parallel with a global ageing population. AAA is commonly asymptomatic, and in the absence of routine screening, diagnosis is usually incidental when imaging to assess unrelated medical complaints. In the absence of approved diagnostic and prognostic markers, AAAs are monitored conservatively via medical imaging until aortic diameter approaches 50–55mm and surgical repair is performed. There is currently significant interest in identifying molecular markers of diagnostic and prognostic value for AAA. Here we outline the current guidelines for AAA management, and discuss modern scientific techniques currently employed to identify improved diagnostic and prognostic markers.

Keywords

Abdominal aortic aneurysm; diagnosis; prognosis; biomarker

1.0 INTRODUCTION

An abdominal aortic aneurysm (AAA) is a dilation of the infra-renal aorta, which appears to result from chronic weakening of the arterial wall, increasing the risk of fatal rupture.[1–3] AAA is also associated with an increased risk of other major cardiovascular events in aneurysmal patients. For example the UK small aneurysm trial (UKSAT), demonstrated that only 16% of deaths in patients with 40–55mm AAAs was related to AAA repair or rupture while ~50% were due to other cardiovascular causes (mainly myocardial infarction and stroke).[4]

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It is estimated that AAA affects up to 8% of men over 65 years of age, and is becoming increasingly common in women.[5,6] Data published by the CDC's National Centre for Health Statistics demonstrate that aortic aneurysm and dissection is amongst the leading 15 leading causes of death for people aged 60–84 years in the USA, accounting for up to 0.7% of total deaths in this age bracket.[7] Furthermore, AAA incidence is predicted to rise in parallel with a global ageing population.[2] AAAs are usually asymptomatic, and in the absence of routine screening, diagnosis is often incidental when imaging to assess other health complaints.[8,9] Vessel dilation is often progressive and a lack of established prognostic indices or drug treatment makes repeat imaging to monitor AAA expansion necessary.[10] Surveillance continues until aortic diameter approaches 50–55 mm, at which point surgical intervention is usually undertaken as the risk of rupture is believed to outweigh perioperative risks for most patients.[11]

Surgical treatment of AAAs is primarily by open or endovascular aneurysm repair (EVAR) or in some instances via a laparoscopic approach.[12] Open repair, whereby the AAA is repaired transabdominally, has a perioperative mortality of approximately 5% in elective patients.13 The less invasive EVAR, in which a stent-graft is inserted via the femoral artery under angiogram guidance, has a lower perioperative mortality of 1–2%.14,15 However, follow up is associated with reduced intermediate and long-term durability and similar all-cause mortality to open surgery.[16,17] Up to 20% of patients require reintervention within 5 years, making costly long term follow up necessary.[17,18] In-hospital surgical management of AAA is estimated to cost ~US$25,000 in Australia, US$16,000 in Canada and US$23,000 in the USA per individual per annum.[19,20] Given the high prevalence of AAA in the elderly population, global disease management costs billions of dollars each year.[2,21,22]

1.1 AAA pathology

Macroscopically, an AAA can be considered a dilatation of the infrarenal aorta, giving rise to a permanent vessel diameter >30mm (typical abdominal aortic diameter ranges from 15 to 25mm).[23–27] AAA vessel dilation is commonly progressive, and is often accompanied by the formation of a laminated, non-occlusive, intraluminal thrombus.28–29 Thrombus size and location varies between patients, and the arterial wall may be partially or completely covered by the thrombus (Figure 1A and B).[30] The thrombus remains in permanent contact with circulating blood and is continually remodeled,[31,32] and thrombus size increases in parallel with aortic dilation. Due to constant remodeling the thrombus is a laminated structure comprising a red blood cell-rich luminal layer in contact with the flowing blood, progressing to a brown fibrinolysed layer at the aortic wall.[29] Localised hypoxia has been demonstrated in regions of the aorta covered by the thrombus and this has been suggested to contribute to physiological stresses within the arterial wall.[33] Similar to other vascular diseases, AAA tissues may become calcified (Figure 1C), although the extent of calcification varies between patients, and this may prevent or complicate surgical correction.[34]

At the cellular level, histological examination demonstrates that pathophysiological processes in AAA involve all layers of the aortic wall including the aortic media, contrasting to those observed for occlusive atherosclerosis.32,35 Characteristically, AAA biopsies demonstrate significant degradation of extracellular collagen and elastin fibres, reductions in the number of vascular smooth muscle cells (VSMCs), and medial and adventitial infiltration by mononuclear lymphocytes and macrophages (discussed in detail by Hellenthal *et al.* (2009)).[36,37] An increase in medial neovascularisation has also been reported in aneurysmal tissue biopsies (Figure 2).38 The action of proteolytic enzymes, notably matrix metalloproteases and serine proteases, has long been associated with the destruction of the extracellular matrix.[39] Typically, protease activity is regulated by endogenous inhibitors (e.g. α2-macroglobulins, α 1-antitrypsin and tissue inhibitors of metalloproteinases), and

unbalanced proteolysis within the aortic media suggests that over-expression of proteinases, or deficiency in protease inhibitors may be involved in AAA pathophysiology.[40–42] The proteolytic generation of elastin and collagen degradation products can attract circulating inflammatory cells such as macrophages and mononuclear lymphocytes which enter the aortic wall.[43–45] Once activated, inflammatory infiltrates produce (amongst others) proinflammatory cytokines, chemokines, prostaglandin derivatives, immunoglobulins and proteolytic secretions.[46,47] thereby perpetuating the remodeling process. This infiltration of proinflammatory cells and the observation that IgG purifed from AAA tissue is reactive to aortic extracellular matrix proteins suggest that AAA development may have an autoimmune component.[47,48]

It is important to note that although the physiological hallmarks of AAA have been well characterized, the mechanisms underpinning these changes, particularly those which act as an initial trigger for AAA formation, are incompletely understood. It is accepted that an AAA results from destruction and weakening of the arterial wall which leads to vessel dilatation,[49] and is broadly thought to result from a culmination of proteolytic degradation of aortic wall components, genetic predisposition to disease, stresses within the aortic wall, and/or inflammation and autoimmune response.

2.0 RISK FACTORS OF AAA

In an attempt to better clarify AAA pathogenesis, four phases have been described, namely 1) initiation, 2) formation, 3) expansion, and 4) rupture. The mechanisms driving these different pathological changes may be distinct but remain unclear, and risk factors for each stage of the disease have been identified. In this section we will discuss the risk factors relevant to AAA.

2.1 Risk factors for AAA initiation and formation

Epidemiological studies reveal clear predisposing factors for AAA. For example, AAA is positively associated with male gender, advanced age, dyslipidaemia, smoking, hypertension, family history and obesity with the presence of AAA (Table 1).[1,21,23,50–58] AAA exhibits a strong gender bias with a male: female ratio of 5:1 reported,[21] although recent data demonstrate an increase in the number of cases in females.[6,51] There is a strong association between smoking and AAA,[21,59] with active smokers more susceptible to developing AAA than non-smokers, or those who have previously smoked.[50,59,60] This is reflected by an >4 fold increase in the prevalence of AAA in lifelong smokers than non-smokers.[21] Also linked to AAA predisposition is a positive family history and ~20% of patients have first degree relatives with the disease.[1,53,54] The influence of ethnicity in the predisposition to AAA has also been elaborated with the disease being more common in white northern Europeans than in their Asian or African counterparts.[1,52,53]

2.2 Risk factors associated with AAA growth

It is estimated that 60 to 80% of AAA between 40–49mm will enlarge and require surgery within 5 years,[61,62] although the determinants of AAA progression are, at present, poorly defined. Currently, the most accurate independent positive predictor of increased expansion rates is initial AAA diameter and this is usually used to determine the intervals between imaging assessments. Currently, there appear to be discrepancies in the recommended imaging regimes, possibly reflecting differences in surgical intervention criteria and perceived cost-effectiveness (Table 2).23 The UKSAT participants report that average annual linear growth rate of a small AAA increases by 1.29 mm (95% CI 1.05–1.53) per 10mm larger initial AAA diameter.[23] The investigators monitored AAA growth by ultrasound (US) and reports there were “growth spurts” in some patients and even regression

in 6%. This variability made the use of initial AAA diameter alone in predicting AAA expansion problematic.23 However, most AAAs initially measuring <40mm were very unlikely to expand to a size requiring AAA repair within 5 years.61 The inter- and intra-patient variations in AAA progression suggest that AAA growth may be influenced by endogenous and environmental factors which vary over time, although the factors involved are currently not well defined. For example, smoking history may influence the AAA progression and variation in smoking habit could impact on changes in AAA growth rates. AAAs progress faster and rupture more frequently in smokers compared to non-smokers,23 possibly through increased inflammation, localized up-regulation of protease activity and reductions in collagen metabolism.63 Many studies including the UKSAT reported a significant increase in growth rates in self reporting smokers of 0.4 to 1.1mm/year, compared to non-smokers.[23,26,64,65] In a smaller cohort plasma cotinine levels were measured but showed no relationship between cotinine concentration and expansion rates.[65] Other well designed studies including the large Aneurysm Detection and Management (ADAM) trial, did not establish a relationship between self reported smoking and increased AAA growth rates.[24,66,67]

Hypertension has long been regarded a risk factor for AAA, however the association between hypertension and AAA expansion is debatable. The ADAM trial showed a relationship between hypertension and moderate AAA expansion of >4mm/year (p=<0.01; odds ratio, 2.5).[24] While additional studies concluded similar results, the majority of published studies, including UK SAT, show no correlation between hypertension and increased expansion.[21,23,26]

Recently, abdominal aortic calcification has been associated with increased diameters at the superior mesenteric artery in non-aneurysmal patients,[68] however, in AAA patients calcification has been associated with reduced expansion rates.[69] In a prospective study of 122 men with AAA sized 30–49mm as detected by screening, Lindholt *et al*. (2008) conducted an ultrasound-based assessment of the extent of AAA wall calcification. The investigators reported that males with greater than 50% AAA wall calcification had significantly lower growth rates than their less-calcified counterparts (1.72mm/year versus 2.97mm/year, p=0.001), after adjusting for age, smoking and aspirin use.[69] However, earlier small studies using repeat CTA assessments in primarily small AAA failed to find an association between aortic calcification and growth (p>0.1).[61,70,71] Chronic limb ischemia,[61] and carotid artery disease,[70] have been associated with slower AAA expansion (p<0.05) in some series. Diabetes has also been linked with reduced AAA expansion and could explain the association between aortic calcification and slower AAA growth.[58]

A recent study demonstrated a close correlation between thrombus volume and both total aortic volume (r=0.87, p<0.0001) and maximum AAA diameter (r=0.74, p<0.0001).[72] This was in keeping with previous smaller studies which quantified AAA thrombus.[73,74] There is current controversy regarding the role of thrombus in AAA-related outcomes.[33] Initially many investigators argued that rupture rates were unchanged or reduced with increased thrombus formation.[75,76] Siegel *et al.* (1994) even found more thrombus surrounding unruptured compared to ruptured AAA (p=0.014).[76] Similarly, mathematical models concluded intraluminal thrombus decreases AAA wall stress and rupture risk.[77,78] Recent data support a role for thrombus as a predictor of rupture. Autopsy studies show thrombus commonly at the site of rupture as do most CTA studies.[79–82]

Experiments in rat models suggest thrombus is important in AAA progression since abciximab,[83] and AZD6140 reduce thrombus development and AAA enlargement.[84] This implicates mural thrombus formation as a driving force behind AAA progression, although few human studies have evaluated this hypothesis. Wolf *et al.* (1994) demonstrated that

increased thrombus arc, thrombus percent and thrombus area was associated with increased diameter expansion ($p<0.001$ in all variables).[70] A recent longitudinal, prospective studyfound patients with continuous growth patterns (rapid) more commonly developed eccentric thrombus ($p=0.05$).[71]

2.3 Factors associated with AAA rupture

Aortic rupture is the most feared outcome of AAA, and is thought to occur when the aortic wall is unable to oppose the luminal blood pressure resulting in the wall tangential stress exceeding the tensile strength of the vessel.[85] According to the law of La Place, wall stress is determined by blood pressure, blood vessel diameter and wall thickness. This model can be theoretically applied or invasively investigated but may provide inaccurate information regarding the true wall stress.[86] AAA size is considered the main predictive factor of rupture.60›76 AAAs measuring<50mm are thought to rupture at a rate of <1% per year,87 while those >60mm are associated with a rupture risk of approximately 10% per year.60 However, small AAAs may also rupture, suggesting that our current understanding is incomplete. Furthermore, AAAs in females appear to rupture at smaller diameters than male counterparts. In the small number of subjects who had AAA rupture during monitoring in the UKSAT the AAA diameter was smaller in women (mean 50mm) than men (mean 60mm).[88] These and other data suggest a worse prognosis for AAA in women (discussed in detail by Norman and Powell (2007)).6

Siegel *et al.* (1994) reported that a high-attenuation crescent or focal gap of otherwise circumferential calcification, but not quantity, was associated with AAA rupture ($p=0.008$). [76] Other putative predictors of rupture include increased cross-sectional aortic asymmetry, no or mild aortic tortuosity, current self reported smoking,[75] plasma cotinine levels,[89] and peak wall stress.[90]

Four studies focused on AAA expansion rates as a predictor of rupture and concluded that rapid expansion was not associated with increased rupture rates.[60,64,91,92] There is no evidence to support using rapid expansion as an indication for surgery in our opinion.[93] However, as rapid growth allows the AAA to reach greater diameters more rapidly, focus has been placed on maximal diameter and growth rates as a surrogate marker of AAA clinical outcomes. It should be noted that rupture estimates are based on limited data since most large AAA patients undergo surgery unless unfit for surgery and post-mortem rates are often low.

3.0 CURRENT DIAGNOSIS OF AAA

The Society for Vascular Surgery(SVS) has recently reviewed their practice guidelines for AAA management. Here we discuss the common clinical findings of AAA, although detailed discussion is outside the scope of this article. Readers are referred to the comprehensive SVS document for detailed advice on recommended patient management protocols.[94]

3.1.1 Clinical diagnosis of AAA—AAAs are typically asymptomatic and identification is usually achieved by incidental imaging. Recent trials have demonstrated that ultrasound-based screening of at risk populations is effective in reducing AAA-related mortality.[95,96] AAAs can be identified by physical examination of the abdomen however this is an insensitive means of diagnosis, particularly in overweight subjects or those with small AAAs.[9,97] In a small proportion of cases, patients report abdominal or back pain without evidence of rupture of the AAA and no other obvious cause for the symptoms. In these instances, the AAA is usually labeled as ‘symptomatic’, and often prompts more urgent

consideration of surgical repair. The mechanisms responsible for symptom development in these cases is poorly defined although in some cases a more marked retroperitoneal inflammation has been implicated.[98] AAA rupture leads to haemodynamic shock and in these instances the patient presents with hypotension, other signs of shock and a variety of abdominal signs including a pulsatile abdominal mass, a distended abdomen and Grey-Turner's sign.

3.1.2 Differential diagnosis—Differential diagnosis of an emergency presentation of AAA can be divided based on haemodynamic stability. If stable, possible diagnoses include bowel obstruction, gastritis, intestinal ischemia, musculoskeletal pain and mild pyleonephritis or pancreatitis. If the patient is haemodynamically unstable possible life threatening causes must be ruled out including perforated viscus (appendix, peptic ulcer, gallbladder or diverticulitis), myocardial infarction and pulmonary embolism. Clinical suspicion of AAA should always invite appropriate investigation to exclude this life threatening condition.

3.2 The role of Imaging in AAA management

Currently identification and assessment of AAA is usually performed with ultrasound (US) and computed tomography angiogram (CTA). Maximal axial aortic diameter is the main method used for diagnosis and risk stratification. Initial aortic diameter provides the most accurate independent positive predictor of increased expansion rates as noted earlier.

US-based assessments quantify the maximal anterior-posterior and transverse diameter of the aorta and is the method of choice for AAA screening and follow up as it is non-invasive, non-ionizing and inexpensive. Furthermore, US estimates orthogonal diameter, which may provide a more accurate assessment of AAA size.99 The reported sensitivity and specificity of US for AAA diagnosis is 87.4–98.9% and 99.9%, respectively,[100] although accuracy can be significantly reduced by obesity and bowel gasses. Consequently, assessment can be subject to large intra- and inter-observer measurement error with only 65% of scans considered highly reliable (<2mm inter-observer variation).[101] Such variation should be considered when analyzing AAA growth, or assessing patients for surgery. Currently, most small AAAs are managed conservatively with repeated imaging at intervals. The measurement error typically seen with US can make it problematic to define which AAAs have altered in size.

The other main modality used to diagnose and assess AAA is CTA. This technique has the drawback of exposing the patient to ionizing radiation and intravenous contrast. CTA however, provides much more accurate assessment of the morphology of the AAA which is required for decisions regarding surgical repair. Whilst there is still some controversy regarding this, CTA also provides a more accurate measurement of AAA diameter. Reported reproducibility of aortic diameter measurement using CTA is more favourable to that of US. Using CTA, over 95% of measurements are considered highly reproducible (<2mm intra-observer variation in aortic diameter measurements).[102]

In routine practice, AAA risk stratification is commonly carried out using diameter measurements from axial CT slices. The accuracy of axial measurements is questionable in tortuous regions of the vasculature. Horizontal axial slice measurements are to be considered over estimated when the aorta is angulated greater than 25 degrees,[99] and *orthogonal* diameter which maps the aortic lumen and measures perpendicular to this line, should be used in such instances. Figure 3 displays the difference between orthogonal and axial diameters in a moderately tortuous AAA. Note that the axial slice has a greater diameter than the orthogonal diameter. The importance of this is noted by discrepancies between

changes in maximal orthogonal diameter and total AAA volume.[103] Currently, most clinical and research facilities still measure aneurysm size based on axial diameters.

3.2.1 Total aortic volume—Given the concerns over the accuracy of US and axial CT measurements of AAA diameter to monitor small changes in AAA size, there is interest in employing other techniques. Diameter measurements only provide information at one site within the AAA. It is postulated that a more complete stratification of AAA rupture risk may be provided by more detailed morphological imaging. Measurement of total aortic volume for instance, may have greater sensitivity to detect small changes in AAA size. In one series, total abdominal aortic volume varied from 14 to 370 mm^3 while maximal diameter only varied from 17–76 mm.104 This greater distribution may equate to a greater ability to detect which AAAs have progressed over time. Total AAA volume analysis has been successfully employed in patients following endoluminal AAA repair.103،105–107 For example, Wever et al. (2000) discovered that one third of patients had significant volume change without maximal orthogonal diameter change.[106] The value of CTA volume measurement in determining clinical management is currently unknown. Volumetric analysis however, may be particularly value in trials to assess the efficacy of new therapies for small AAAs.

3.2.2 Calcification and thrombus—Recently there has been increasing interest in the role of abdominal aortic calcification and thrombus in AAA development,[68,108] progression,[69–71,104] and rupture.[80،81] Calcification,109،110 and thrombus volumes,72 have been assessed in research settings with excellent reproducibility. In a study involving 75 patients, accurate assessment of thrombus volume using CTA was evidenced by low intra- (Pearson correlation coefficient 0.9974 (P<0.001), mean coefficient of variation 2.9%), and inter-observer (Pearson correlation coefficient 0.9983 (P<0.001), mean coefficient of variation 4.3%) variation.[72] However, assessment is hindered by difficulty in delineation of surrounding anatomy and thrombus and high time requirements. Assessment of aortic calcification appears even more robust with low intra- and inter-observer variation reported (intra observer Pearson correlation coefficient 0.999 (P<0.01), mean coefficient of variation 0.54%; inter observer Pearson correlation coefficient 0.999 (P<0.01), mean coefficient of variation 0.9%).110 It is possible that a more complete morphometric assessment of the AAA may provide better risk stratification, but this remains unproven.

3.2.3 Small AAAs—A small AAA is usually defined as a maximal diameter between 30–55mm, or sometimes <50mm. The use of the term is often restricted to AAAs which are considered too small for repair, and since selection criteria vary between centres, the definition based on size also varies. Currently there is controversy over how to best manage patients with small AAAs for a number of reasons. Firstly, approximately 70% of patients with an initial AAA diameter between 40–49mm will require treatment within 5 years.[61,62] Secondly, the possibility of rupture is present, albeit less than <1% per year.[87] Lastly, cardiovascular mortality is increased in this group of patients.[65] Two large randomized controlled trials, UK SAT and the ADAM trial found that early elective open surgery did not reduce mortality compared to a watchful waiting approach for patients with 40–55mm AAAs.62،111 In these studies, the conservative groups received intervention if the AAA was deemed to have become symptomatic or reached 55mm in diameter.62–111 The PIVOTAL (Positive Impact of endo Vascular Options for Treating Aneurysm earLy),[112] and CAESAR (Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair), 113 studies are randomised controlled trials currently underway to assess if small AAA should undergo EVAR. A presentation at a recent meeting of the European Society of Vascular Surgery reported that at 3 years, early elective EVAR did not reduce mortality for patients with 40–54mm AAAs.114 Longer term results are awaited.115،116 Recently, it has been suggested that delaying surgery does not alter the anatomical suitability for EVAR.[117]

As a result conservative treatment, entailing regular ultrasound imaging, is the mainstay until AAA becomes symptomatic or reaches 50–55mm, depending on the sex of the patient, suitability for surgery and local protocol. Current guidelines for surveillance of small AAAs are illustrated in Table 2 although these figures are based on surgical intervention at 55mm. In facilities where intervention occurs at 50mm, follow-up of AAA often occurs yearly and half yearly for maximal aortic diameters of 30–40 and 41–50mm, respectively.

3.2.4 Staging the AAA—Prior to surgery the AAA is staged using contrast enhanced aorto-iliac CTA. The CTA is used to image the whole abdominal aorta, and if performing EVAR, all potential access routes. Table 3 displays the common features used to stage an AAA prior to surgery. It is advisable that assessment occurs less than 6 months prior to treatment to minimize the risk of significant changes in anatomy.[118]

3.2.5 Post-surgical follow-up—Currently, the SVS recommends non-contrast CT imaging at 5 year intervals following open aneurysm repair. Imaging protocols following EVAR are controversial and currently under revision. The SVS recommends post-operative contrast enhanced CT imaging at months 1 and 12. Additional evaluation after 6 months is recommended if abnormalities or endoleaks are detected at the first assessment to monitor any expansion of the AAA sac.[94] More recently, most clinicians have radically reduced the number of CTAs, particularly if the first follow-up CT is unremarkable. Many investigators now follow patients almost exclusively by ultrasound to measure maximum AAA diameter and only obtain further imaging if the AAA sac fails to shrink, expands >5mm.

4.0 FUTURE PROSPECTS OF AAA DIAGNOSIS AND MONITORING

Significant shortfalls exist within current AAA management pathways. The current strategy of using morphological imaging as a stand-alone approach to diagnose and provide prognostic information regarding AAA has a number or limitations. Firstly, imaging may not always be feasible as variations in patient characteristics such as obesity or renal impairment may prove prohibitive. Secondly, imaging assessments do not provide complete data to identify which AAAs are most likely to continue to increase in size and be at risk of rupture. Small AAAs with similar initial diameter can vary in growth pattern significantly.[23] A more complete ability to predict AAA progression may allow significant streamlining of current management practice which involves prolonged intermittent imaging.

There is significant current interest in the detection of biologically relevant markers which can be used to better characterize AAA behaviour. Biological information about the AAA could potentially highlight therapeutic targets for non-surgical intervention, and provide a means to assess the physiological response to such medications.

The Food and Drug Administration of the USA defines a biomarker as a characteristic which can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[119,120] Furthermore an ideal biomarker would reliably predict the risk of contracting a specific illness and identify the presence (from early onset) and/or severity of a disease,[121] thereby providing information on which to accurately stratify patients. Whilst such molecules may be expressed within diseased tissues, those that can be detected within bodily fluids such as serum, plasma and urine are highly desirable due to relative ease of sample collection. Blood is a particularly attractive source for putative biomarkers since it is in contact with all tissues of the body, thus markers for a variety of diseases may be carried within the circulation.122 Currently, there is much emphasis placed on the discovery of markers for a broad spectrum of diseases, and there is a significant body of work

documenting such investigations for AAA, although at the time of writing, the clinical value of these new markers remains unknown.

Experimental approaches to discover molecules with diagnostic, prognostic or monitoring potential fall broadly into one of two categories: 1) those investigating specific molecules due to a hypothesised involvement in disease processes; or 2) those applying high-throughput techniques to analyse many thousands of putative markers in a non-biased manner. Studies to identify biomarkers for AAA employ a number of experimental designs including animal investigations, use of human AAA biopsies, assessment of blood samples and targeted imaging techniques. In the following sections we will discuss current approaches to identify AAA biomarkers.

4.1 Hypothesis-driven research

Hypothesis-led studies have been mostly based on mechanisms believed to be critical in AAA formation and progression. For example, the expression of inflammatory markers and selected proteolytic enzymes has been widely investigated to determine an association with AAA. In general, hypothesis-led investigations require little in the way of specialized equipment and may consequently be performed using standard laboratory apparatus. Accordingly, there is a considerable body of work documenting hypothesis-based biomarker discovery investigations for AAA. This area has recently been reviewed,[8,36,37,123] thus we will briefly discuss the techniques used to assess putative biomarkers and illustrate with appropriate examples.

4.1.1 Genetic markers of AAA—AAA shows a clustering pattern and ~ 20% of patients have first degree relatives with the disease, suggesting that genetic factors may be involved in generation of the aneurysm phenotype.54,[124] Accordingly, considerable effort has been expended in studying genetic variations associated with AAA. Usually this has been achieved by examining the frequency of common variations (polymorphisms) of genes thought to code for, or regulate proteins involved in AAA pathogenesis. In particular, studies have focused on associating single nucleotide polymorphisms (SNPs) with AAA (examples shown in Table 4).[125–130]

In general terms, the aim of genetic investigations is to highlight germline defects which may underpin susceptibility to AAA. However, the genome is a static system, i.e. genetic sequences are consistent in all physiological states and will not alter in response to disease. In this light, the value of genetic markers as diagnostic sentinels seems questionable since the presence of a genetic risk factor does not automatically confer disease phenotype and the effect size of most markers associated with complex disease is low (usually less than 1.5; Table 3). On the other hand, genetic studies have great potential in unraveling the mechanisms behind AAA formation. Furthermore, a genetic marker will be present within all nucleated diploid cells (although there is some evidence to suggest that different polymorphisms may be tissue-specific),[125] and are thus easily accessed and sampled in a relatively non-invasive manner. Thus, genetic screening may be useful to determine AAA susceptibility in at-risk populations, and this may prompt firm diagnosis through measurement of dynamic biological systems which more actively reflect current aortic phenotype.

4.1.2 Protein markers of AAA—Proteins are attractive biomarker candidates as they are effector molecules, and their expression determines cellular phenotype.[131–133] Furthermore, protein expression is dynamic and protein regulation is linked to the physiological processes occurring within individual cells or tissues. Consequently, the polypeptide profile of diseased tissues may be distinct to that of healthy controls and identification of significantly

over- or under-expressed proteins highlights molecules of diagnostic potential. Investigation into the expression of individual proteins has been facilitated by the commercial availability of an increasingly broad range of specific antibodies which can be employed in experimental formats including western blotting, immunohistochemistry and/or ELISA tests. More recently, techniques such as real-time PCR have been increasingly employed to assess protein expression based on the abundance of mRNA transcripts coding for individual polypeptides. Using these approaches, the regulation of a wide variety of proteins presumed to be involved in AAA pathophysiology has been appraised. As previously noted, AAA biopsies typically demonstrate fragmentation of the aortic extracellular matrix, a decline in the number of VSMCs, the presence of inflammatory cells within the aortic wall and formation of a large laminated thrombus. These observations have prompted assessment into the expression of a wide range of proteins including markers of matrix degradation and turnover, proteolytic enzymes, proinflammatory cytokines and thrombosis-related proteins.

4.1.2.1 Markers of proteolysis: The characteristic degradation of structural proteins within the aortic wall has stimulated much interest in the expression of proteolytic enzymes in AAA, and a strong body of evidence supports the hypothesised role of proteases in AAA pathogenesis (detailed in by Hellenthal *et al.* (2009)).[36] The positive association of protease activity with AAA phenotype has been further confirmed by observed reductions in AAA development following treatment with the broad spectrum proteinase inhibitor, doxycycline.[40,134] The regulation of zinc-dependant metalloproteinases secreted from activated inflammatory cells has attracted considerable attention due to the correlation of neutrophil content and destruction of the aortic extracellular matrix.[29,135] Thus, MMP production by inflammatory cells within the arterial wall is considered a critical event that drives aortic dilation and may contribute to AAA rupture.[136–137] In addition to this, the mural thrombus has been identified as a site for polymorphonuclear leukocyte accumulation and protease activation and release,[29,32] suggesting that biochemical processes outside the arterial wall may contribute to AAA development. Several MMPs including MMP-1, -2, -3 and -9 have been proposed as putative markers for AAA.[8,123] However, poor correlation between circulating MMP titres and vascular phenotype suggests that these are unreliable sentinels with which to stratify AAA patients.[138–140] The expression of other proteolytic enzymes including cathepsins,[141,142] and serine proteases,[143] has been investigated. However, whilst these analyses reveal putative therapeutic targets, the diagnostic potential of these proteins has not been elaborated.

An alternative approach to assess the destruction of the aortic wall in AAA is to determine the abundance of degradation products generated as a consequence of proteolysis of structural proteins or vascular remodelling.[36,144] Enzymatic cleavage of elastin and collagen generates a series of peptides which can be detected within aortic biopsies,[145,146] and these have also been demonstrated within non-vascular tissues of AAA patients.[138,147,148] Furthermore, the characteristic destruction of arterial elastin fibres during the course of AAA development is accompanied by an increase in collagen turnover.[138,149,150] Accordingly, the N-terminal propeptide procollagen III (PIIINP), and the C-terminal propeptide of type I procollagen (PCIP) which are liberated when structural pro-proteins are processed to their mature forms, have been investigated as putative markers of aortic extracellular matrix remodelling in addition to serum elastin peptides. Published data provide conflicting evidence of the correlation between serum concentrations of PIIINP and aneurysm progression.[138,146,151] However, Lindholt *et al.* (2001) have suggested a predictive model for expansion of small AAAs based on initial aneurysm size and the concentration of serum elastin peptides and PIIINP. In a small patient cohort, they report that this model is suitably sensitive to detect 90% of cases which require surgical intervention within 5 years, although this approach has not yet been accepted as a tool for AAA management.[148]

4.1.2.2 Markers of inflammation and immune response: During the course of AAA, a cascade of cytokines secreted by invading inflammatory cells activate proteases, contributing to aortic wall degradation. Resultant elastin and collagen degradation products within the aortic wall promote recruitment of inflammatory cells which in turn generate leukotrienes, proinflammatory cytokines, chemokines, prostaglandin derivatives, immunoglobulins, and cysteine and serine elastases, perpetuating aortic wall degradation and vascular smooth muscle cell apoptosis.[29,43,152] The expression of helper T-cell type-1 (Th1) and type-2 (Th2) cytokines have been reported in both human AAA and animal models.[153] Inflammatory molecules such as interleukin-6 (IL-6), interferon gamma, TNF-α, IL-8 and monocyte chemoattractant protein-1(MCP-1) have been shown to be higher in AAA tissue than non-aneurysmal equivalents.[154–155] In addition, there is evidence to suggest that inflammatory markers are released from AAA tissue. For example, Dawson *et al* (2007) employed an ELISA-based strategy to demonstrate that plasma samples collected distallyto an AAA are significantly enriched in IL-6, compared to plasma from the proximal aorta. In the same investigation, a correlation between AAA surface area and plasma IL-6 concentrations was demonstrated, and a significant elevation in plasma IL-6 titres in aneurysmal patients compared to non-aneurysmal controls was reported.[156] Similarly, elevated serum titres of C-reactive protein have been reported in AAA patients (discussed by Hellenthal *et al.* (2009)).[37] However, available data suggest that circulating concentrations of inflammatory markers, including IL-6, and C-reactive protein do not correlate with AAA expansion.[37,140] Despite the obvious role of inflammation in AAA, the suitability of inflammatory markers as putative sentinels for aneurysm remains in doubt. Inflammation is by no means specific to AAA and is a key pathological feature of a wide variety of diseases. A recent analysis by Golledge *et al.* (2009), suggests that tumour necrosis factor alpha, interferon gamma and chemokine CC motif ligand 2 may be more closely associated with AAA than atherosclerosis, however, expression of these cytokines needs to be further elaborated in large patient cohorts.[155]

4.1.2.3 Markers of thrombosis: The formation of a laminated intraluminal thrombus in many AAA cases has prompted assessment of the expression of thrombotic and coagulation pathway proteins as potential markers for abdominal aortic aneurysm. As previously mentioned, the thrombus is continually remodeled due to close association with flowing arterial blood, thus there is potential for clot-related proteins to enter the circulation. Based on this hypothesis, raised plasma concentrations of a variety of proteins including fibrinogen, von Willebrand factor antigen, D-dimer, thrombin-antithrombin III complex and α2 -plasmin inhibitor-plasmin complex have been demonstrated in AAA patients, suggesting that coagulation pathways are activated during the course of disease.[157–159] However, the publication of conflicting data implies that measurement of thrombus-associated may not be sufficiently specific to distinguish stable AAAs from age-matched controls.[160] Despite this, elevated concentrations of thrombotic proteins have been demonstrated in cases of large,[161] and ruptured AAA when compared to small non-ruptured aneurysms suggesting that thrombus-associated markers may have prognostic potential.[162] In a western-blot and ELISA based approach, Touat *et al*. (2006) examined the proteins expelled from mural thrombus explants during *in vitro* culture, demonstrating the release of pro-coagulant molecules including phospholipids and the tissue factor protein. *In vitro* findings were mirrored by significant increases in the concentration of these proteins in the blood of AAA patients.[83] Furthermore, Serino *et al.* (2002) reported significantly higher D-dimer concentrations in postoperative venous blood samples from patients with non-shrinking aneurysms (mean 1272 + 728 ng/mL, $p < 0.0005$), or type 1 endoleaks (mean 1931 + 924 ng/mL, $p < 0.005$) as a measure of incomplete EVAR, when compared to patients with successfully repaired aneurysms.[160]

These findings demonstrate that the release of products from the AAA intramural thrombus may provide a source of putative diagnostic markers. Whilst these data are promising, further evaluation of the specificity of thrombotic markers to AAA needs to be evaluated to determine their suitability to distinguish aneurysmal patient samples from those of patients with other thrombotic disorders.

4.2 Non-hypothesis-driven research

As discussed above, putative biomarkers for AAA have traditionally been discovered using a targeted approach to assess disease-related expression of preselected candidates. However, in a multifactorial disease such as AAA, it seems unlikely that observed pathologies result from a change in the expression of single molecules. Rather, it is more probable that the AAA phenotype results from the concerted actions of large numbers of molecules which are regulated in response to a variety of genetic and environmental factors over a prolonged time period. Thus, a focused, hypothesis-led approach may miss important molecular changes if such molecules are not a direct target of the investigation. This shortfall has, to some extent, been addressed in the post-genomic era through the development of increasingly powerful technologies (referred to herein as “omics” techniques), which permit the simultaneous analysis of thousands of candidates from a single biological specimen. Using these approaches, it is hypothesized that the likelihood of identifying key physiological changes is greatly increased.

The commercialization of common reagents has contributed to the standardization and reproducibility of high throughput omics techniques, and has made these tools accessible to a broad spectrum of researchers. These techniques are sufficiently flexible to permit analysis of a wide variety of biological samples, and have great potential to further our understanding of a broad spectrum of physiological processes. Furthermore, completion of the human genome project, ongoing genetic characterization of common animal models and advances in bioinformatics have greatly facilitated investigations using post-genomic technologies.[132,163] Currently, the application of omics-approaches to AAA is still relatively limited, however the use of these technologies is becoming more routine, and it is likely that the next generation of biomarker-focused investigations will employ these techniques although their value in delivering clinically useful applications remains unproven. Traditionally, post-genomic disciplines have been used as stand-alone tools, although there is increasing interest in combining two or more omics techniques to amplify their power in detailed ‘systems biology’ investigations of disease processes.[164,165] In this light, we introduce the commonly used omics technologies in vascular research and discuss their potential to deliver improved diagnostic handles for AAA.

4.2.1 Genomics—As previously mentioned, the focus of many DNA-based investigations has been to assess the associations of SNPs with AAAs. These approaches have been greatly facilitated by the development of powerful array platforms which can investigate millions of SNPs within single biological specimens.[163,166] Data from these studies highlight regions of the genome which may be linked to the aneurysm phenotype, with SNPs of loci present on chromosome 19 commonly associated with AAA susceptibility.[124,167,168] Genetic variations within loci carried on chromosomes 4, 9, and 11, have also been linked to the development of AAA.[124,169,170] These findings may in the future provide insight into the mechanisms driving the development of AAA with the potential to highlight novel therapeutic pathways, although at present the pathways underlying this association with genetic loci are incompletely understood. For example, the loci on chromosome 9 which show association with AAA contain no known coding regions. However, the recent association between the chromosome 9p21.3 rs10757274 SNP and aortic compliance

suggests that genetic variation(s) which alter mechanical properties of the arterial wall may be involved in the AAA phenotype.[171]

4.2.2 Transcriptomics—Transcriptomics is a discipline of science which permits quantitative investigation into the expression of mRNA produced as a result of changes in gene expression (detailed by Gomase *et al.* (2008)).[172] Unlike the genome which is static, the transcriptome is a dynamic system, as genes will be 'activated' or 'deactivated' in response to endogenous and exogenous stimuli; thus, it is anticipated that phenotypic changes associated with disease will be accompanied by aberrant gene expression patterns. Consequently, by comparing transcript expression between diseased and control tissues, it may be possible to identify genetic pathways which drive/indicate AAA pathology, or map changes in gene expression in response to therapy.173 Transcript analyses have been employed to examine gene expression in a wide variety of tissues from AAA patients and animal models of disease including peripheral blood,174,175 and aortic wall biopsies.[176–178] Commonly, these studies employ powerful microarrays which permit genome-wide assessment of transcript expression, after which individual genes of interest can be further investigated using targeted approaches such as real time PCR. Collectively, the data from transcript based analyses reveal a clear trend in the up-regulation of genes associated with immunity, matrix metalloprotease activity, inflammation and extracellular matrix remodeling in AAA tissue.[178–180] Thus, these data confirm that well-characterized AAA-related physiological changes within the arterial wall are reflected at the molecular level. Whilst these findings are interesting from mechanistic and chemotherapeutic viewpoints, the value of these data in a diagnostic setting remains questionable since sampling vasculature to determine gene expression is clearly impractical. Despite this, the panel of aneurysm-associated molecules identified in tissue based studies may indirectly suggest which gene products can be detected in the circulation of AAA patients. This is exemplified in a recent study by Giusti *et al.* (2009) who compared gene expression within the peripheral blood of AAA patients and age/gender matched controls. In this way an increase in the expression of genes involved in oxygen transport, positive regulation of protein kinase activity and lipid metabolic processes was associated with AAA. Furthermore, their data revealed reduced expression of the low density lipoprotein receptor related protein (LRP5) gene in AAA patients analogous to that observed from tissue biopsies.[179] Decreased LRP5 expression was related to an increase in the concentration of serum lipoprotein A (median 248 mg/L compared to median 105 mg/L, $p = 0.049$). The authors suggest that alterations in the expression of erythrocyte genes and LRP5 may be characteristic of AAA, although the lack of correction for common co-morbidities such as atherosclerosis raises doubts over the specificity of observed gene expression changes.174 Nonetheless, clear differences in gene expression profiles between aneurysms of the abdominal and descending thoracic aorta tentatively suggests that a specific transcriptomic signature may exist for AAA,180 although exhaustive analyses to characterize a broad spectrum of cardiovascular diseases may be required before this signature is uncovered.

To date, the majority of transcriptomic investigations have documented the gene expression patterns associated with established aneurysms. Thus, whilst data generated in this way may potentially reveal mRNA signatures to confirm AAA presence, the prognostic value of these findings is difficult to evaluate without further investigation. This may be overcome by comparing transcripts produced at different stages of AAA disease. Sadek *et al.* (2008) recently created experimental aneurysms in the infra-renal aortas of Yorkshire swine and examined resultant gene expression patterns during the postoperative period. In this way, they demonstrated an increase in the number of significantly up-regulated genes as aneurysm formation progressed (232, 313, 406 genes up-regulated 1, 2 and 4 weeks after surgery respectively), confirming that expression of genes involved in extracellular matrix remodeling (notably MMP-2 and -3), increases concomitantly with aneurysm progression.

[177] In a similar manner, longitudinal experiments by Choke *et al.* (2006, 2009) investigated genes involved in aneurysm rupture by comparing mRNA expression within biopsies collected at the site of rupture with control biopsies sourced from the same patient. Pilot data confirmed that increased expression of genes involved in apoptosis, angiogenesis and inflammation may contribute towards AAA rupture.[181] These findings were expanded in a stringent follow-up study, identifying 139 significant changes in gene expression between ruptured, and non-ruptured AAA biopsies (>2.5 fold increase/decrease in expression, $P<0.005$). Quantitative real time PCR analyses confirmed over expression of 8 pro-immune/pro-inflammatory genes (including selectin E, prostaglandin-endoperoxide synthase 2, prokineticin 2 and interleukin-6 and -8) at the site of aneurysm rupture. These genes were proposed as novel therapeutic targets to inhibit aneurysm rupture, although the prognostic significance of increased expression was not considered.182

4.2.3 Proteomics—The Human Proteome Organization defines a the proteome of an organism as the complete set of proteins from the information encoded on a genome which can be expressed and modified by a cell, tissue or organism (definition sourced from http://www.hupo.org/overview/glossary/). Proteome complexity is not strictly limited to the number of genes within the genome as each open reading frame may give rise to multiple protein products. In the case of humans, the genome comprising 23,000–40,000 genes is estimated to give rise to up to one million proteins in addition to approximately 600,000 serum immunoglobulins which vary in their epitope binding regions.183¯185 Like the transcriptome, the proteome is a dynamic system in which expression of specific gene products alters in response to endogenous and exogenous stimuli, however, it is important to note that mRNA levels do not always correlate with protein expression.[186] Furthermore, it is proteins rather than transcripts which determine cellular phenotype, and protein activity may be altered through post translational modifications (e.g. phosphorylation, glycosylation, deamidation) during the course of cellular metabolism and homeostasis. These modifications can not be predicted from genetic sequences.[131] Thus, by investigating protein expression patterns under defined physiological conditions, it is possible to generate data which is difficult to assess using other techniques, and identify molecules which are directly involved in disease pathogenesis.187

The recent development of a suite of modern sample preparation, fractionation, separation and analysis protocols collectively termed ‘proteomics’, enables researchers to simultaneously profile many thousands of proteins extracted from a single biological specimen in a non-hypothesis led manner. Quantitative comparisons of the expression of large numbers of proteins between biological samples (e.g. diseased vs. control tissues) aim to identify significant changes in protein regulation, thereby identifying molecules of mechanistic, diagnostic and/or therapeutic interest (detailed in references 132،187). This can be achieved in a similar manner to gene microarrays, where panels of antibodies or ligands specific to groups of related proteins (e.g. inflammatory markers) are employed to assess the relative expression of thousands of pre-defined polypeptides, greatly extending the multiplex ability of traditional protein analysis techniques.165 Using this approach, Middleton *et al.* (2007), profiled the proteins within AAA biopsies and aortic samples from cadaveric controls reporting significant differences in the expression of 15 proteins, including pro-inflammatory cytokines (IL-1α, IL-1β, TNF- α, TNF-β oncostatin M, and IL-6), chemokines (ENA-78, GRO, IL-8, MCP-1, MCP-2 and RANTES), anti-inflammatory cytokines (IL-10 and IL-13), and growth factors (Angiogenin, GCSF, EGF, SCF, leptin, IL-3, IL-7 and thrombopoietin).[133] These data provide valuable mechanistic insight into the pathogenesis of AAA, however, protein microarray investigations are still limited by the same constraints as hypothesis-led approaches as relatively few pre-defined proteins are assessed. In contrast, the recent development of techniques such as two dimensional electrophoresis and quantitative mass spectrometry enable a less-biased assessment of protein expression.

The application of proteomics to vascular medicine has been limited, with diseases such as atherosclerosis attracting the most attention, although a recent increase in the number of published studies suggests that the utilisation of proteomics for AAA research is becoming more widespread.[188,189] Despite this, at the time of writing there is little published proteomic data generated using modern techniques which specifically relates to AAA. A recent study by Urbonavicius *et al.* (2009) employed two-dimensional electrophoresis (2DE), and mass spectrometry (MS), to compare proteins expressed within the walls of ruptured and non-ruptured aortic aneurysms. Using this approach, they reported significant up-regulation of 4 proteins including peroxiredoxin 2 and actin in the walls of ruptured AAAs, and a decrease in the expression of vitronectin and albumin, when compared to non-ruptured tissues (>2 fold change in protein expression, $P<0.05$). These findings confirm that physiological hallmarks of AAA such as oxidative stress, extracellular matrix destruction and vascular remodeling are reflected at the protein level. The potential of identified proteins as biomarkers for AAA was not assessed, however these findings provide a firm basis upon which other proteomic investigations into AAA can be built.[190]

Despite this, proteomic data generated from other vascular investigations provide valuable insights into the molecular biology of arterial tissue and are directly relevant to aneurysm disease. For example, Mayr *et al.* (2005) compiled a protein map to identify 154 abundant cytosolic proteins expressed by mouse aortic smooth muscle cells (SMCs) following *in vitro* culture. This map is a generous reference tool to which protein profiles of SMCs extracted from vascular tissues can be compared,[191] (see also http://www.vascular-proteomics.com). Thus, there is a considerable wealth of information within the public domain which can greatly facilitate prospective proteomic research into AAA.

5.0 Conclusion and future perspective

The coming decade promises considerable change in the management of AAA including:

- **a.** Blood markers which can be used to screen for AAA and contribute to risk stratification
- **b.** Prognostic markers which can better stratify patients with clinically important AAAs
- **c.** Improvement in the methods to monitor AAA following repair or receiving other therapy
- **d.** Markers useful for guiding medical therapy of small AAAs

In order for this promise to be fulfilled carefully planned hypothesis-led and more global screening studies are required with large scale validation of putative biological markers identified. The considerable interest in this area suggests that despite significant challenges, successful identification of clinically useful biomarkers will occur.[132] When clearly identified new biomarkers can potentially form part of standard blood tests or be used for targeted or functional imaging.[192]

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ABBREVIATIONS USED

AAA	Abdominal aortic aneurysm
EVAR	endovascular aneurysm repair
UKSAT	UK small aneurysm trial
SVS	The Society for Vascular Surgery

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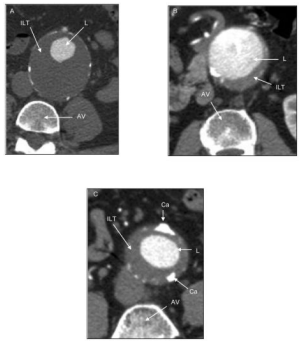

Figure 1.

A) Axial computed tomography image of abdominal aortic aneurysm displaying large quantity of posterior-eccentric thrombus. B) Axial computed tomography image of abdominal aortic aneurysm a moderate quantity of posterior-eccentric thrombus. C) Axial computed tomography image of an abdominal aortic aneurysm with moderate quantity of concentric thrombus and two large calcium deposits at 12 and 5 o'clock. ILT = intraluminal thrombus; L = lumen; AV = abdominal vertebra; Ca = calcium deposit.

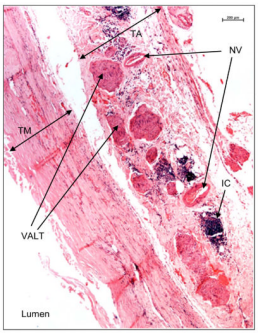

Figure 2.

Magnified (× 40) view of a Haematoxylin and eosin stained human AAA biopsy recovered during the course of surgical repair. Note that the tunica media (TM) is thinned and disorganised, (separated from the tunica adventitia (TA) during the course of histological preparation). Examination of the TA reveals the presence of invading inflammatory cells (IC), evidence of neo-vascularisation (NV), and the formation of vascular associated lymphoid tissue (VALT) follicles. The tunica intima has thinned and eroded. Microscope image kindly provided by Drs Alexandra Trollope and Corey Moran, Vascular Biology Unit, James Cook University, Australia.

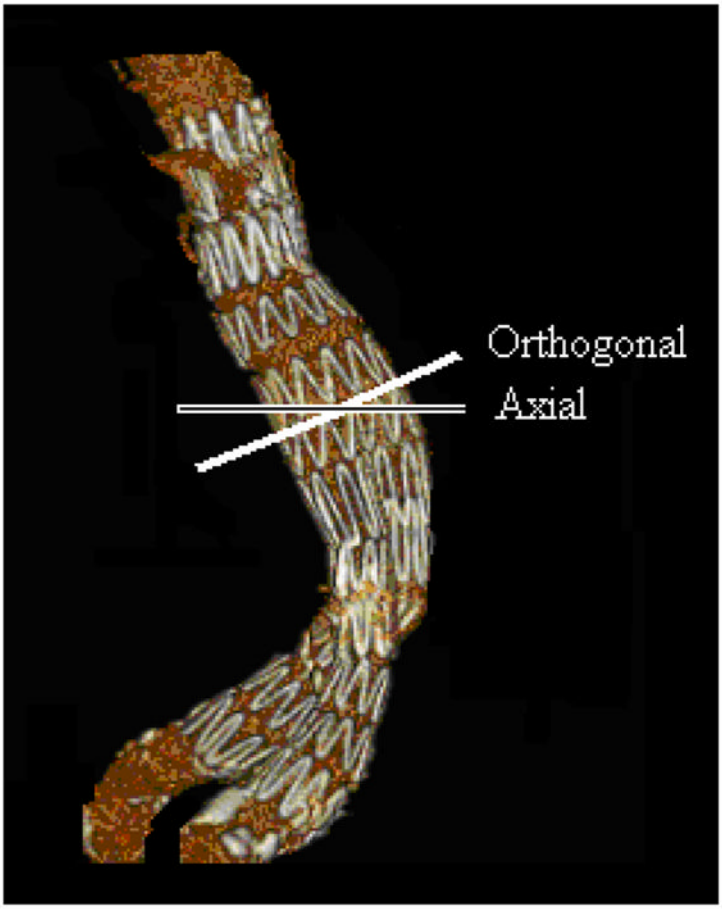

Figure 3.
A lateral 3D reconstruction of a mildly tortuous AAA post-treatment. In angulated aortas axial diameters tend to over-estimate the true orthogonal diameters.

Table 1

Risk Factors Associated with AAA

Predisposing Factors	Protective Factors
Smoking [1,21,50]	Diabetes Mellitus‡ [50,57,58]
Male Gender [1,21,23,51]	African and Asian race [1,52,53]
≥ 60 years of Age [1,21,23]	Female Gender$^{\psi}$ [1,21,23]
Northern European/Caucasian race [1,52,53]	≤ 50 years of Age [55]
Family History [1,53,54]	
Hypertension [1,21]	
Dyslipidaemia$^{\phi}$ [1,55]	
COPD$^{*\phi}$ [1]	
Obesity [56]	

*Chronic Obstructive Pulmonary Disease

$^{\phi}$Not conclusive

$^{\psi}$Women tend to have poor prognosis

‡It should be noted that some well designed studies have failed to find significant associations between diabetes and AAA [1,27]

Table 2

Recommended screening intervals for small aneurysms.

UKSAT recommendations [23]*		**SVS recommendations [94]**	
Aneurysm maximal diameter (mm)	**Ultrasound follow- up intervals**	**Aneurysm maximal diameter (mm)**	**Ultrasound follow- up intervals**
≤40	2 years	26–29	5 years
41–45	12 months	30–34	3 years
46–50	6 months[a]	35–44	12 months
>50	3 months	45–54	12 months

* Imaging frequency based on the likelihood of<1% patients developing AAAs exceeding 55 mm on return visit.

[a] UKSAT participants report that 6 month intervals for AAA ≥46 mm is safe in practice based on findings from the ADAM study [62]

Table 3

Displaying the important features to establish prior to AAA surgical intervention. Adapted from Geller (2003).[118]

CTA staging for AAA surgery
Maximal aortic diameter; axial and orthogonal; infra-renal and at the bifurcation
AAA length
Proximal and distal landing zone; length, diameter and quality.
Potential access routes; diameter, angulation and distance to aneurysm
Lowest renal artery distance to aortic and iliac bifurcation
Presence and location of thrombus and calcification
Presence of AAA rupture
Coexisting disease; aortic inflammation, aneurysms or occlusive disease at distant sites
Relative position and patency of major abdominal arteries

Table 4

Examples of gene polymorphisms linked to AAA

Gene	Gene product	Summary of findings
BAK1	Pro-apoptotic protein	SNPs encoding single amino acid substitutions at positions 42 (arg>his) and 52 (val>ala) detected in aortic biopsies of AAA patients and non-diseased controls. Analysis of SNPs in circulating blood revealed this mutation in AAA patients only suggesting that polymorphisms may need to be constitutively expressed across all tissues to influence aneurysm phenotype.[125]
HLA	Human leukocyte antigen	Correlation between AAA and the HLA-DQA1 polymorphism was demonstrated within a Belgian population (P = 0.019). Authors suggest that HLA-DQA1 locus harbours a genetic risk factor for AAA, further suggesting an autoimmune aspect in AAA pathogenesis.[126]
IL-10	Interleukin 10	'A' allele SNP in IL-10 promoter region demonstrated to be more frequent in AAA patients compared to controls (P=0.006). 'A' allele was considered a risk factor for AAA (OR 1.50, 95% CI 1.09–2.07), but did not appear to influence growth of small aneurysms.[127]
MMP3	Matrix metalloproteinase 3	5A polymorphism in promoter region of MMP-3 gene was demonstrated to be higher in AAA patients than controls (P = 0.0053, OR 1.32, 95% CI 1.09–1.61), and patients with aortic occlusive disease (P = 0.0004, OR 1.68, 95% CI 1.26–2.25), and was suggested a s a genetic predisposition to AAA.[128]
MMP9	Matrix metalloproteinase 9	SNP (position 1562 C>T) of MMP9 promoter was demonstrated to be more common in AAA patients than non healthy controls (P = 0.025) and peripheral vascular disease (0.003).[129]
TIMP2	Tissue inhibitor of metalloproteases	SNP of the TIMP2 gene (position 479 C>T) was more frequently expressed in AAA patients and controls (n= 50 and 41 respectively, p=0.054).[130]

SNP = Single nucleotide polymorphism; OR = Odds ratio; CI = Confidence Interval