Preoperative Supervised Exercise and Outcomes Following Elective Abdominal Aortic Aneurysm Repair

A Thesis submitted by

Hashem M. Barakat (MBBS, MRCS)

for the Degree of Doctor of Medicine (MD)

The University of Hull and The University of York

Hull York Medical School

December 2014

Prizes

The Vascular Society of Great Britain and Ireland – The Sol Cohen (Founder's) Prize for best clinical paper: November 2014

Publications

Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Role of pre-operative multiple gated acquisition scanning in predicting long-term outcome in patients undergoing elective abdominal aortic aneurysm repair. World J Surg. 2013 May;37(5):1169-73. PMID 23400591.

Barakat HM, Shahin Y, Barnes R, Gohil R, Souroullas P, Khan J, McCollum PT, Chetter IC. Supervised exercise program improves aerobic fitness in patients awaiting abdominal aortic aneurysm repair. Ann Vasc Surg. 2014 Jan;28(1):74-9. PMID 24332259.

Barakat HM, Shahin Y, McCollum PT, Chetter IC. Prediction of organ-specific complications following abdominal aortic aneurysm repair using cardiopulmonary exercise testing. Anaesthesia. 2015 Jun;70(6):679-85. PMID 25656939.

Barakat HM, Shahin Y, McCollum PT, Chetter IC. (Abstract). Cardiopulmonary exercise testing as a predictor of postoperative cardiac and pulmonary outcomes, early mortality and length of hospital stay in AAA repair patients. British Journal of Surgery 2014; 101 (S4): 2–49.

Barakat HM, Shahin Y, McCollum PT, Chetter IC. (Abstract). Hospital based exercise programme improves preoperative aerobic capacity in abdominal aortic aneurysm patients. British Journal of Surgery 2014; 101 (S2): 7–14.

Abstract

Objective

The aim of this research was to evaluate the role of preoperative supervised exercise training on perioperative outcomes and cardiopulmonary exercise testing (CPET) parameters in patients undergoing elective abdominal aortic aneurysm (AAA) repair, and to analyse the value of different preoperative risk assessment tools in predicting postoperative complications following this intervention.

Methods

Participants in this project were patients with large AAA (≥ 5.5 cm), awaiting elective open or endovascular repair.

Study 1: was a prospective randomised controlled trial. Participants were randomised in two parallel groups: a 6-week preoperative exercise training programme or standard treatment.

The primary outcome measure was the composite endpoint of postoperative cardiac, pulmonary and renal complications. Secondary outcome measures were: lengths of hospital and critical care stay, APACHE II scores recorded within 6 hours postoperatively, SIRS criteria, thirty-day mortality, reoperation and postoperative bleeding. Patients were followed up for 3 months postoperatively.

Study 2: was a sub-group study within *Study 1*.

A sub-group of patients from *Study 1* consented to undergo two rather than one preoperative CPETs: the first at baseline, and a second following

completion of 6 weeks of exercise or on the day immediately prior to surgery. The primary outcome measure was the effect of exercise on CPET parameters.

Study 3 utilised univariate and multivariate analysis to assess the value of different preoperative risk assessment tools in predicting postoperative complications in patients undergoing elective AAA repair.

Results:

Study 1: 136 patients were recruited, 12 withdrew before operative interventions and were not included in the analysis.
A total of 124 patients (62 in each group) were included (111 men, mean (s.d.) age 73 (7) years), of which 46 patients underwent EVAR (23 in each group).
14 patients (22.6 per cent) sustained postoperative complications in the exercise group, compared to 26 (41.9 per cent) in the non-exercise group (P=0.021). Four patients (3.2 per cent; 2 in each group) died within 30 days postoperatively.

Length of hospital stay was significantly shorter in the exercise group (median (IQR) 7 (5-9) days) than the control group (median (IQR) 8 (6.0 - 12.3) days) (P=0.025).

There were no significant differences in the length of critical care stay (P=0.845), APACHE II scores (P=0.256), incidence of re-operations (P=1.000) or postoperative bleeding (P=0.343) between the two study groups.

Study 2: 48 patients were recruited: 33 patients in the exercise group, and 15 in the control group. All participants completed their two CPET assessments. A 6-week exercise schedule improved aerobic fitness parameters compared to the control group. Median (IQR) VO_2 peak improved from 18.4 (15.0-20.9) to 20.0 (16.9-21.3) ml O_2/kg/min; P=0.004, and median AT improved from 12.0 (10.4-14.5) to 13.9 (10.6-15.1) ml O_2/kg/min; P=0.012. There were no statistically significant changes in CPET parameters in the control group.

Study 3: In 124 patients undergoing elective AAA repair, lower AT (OR 0.59, 9% C.I. 0.38 to 0.89, p=0.014) and higher V-POSSUM scores (OR 1.42, 95% C.I. 1.16 to 1.75, p=0.001) were the only independent predictors of postoperative complications.

A low AT was an independent predictor of cardiac complications (OR 0.59, 95% C.I. 0.36 to 0.96, p=0.034) and a high V_E/VCO_2 predicted pulmonary complications (OR 1.24, 95% C.I. 1.03 to 1.51, p=0.027).

Conclusion

Preoperative supervised exercise training appears to reduce postoperative complications and length of hospital stay in patients undergoing elective AAA repair. The mechanism appears to be an improvement in aerobic fitness preoperatively.

CPET is a valuable preoperative assessment tool for elective AAA patients as it predicts organ-specific complications and may be useful in directing perioperative care.

Table of Contents

Study 2; A Prospective Observational Study to Assess the Effect of Exercise on Aerobic Fitness in Patients Awaiting Elective Abdominal Aortic Aneurysm Repair

Study 3; The Value of Different Preoperative Assessment Tools in Predicting Postoperative Complications Following Elective Abdominal Aortic Aneurysm Repair

List of Figures

List of Tables

Table 16: Multivariable logistic regression with the dependent variable of postoperative cardiac complications.

Table 17: Multivariable logistic regression with the dependent variable of postoperative pulmonary complications.

Table 18: Multivariable logistic regression with the dependent variable of postoperative renal complications.

Acknowledgements

I thank God Almighty, and I thank my parents: Mohammad and Mariam Barakat for the continuous help and support through all stages of my life and my career. Without my parents' believe in me I would've never become the man I am today and I would've found it difficult to pursue my dreams.

I would like first to thank my supervisor Professor Ian Chetter, who dedicated time and effort to help me throughout the stages of this project and believed in me from the start by giving me the opportunity to undertake this research. Professor Chetter opened the doors wide for me to enter the academic field, and was an inspiration to me since my early years in clinical practice. I will be forever, grateful.

Secondly, I would like to thank Professor Peter McCollum, who helped me throughout this research and continuously provided me with advice and support. I am also thankful to have great colleagues like Yousef Shahin, Risha Lane, Rachel Barnes, Panos Souroullas, Sandip Nandhra, Daniel Carradice, Joseph El-Sheikha and Augustine Smithies. They were close friends and helpful colleagues and because of them I enjoyed my academic years despite all the challenges. I would like to thank Junaid Khan and Romesh Sarvanandan for helping me conduct this research project at various stages. I am grateful to everyone at the Academic Vascular Surgical Unit At Hull York Medical School who made the work environment very comfortable for me, I would never forget the three years I spent working there. I am grateful to the consultants in the Vascular Department: Mr Paul Renwick, Mr Brian Johnson, Mr Rakesh Kapur and Mr Bankole Akomolafe, who with their help and guidance I have managed to finish my research and progress to the next step.

Finally, warm thanks to my brother Zaid and sisters Yasmine and Rawan, and to my favourite little person; my niece Lamar, because they fill my heart with love and desire to come back home with success. I am thankful to my great friends Ahmad, Mos'ab, Wajdy, Deyaa and Mahdi, and to Zaher, Ahmed, Eyad, Modar, Zaid, Almar, Mafa, Moe, Neeraj, Ravi, Antony, Rob, Paul and Auos, I am lucky to have their continuous care and support and to have them as colleagues and real friends during good and difficult times.

Author's declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the Internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.

I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

CHAPTER 1: INTRODUCTION

1.1 Abdominal Aortic Aneurysms

1.1.1 History and overview

Albert Einestein was perhaps the most famous patient to undergo surgery for an abdominal aortic aneurysm (AAA) (Figure 1).

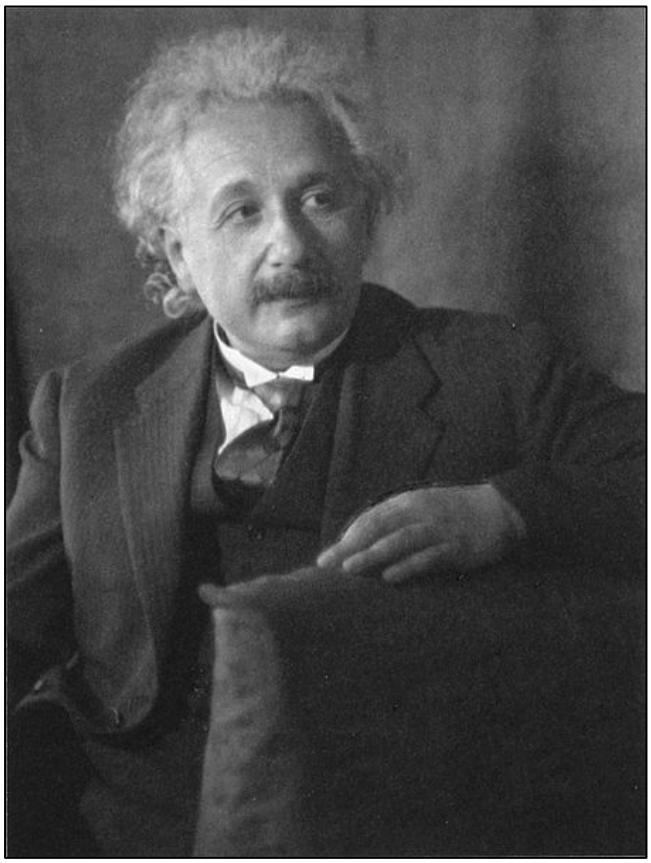


Figure 1: Albert Einstein; German-born theoretical physicist and philosopher of science. (14 March 1879 – 18 April 1955)- portrait by Doris Ulmann, 1931

Einestein was first diagnosed with an AAA at the age of 69. Back then, he smoked pipe and was a little overweight. Einestein initially presented to his

physician with intermittent upper abdominal pain and was found to have a pulsatile central abdominal mass when examined. In December of 1948, Einestein underwent an operation during which the anterior wall of his abdominal aorta was wrapped with cellophane to provide strength, stimulate fibrosis and in theory, prevent rupture. He was discharged following that and survived for over 6 years. He eventually died from a ruptured AAA on April 18th, 1955. At that time, Einestein refused further surgery, and was quoted saying:

"I want to go when I want. It is tasteless to prolong life artificially. I have done my share, it is time to go, I will do it elegantly".

The history and development of the management of AAA disease is a remarkable example of the advances made in medicine over the last 2000 years. However, it is thought that the first description of an arterial aneurysm was included in a paragraph from the *Ebers Papyrus* [1], which is probably the most well known ancient Egyptian medical document, written 1500 B.C. or earlier (Figure 2).

Figure 2: A passage from Ebers Papyrus; containing what appears to be advice to avoid surgery in aneurysmal disease

During the second century A.D., one of the pioneers in surgery; *Antyllus*, provided the first recorded description of the surgical management of an aneurysm: *'The Antyllus method'*, this included instructions to ligate the artery above and below an aneurysm, followed by incising and emptying the aneurysmal sac [2].

The first specific description of an abdominal aortic aneurysm was by the 'father of modern anatomy': *Andreas Vesalius* in the 16th century, when he gave anatomical and pathological descriptions of the disease correcting the mistakes of others before him.

British surgeons William and John Hunter performed operative ligations on a number of peripheral arterial aneurysms. Their scientific contributions from the 18th century on topics such as aneurysm aetiology, pathology and surgical management laid the foundation for many modern surgical concepts. Another British surgeon and scientist; Sir Astley Cooper, was the first to surgically ligate the abdominal aorta for a ruptured iliac aneurysm in 1817; the aortic specimen from that operation remains to date at the museum at St Thomas's Hospital in London (Figure 3).

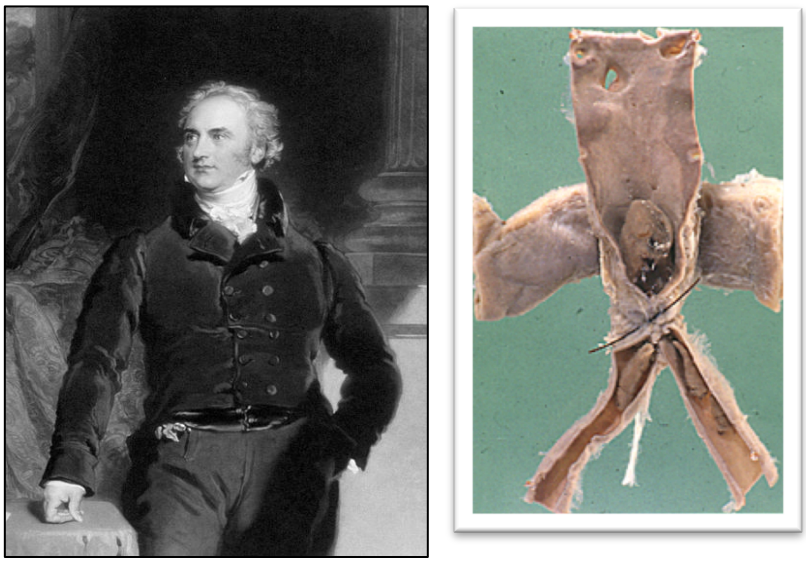


Figure 3: Sir Astley Cooper (1768-1841); English surgeon and anatomist and the specimen of the ligated abdominal aorta at St Thomas's Hospital.

Rudolf Matas, a prominent American surgeon, developed the concept of endoaneurysmorrhaphy in 1888, and it was a major advance in the surgical management of AAA disease. He did that by obtaining proximal and distal control of the aorta, which enabled him to obliterate the aneurysmal sac, sew collaterals and in doing so, preserve a lumen for blood flow (Figure 4).

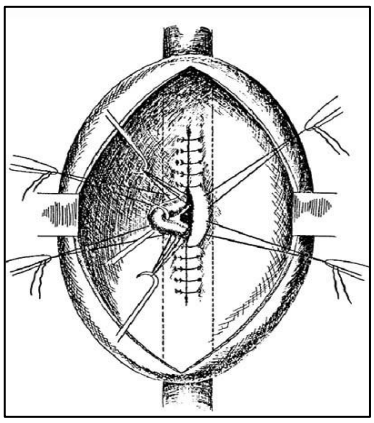


Figure 4: Technique for endoaneurysmorrhaphy by Rudolph Matas. A lumen is preserved and the aneurysm is plicated.

The world-renowned cardiovascular surgeons; Dr Michael Ellis DeBakey and Dr Denton Arthur Cooley, contributed largely to the development of the more modern techniques in aortic aneurysm surgery during their time at the Methodist Hospital and Baylor University (Houston, Texas) in the 1950s [3] (Figure 5).

Figure 5: Dr Michael E. DeBakey (Left) and Dr Denton A. Cooley (Right)

Juan Parodi performed the first successful endovascular repair of an AAA on the 7th of September 1990 [4]. He was inspired by the need of a less invasive technique for AAA repair, having seen a few complications of open repair during his training in the United States. Since then, a remarkable development on endovascular technologies meant that this minimally invasive technique is the most commonly used approach for AAA repair today.

1.1.2 Terminology and Definition:

An aneurysm is defined as a permanent, localised dilatation of a blood vessel or a heart chamber. The term itself is derived from the Greek word *ανευρυσμα* (aneurusma), which means widening.

AAAs refer to aneurysms affecting the abdominal aorta anywhere below the diaphragm. They are the most commonly diagnosed arterial aneurysms in humans. AAAs, most commonly affect the infrarenal part of the abdominal aorta (i.e. below the origins of both renal arteries), however, they can extend proximally to, or above, the origins of the renal arteries and will then be referred to as: para-renal or supra-renal aneurysms. They can also involve the aortic bifurcation and the common iliac arteries distally.

The normal abdominal aortic diameter varies with age, sex and body habitus [5, 6]. In elderly men, in whom AAAs are most common, the maximum measured diameter of the infra-renal aorta ranges between 1.5 to 2.4 cm [6]. In 1991, the Society for Vascular Surgery and the International Society for Cardiovascular Surgery agreed the criteria for defining AAAs as an infrarenal diameter 1.5 times the expected normal diameter [7]; this is generally considered when the maximum aortic diameter reaches or exceeds 3.0 cm [8].

Aneurysms can be further classified as true or false, or described according to their shape or behaviour. True aneurysms are those involving the three layers of the blood vessel's wall: intima, media and adventitia. A false aneurysm, also called a pseudoaneurysm, is essentially a haematoma that forms outside the vessel wall, most commonly as a result of preceding trauma. By definition, a pseudoaneurysm still communicates with the arterial lumen. It usually presents as a pulsatile swelling involving the soft tissue surrounding the affected vessel.

AAAs can also be described according to shape. Most AAAs are fusiform, (i.e. the whole arterial circumference is dilated), but they can also be saccular; where only part of the circumference is involved. Some AAAs can be associated with extensive inflammatory reaction that leads to the formation of retroperitoneal fibrosis, raised inflammatory markers and perianeurysmal adhesions to adjacent organs. These are commonly referred to as inflammatory aneurysms.

1.1.3 Epidemiology

AAAs are most commonly seen in men aged 65 years and older and represent a significant burden on health organisations in developed countries. The most feared complication of AAA disease is rupture; typically presenting acutely with abdominal pain and life-threatening haemorrhage, leaving patients with limited chances of survival. Ruptured

AAAs are the cause of approximately 6000 deaths per year in the United Kingdom [9]. The prevalence rates of AAA vary according to age, gender and geographic location; ranging between 1.3 - 8.9 % in men, and 0.7 - 2.2 % in women [10].

The last two decades has witnessed an interesting change in the epidemiology of AAA disease. In terms of AAA rupture; it was previously noted that the incidence of AAA was steadily increasing due to the ageing populations and improved diagnostic techniques, however, recent data from 1997 onwards may suggest the opposite [11,12]. A rapid decline in overall mortality from AAA rupture was noted from 1997 to 2009 [11,13]. Interestingly, this was most evident in patients younger than 75 years, in whom elective repairs did not increase as it did for the older age group. In addition, the age at which clinically relevant aneurysms (large, symptomatic or ruptured) are being detected, has increased by 5-10 years, and the overall incidence of AAA declined at the same time, especially in those younger than 75 years. The reasons for these observations are not clear, but may be due to the changes in smoking habits seen in most western populations, amongst other epidemiological changes; namely: an increase in the number of elective repairs, in addition to modern medical treatments for hypertension and hyperlipidaemia.

Screening for AAA was introduced based on the fact that AAA disease is an asymptomatic health hazard amongst elderly men. Population-based screening studies provided the best available data for the epidemiology of

AAA disease. The value of population-based AAA screening is supported by strong evidence for appropriate patient groups; it has been shown to decrease all-cause mortality for men aged 65 years and older [14]. In addition, the postoperative mortality rates for patients who have been diagnosed with AAA by screening are also lower than those diagnosed incidentally [15]. The mortality rate from elective infrarenal AAA in the UK has decreased over the last few years. The reported mortality rate was 7.5% in 2008, and that has decreased to 1.8% by the end of 2012 (3.8% for open repair versus 0.8% for EVAR) [16]. This is primarily due to a nationwide movement towards improved perioperative teamwork and multidisciplinary risk management implemented by quality improvement programmes.

1.1.4 Aetiology and risk factors

The development of AAA is a degenerative process that shares many of the features of atherosclerotic arterial diseases. Traditionally, AAA disease has been viewed as a consequence of aortic atherosclerosis. However, more recent research has challenged this theory and raised an interest that the aetiology of AAA differs, at least in part, from that of other atherosclerotic diseases.

Along with male gender and advanced age, cigarette smoking is now considered one of the most important risk factors associated with AAA

disease. Smoking is related not only to the risk of developing AAA, but also to the risks of more rapid AAA expansion and rupture [17-21]. This associated risk is higher than that for coronary artery disease or stroke [21]. This is reinforced by the observation that the drop in smoking prevalence in western countries during recent years appears to have a pronounced effect towards the improved overall outcomes of AAA rupture [12].

A history of coronary artery disease [19], hypertension [18,19], hyperlipidaemia [17,19], cerebrovascular disease [22], increased height [19] and the presence of other arterial aneurysms [22,23], are all factors associated with higher chances of developing AAA. A genetic predisposition explains why it is not uncommon for AAA patients to have a positive family history, especially in first-degree male relatives. Variants of chromosome *9p21* have been documented and the presence of rs7025486[A] in the DAB21P gene has been associated with a 20% increase in the risk of developing AAA [24]. Some HLA DR2 B1 alleles are associated with increased risk of AAA development and with increased aneurysmal inflammation.

On the other hand, diabetes, Black or Asian racial backgrounds are factors that appear to be negatively associated with AAA development. Weak evidence supports the association with factors such as homocyteinemia, high level of lipoprotein-a and plasminogen activator inhibitor-1 [25]. Less frequent associations also include: Marfan syndrome, Ehlers-Danlos syndrome and other collagen-vascular diseases [26], in

addition to: cystic medial necrosis, arteritis and trauma. Less than 5% of AAAs are mycotic aneurysms; commonly a result of gram-positive bacteria locally damaging the vessel walls leading to weakening and dilatation.

1.1.5 Natural history

In general, surgical treatment of non-ruptured AAAs is a prophylactic procedure that is usually planned on the basis of relative risks of rupture, perioperative morbidity, mortality and patient's life expectancy.

Large AAA diameters are associated with higher expansion rates: the average growth rate for aneurysms 3.0 – 5.5 cm in diameter is between 0.2-0.3 cm per year. However, there is a large variation between individual patients [27,28].

Data from the UK Small Aneurysm Trial (UKSAT) show that for aneurysms smaller than 4.9 cm in maximum diameter, the annual risk of rupture is estimated at 1.5%. For those 5.0-5.9 cm in diameter, the annual risk of rupture is increased to 6.5% [29]. This annual risk rises considerably for aneurysms above 6.0 cm in maximum diameter.

Ultrasound surveillance is regarded as a safe method to 'watch' small aneurysms (<5.5 cm) and based on UKSAT; repair is recommended when

aneurysms reach 5.5 cm in maximum diameter, show an unusual increase in growth rate (more than 0.5 cm over 6 months) or present with new onset of alarming symptoms. To date, there are no medical treatments that can slow growth rates in AAAs. Statins [30-33], beta blockers [34], and other medications have been investigated as potential agents that can alter growth rates in aneurysms with controversial results. Cigarette smoking is known to be associated with increased aneurysm expansion rates [28,35], and early smoking cessation is strongly recommended in this patient population. On the other hand, some studies suggest that diabetes has an interesting relationship with AAA disease, as it has a negative association with AAA development and expansion [36,37], unlike its role in the progress of peripheral arterial disease.

The risk of rupture remains the main concern. Large aneurysm diameters at diagnosis (or first imaging) are independently associated with increased risk of rupture [29,38]. The annual risk of rupture for AAAs of a maximum diameter between 6.0-6.9 cm is estimated between 10-22%, while for diameters above 7.0 cm the annual risk rises to above 30% [39]. Female gender [38,40], smoking [41], hypertension [38,42], rate of aneurysm expansion [38] and peak aneurysmal wall stress [43] are all factors that have been found to predict an increased risk of rupture.

1.1.6 Pathogenesis

In AAA, the underlying structural problem is the weakening of the aortic wall, resulting in progressive dilatation and eventual rupture if left untreated. A large number of studies in the literature investigated the possible mechanisms that can lead to aortic wall weakening [44], including changes in aortic wall histology, circulating biomarkers, specific protein concentrations and possible genetic factors.

Deficits in extracellular matrix proteins, abundance of proteolytic enzymes and features of chronic inflammation are common findings in the walls of human AAAs. A number of circulating biomarkers were found to be altered in patients with AAA disease, including: high-density lipoprotein, lipoprotein-a, antibodies to chlamydia, metalloproteinase-9, plasminogen activator inhibitor (PAI)-1, tenascin-X, and homocysteine amongst many others [25,45-48]. However, the role of these in AAA pathogenesis is complex and not completely understood [49].

In general, when the pathogenesis of AAA is considered, three main pathological processes should be discussed:

1. Proteolysis of the aortic wall connective tissue
2. Inflammatory and immune responses
3. Biomechanical wall stress

1.1.6.1 Proteolysis of the aortic wall connective tissue

The most important structural proteins in the aortic wall are elastin and interstitial collagens. The primary role of elastin is to support the formation of a complex network of elastic fibres to maintain the viscoelastic properties of the aortic wall. These are found mostly in the media of the blood vessel wall, in addition to vascular smooth muscle cells (VSMCs). Collagens, specifically; fibrillar collagen types: I and III, are found in abundance in both the media and the fibrous adventitia. While elastic fibres maintain the elasticity functions of the aorta, collagens provide the tensile strength of the aortic wall to help maintain its structural integrity.

There is enough evidence to demonstrate an increase in degradation of both elastin and collagen in the aneurysmal aortic wall by the increased action of proteolytic enzymes produced locally by medial VSMCs, adventitial fibroblasts and other inflammatory cells [50]. Much of this evidence is derived from studies on matrix metalloproteinases (MMPs); a large group of calcium-dependent, zinc-containing endopeptidases that have essential roles in the remodelling and degradation of extracellular matrix proteins. The four MMPs capable of degrading elastic fibres are: MMP 2 (72-kD gelatinase), MMP 7 (matrilysin), MMP 9 (92-kD gelatinase) and MMP 12 (macrophage elastase). Other MMPs are specific for their actions on interstitial collagens [51-53]. There are also higher proportions of MMP 2 (in its active form compared to the pro-enzyme: proMMP 2) and MMP 14 (a principal activator for proMMP 2) in aneurysmal walls [54]; suggesting their important role in wall degradation. In addition, the

expression of tissue inhibitors of matrix metalloproteinases (TIMPs); the natural inhibitors of MMPs, is also increased [55]. These are examples of some of the markers of the increased local proteolytic activity. The overall balance between proteases and anti-proteases favours proteolysis during AAA progression. Specifically, the balance between synthesis and degradation of elastin plays an important role in maintaining the overall strength of the aortic wall, and is directly related to the expansion and progress of aneurysmal disease [56].

On the other hand, the balance between collagen synthesis and degradation is thought to be of extreme importance at the critical stages of aneurysm progression. Collagen synthesis is thought to counteract its degradation in the stable and intermediate stages of AAA expansion. However, a more rapid collagen degradation may result in rapid expansion and rupture. Both MMP 1 (collagenase-a) and MMP 13 (collagenase-3) are implicated in this process [57,58].

It is also worth adding that a reduction in the density of smooth muscle cells is regarded as another important factor in the development of AAA disease [59]. VSMCs play a role in the remodelling of the vessel wall and they play a protective role against proteolysis and inflammation. Under cyclic stretching in-vitro; VSMCs has been shown to produce less monocyte chemotactic protein-1 (MCP-1); a major mediator in regulating the inflammatory process in AAA pathology, which is potentially an important protection mechanism that is inhibited in AAA disease.

1.1.6.2 Inflammation and immune response

Much of the connective tissue changes described above are mediated by inflammatory cells as chronic inflammation is a prominent feature in AAA disease [53]. Inflammatory infiltrates comprised of T-cells, monocytes, macrophages, B lymphocytes, plasma cells and HLA-DR+ T-cells have been demonstrated in AAAs and this raised the possibility of possible auto-immune processes [60,61].

Many proteins that could serve as auto-antigens were characterised in AAA walls, including aneurysm-associated antigenic protein -40 kD (AAAP-40); a specific antigen protein found most prominently in the abdominal aorta and iliac arteries. An antibody raised against a specific oligopeptide in AAAP-40 was demonstrated in abundance in adventitial microfibrils associated with collagen. IgG is also abundant in the aortic wall of AAAs. These autoimmune features are inconclusive and further research towards possible implications on treatment of AAAs is being advocated.

The most important pathological feature of human AAAs is probably the infiltration of outer parts of the aortic wall with inflammatory cells; a procedure associated with the induction of intracellular and extracellular cytokines, the expression of cell adhesion molecules, an increase in

protease expression and the release of reactive oxygen species.

Lymphocytes are the main cell population found in AAA-associated inflammation. T-helper (Th) 2-restricted $CD3^+$ T lymphocytes are the main cell type, and they mediate the process by the expression of cytokines that are essential for the regulation of the local immune response and the secretion of MMPs and cysteine proteases, all essential elements in wall matrix remodelling.

Non-conclusive evidence linked lymphocyte activity in AAA walls to exposure to auto-antigens and micro-organisms [62,63]. Serum antibodies against Chlamydia pneumonia have been associated with AAA progress [64], but there is no clear evidence to show that antibiotics against *C.Pneumoniae* can alter AAA progression.

1.1.6.3 Biomechanical wall stress

The biomechanics of stress forces at different levels of the aneurysmal wall are relevant factors to consider in order to appreciate the mechanics of aneurysm progress and rupture.

The wall of the infrarenal aorta differs from other parts of the aorta as there is evidence that the proportion of elastin decreases more distally, owing to an increase in the actions of MMP-9 [65]. There is also a decrease in vasa-vasorum (arterial blood supply to the aortic wall) that may

contribute to localized vessel wall ischaemia [66,67]. In addition, pulsatile blood flow was found to be altered in infrarenal sections of the aorta and this is thought to provide some understanding on the preferential formation of AAAs in that region [56,68,69].

The development of AAAs is associated with a mural thrombus in most subjects. The remodelling and evolution of this thrombus correlates with plasma markers of fibrin formation and degradation as well as circulating levels of complex plasmin-α2-anti-plasmin which are in turn correlated to the changes in aneurysm diameter [70,71]. Thrombus can reduce wall stress, however, its increasing thickness results in medial hypoxia and increased neovascularisation and inflammation [72]. In addition, MMP-9 is found in abundance in thrombi [73]. Further research showed also that plasminogen and its activator u-PA are also present, proposing that this can result in generating and activating more MMP-9 [74].

The research on wall stress and its implication in AAA progress is complicated and also not clearly conclusive. There are little doubts however, that these biomechanical factors play a role in AAA progress and especially the potential risk of rupture.

1.1.7 Presentation

1.1.7.1 Non-ruptured AAA

In most patients, non-ruptured AAAs are generally asymptomatic and the diagnosis is often made when they are investigated for other symptoms or upon screening [20]. Some aneurysms can cause minor non-specific complains such as abdominal discomfort, dyspepsia or back pain. An increasing or a 'new-character' pain should alert the clinician to the possibility of rapid expansion or impending rupture.

Mass or pressure related effects can cause symptoms such as vague abdominal or back pain from direct pressure. Similarly, pressure on the ureters can result in hydronephrosis; this is more common in inflammatory aneurysms or those involving the iliac bifurcation [75]. Rarely, peripheral vascular complications from aneurysms can contribute to the initial symptoms; these can include: distal embolization and acute thrombosis [75].

1.1.7.2 Ruptured AAA

The feared fate of untreated AAAs is acute rupture. This is a surgical emergency characterized by the triad of: acute abdominal pain, hypotension and a pulsatile abdominal mass. This clinical triad is however, only seen in a third of ruptured AAA presentations. Most patients reaching the hospital alive present with an acute onset of severe abdominal pain

penetrating to the back, mimicking other causes of an acute abdomen, which can make it challenging to diagnose unless its always highlighted as an initial diagnosis to exclude.

Nearly 20% of AAA ruptures involve the anterior vessel wall and result in free bleeding in the peritoneal cavity; these patients usually die at the scene from severe haemorrhage. The rest are usually postero-lateral ruptures in the retroperitoneal space forming a retroperitoneal haematoma. Often, the combination of moderate hypotension and the resistance of retroperitoneal tissue can stop the bleeding, at least for a brief period of time. This can be a window of opportunity for prompt diagnosis and operative management, which is virtually the only chance for survival. Less commonly, ruptures can be contained and form a chronic retroperitoneal haematoma. AAAs can also rupture directly into adjacent organs, including the duodenum or the inferior vena cava with a resulting communication between the two (i.e. formation of fistulae). Aorto-caval fistulae can result in high-output congestive cardiac failure and oedema involving the lower body. Aorto-duodenal fistulae can result in sudden acute severe gastrointestinal bleeding that is fatal if not treated promptly [75], they are however, more commonly seen as a complication of previous operative repair rather than an acute complication of a ruptured AAA.

1.1.8 Imaging in the diagnosis of AAA

Anatomic assessment of AAA serves as one of the main steps in preoperative assessment and technical planning. Knowledge of aneurysm morphology will help the surgeon anticipate a difficult dissection and plan extra measures during open surgery. It also plays an essential part in determining the anatomical suitability and technical details for endovascular repair. Computed tomographic angiography (CTA) is now considered the standard pre-operative imaging modality, but many other imaging techniques are also useful for the assessment of AAA.

1.1.8.1 Ultrasound

Ultrasound is considered the modality of choice for detection and surveillance of AAAs. It is reliable, cost-effective and widely available [76-78]. From a technical point of view, bowel gas can obscure the image of the aorta and clear demonstration can be also difficult in obese patients. In addition, ultrasound does not demonstrate peri-aortic anatomy clearly [79,80] and is generally operator-dependent [81]. It is acceptable to perform additional imaging if aneurysms show rapid expansion or reach the size at which intervention will be considered. More details on the use of ultrasound imaging will be discussed later in this chapter where screening for AAA is covered.

1.1.8.2 Angiography

Digital subtraction angiography (DSA) allows visualisation of the true lumen of the aorta and its branches. However, it is invasive, exposes the patient to iodinated contrast and most importantly, tends to under-estimate the size of the aneurysm, as it doesn't include a clear visualisation of the thrombus or the aortic wall tissue, but rather a reflection of the lumen.

1.1.8.3 Computed tomographic angiography (CTA)

CTA is a fast and widely available imaging modality. It is now considered the standard preoperative imaging modality in most centres [82] (Figure 6).

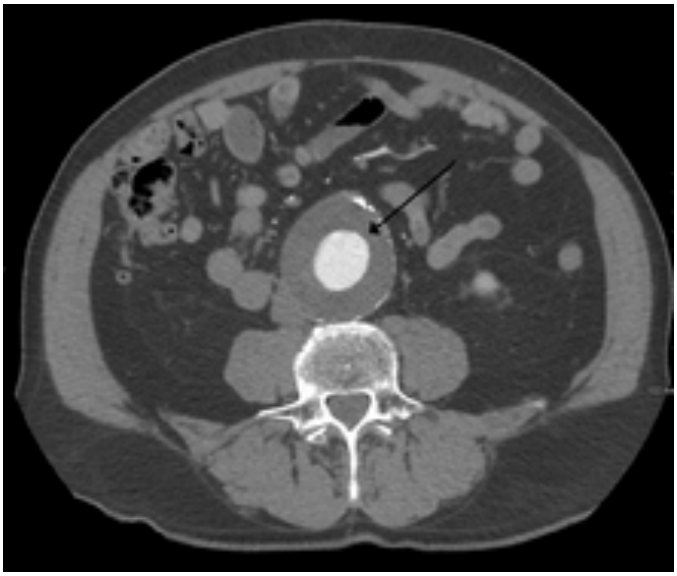


Figure 6: Contrast-enhanced CT scan showing an AAA

Using this modality, images obtained can be reconstructed electronically to accurately demonstrate the morphology of the aneurysm (Figure 7). Any periaortic abnormalities, inflammatory components, anatomic variations of

the renal vessels and the surrounding viscera can be identified [83,84]. These images can be presented in a dynamic 2- and 3-dimensional formats and this has become essential in preoperative planning of open and endovascular repair [85]. Multidetector CT imaging systems of 128 and 256 rows can also present the aortic borders clearly and in different phases of the cardiac cycle [85].

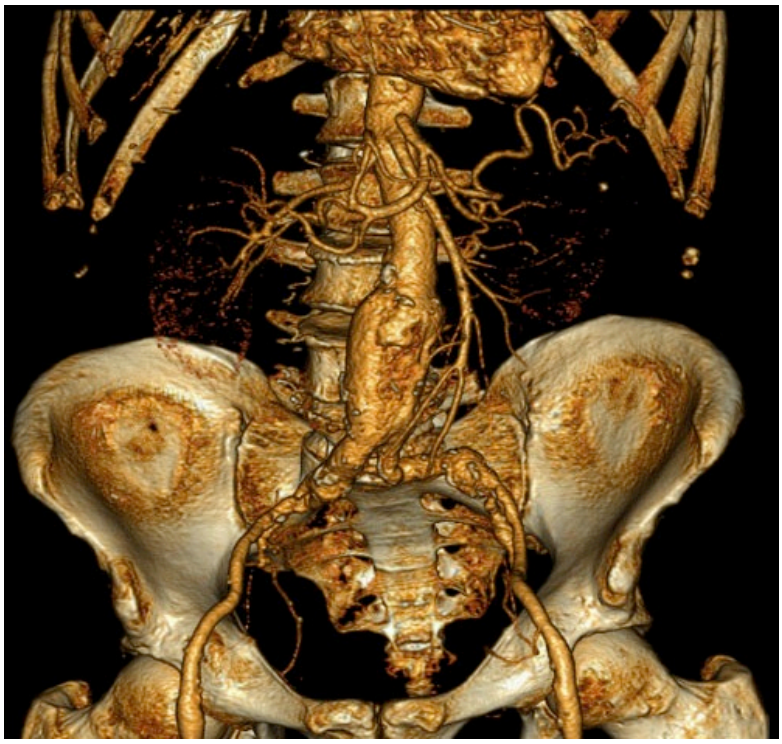


Figure 7: A 3-dimensional reconstructed CT scan of an AAA

CTA can also demonstrate several anatomic features predictive of aneurysm rupture [86]. These include discontinuous calcifications and thrombus morphology. Many studies proposed the use of specifically designed software that can utilise data from CTA also to assess the risk of rupture [87,88]. The main disadvantage of CTA however, remains the use of

ionising radiation and contrast material. Higher detector rows-CTAs are also time-consuming.

1.1.8.4 Magnetic resonance angiography (MRA)

This modality can also be useful; as it offers good soft tissue views, with the possibility to evaluate both the vessel wall and the lumen with clarity [78,85]. It is also accurate in measuring the aneurysm diameter and the extent of surrounding inflammatory reaction [89] (Figure 8).

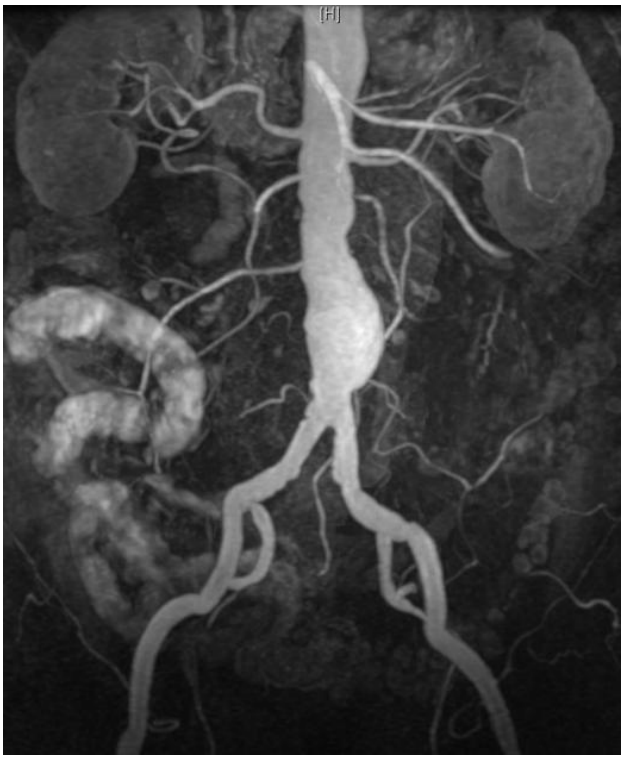


Figure 8: An MRA of an AAA

MRA images are obtained without the use of ionizing radiation and there is no necessity to use contrast material. It offers evaluation of blood vessels in multiple phases of vascular contrast (arterial, venous and delayed). Disadvantages are mainly related to higher costs and time-consumption. MRA can also be affected by artefacts and can be contraindicated in patients with claustrophobia and metallic implants.

1.1.9 Management

As explained, the management of AAA when diagnosed depends on the balance between risk of perioperative mortality and aneurysm rupture. This will be considered here starting from screening; the initial step in diagnosing asymptomatic small AAAs, and covering the current modalities of medical management of small AAAs. Surgical management will also be discussed.

1.1.9.1 Screening and surveillance

The Multicentre Aneurysm Screening Study (MASS) randomised trial [90], showed that population screening reduces aneurysm-related mortality by about 40 per cent over ten years. Based on this and further research, population screening programmes are now common in many western countries [10,91,92]. Men aged 65 years and above are the target group with the highest prevalence of AAA. It is likely however, that further re-evaluation may change the age category to include those 60-65 years

as well. There is not enough evidence to support population screening for women.

Ultrasonography has a high sensitivity and specificity for detecting small AAAs with accurate measurements of external and internal aortic diameters. The standard practice is to document the antero-posterior (AP) diameter during surveillance, as it has better repeatability when compared to the transverse diameter [93]. In addition, it is common practice to use the external diameter measure (also referred to as the outer-to-outer measure); which includes the AP diameter between the outermost borders of the anterior and posterior aortic walls as opposed to the internal diameter (inner-to-inner measure) that measures the AP diameter from the two inner borders but not the mural thrombus (Figure 9).

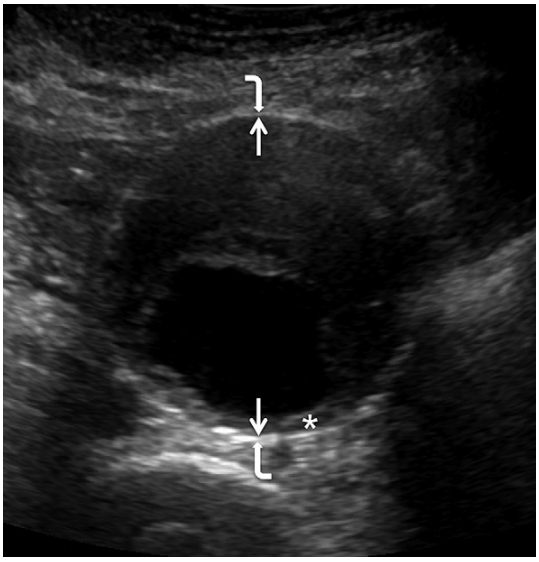


Figure 9: Transverse ultrasound image of an AAA.
The aortic diameter is measured in the AP plane.
The straight arrows indicate the position of the inner anterior and inner posterior wall. The angled arrows indicate the position of the outer anterior and outer posterior wall. The asterisk indicates an area of mural thrombus on the posterior wall

1.1.9.2 Medical management of AAA

The aims of any medical therapy in the context of AAA disease would be:

- To slow aneurysm expansion and delay surgical intervention, and
- To reduce the risk of cardiovascular events, which would normally account for the majority of mortalities in this patient population.

Currently, there are no recommendations to use any pharmacotherapies specifically to limit aneurysm expansion. During surveillance, and especially during the perioperative period, it is important to comply with the best medical therapy in order to reduce the risk of cardiovascular and other unwanted morbidities.

Smoking cessation is considered one of the most important measures for optimising cardiopulmonary risk. In the short term, it can reduce unwanted lung secretions and optimise respiratory function. It should be strongly encouraged to all patients with a diagnosis of AAA, and especially 4-6 weeks before intervention as this has been shown to reduce postoperative cardiac morbidity and hospital stay [94-96].

Further optimisation can be achieved with the use of pharmacotherapy in AAA patients. Statins, antiplatelet agents and beta blockers have shown promise for this purpose [97]. Equally important, is the use of appropriate anti-hypertensives for adequate blood pressure control.

1.1.9.2.1 Statins

Statins, by inhibiting the enzyme HMG-CoA reductase, lower cholesterol production by the liver and stimulates low-density lipoprotein (LDL) uptake. In addition, the hypotheses that statins may have anti-inflammatory roles within atherosclerotic plaques and may also improve endothelial function, initiated several studies to investigate these actions as to whether these can be separate from statins' lipid-lowering properties [98]. The evidence is promising, but still non-conclusive.

Studies have shown that there is a reduction in all-cause mortality following elective interventions in AAA patients on statin therapy. Treatment with statins specifically lowered cardiac morbidity and mortality [99-101]. In patients undergoing major non-cardiac surgery, statin therapy is associated with significant reduction in perioperative morbidity [102]. In a study that included 570 patients with AAA, the incidence of postoperative 30-day mortality or cardiac complications was significantly lower in subjects on statins [103] . An observational study that included more than 1600 patients undergoing vascular surgical procedures, statin use was associated with a three-fold reduction in the risk of death following major vascular interventions, and a two-fold reduction in the risk of postoperative myocardial infarction [104]. In this study, the use of 'chronic statin therapy' was also associated with a reduction in postoperative renal and cerebrovascular complications, but had no effect on the incidence of pulmonary complications. These improvements are thought to be due to a range of local and systematic effects:

1. Inhibition of the development and progress of atherosclerosis
2. Reduction in platelet aggregation
3. Improved endothelial-dependent vasodilation
4. A reduction in the inflammatory response

All patients with AAA should be started on statins at least one month prior to intervention, to reduce cardiovascular risk. Statins should also be continued postoperatively [97].

1.1.9.2.2 Anti-platelets

Aspirin is a salicylate drug, also known as acetylsalicylic acid. It has been used as an anti-inflammatory agent to reduce pain and pyrexia. By inhibiting the action of thromboxane; a natural lipid that facilitates platelet aggregation, aspirin has found an antiplatelet function, and been since commonly used for preventing adverse thromboembolic vascular events [105].

The use of Aspirin is widely accepted as a preventive measure against cardiovascular events during surveillance (i.e. coronary arterial events and cerebrovascular events) of small AAAs, although this is not supported by a high level of evidence. A meta-analysis of primary and secondary prevention randomised trials, which included patients with proven vascular disease (including AAA patients), demonstrated that preoperative use of low-dose aspirin was associated with a reduction in major coronary

events, including non-fatal myocardial infarction and overall coronary-related mortalities [106]. So, it is recommended for patients to be on an antiplatelet agent; preferably low-dose aspirin, preoperatively to optimise their cardiovascular risk profile. This is to be continued throughout the perioperative period [97]. Clopidogrel is an alternative when Aspirin is poorly tolerated.

1.1.9.2.3 Beta Blockers

The perioperative use of beta blockers in non-cardiac surgery, in general, is currently the source of great controversy and regular debate. The fact that a large contribution to this area of research by a Dutch group has been recently discredited due to research misconduct, only adds to the confusion [107,108].

The previous evidence suggested a benefit to beta blockade during non-cardiac surgery, particularly in the high-risk patient population. Beta blocker therapy appeared to reduce the risk of peri-operative myocardial ischemia, decrease the risk of nonfatal MI and lower all-cause mortality [109]. These potential perioperative benefits should now be evaluated with care as latest research suggests that potential harm in the form of increased all-cause mortality can be inflicted by the routine perioperative beta blocker administration [110]. The most recent recommendations from the European Society of Cardiology and the European Society of Anaesthesiology state that beta blockade is not

recommended in patients without risk factors or in those scheduled for low-risk surgery [111]. Continuation of beta blockade is recommended for those who are already on it. These recommendations are similar in terms of content to those by the American Heart Association and American College of Cardiology.

An international double-blind randomised controlled multicentre trial; the POISE trial [112], assessed the effect of perioperative metoprolol administration primarily on cardiovascular deaths and non-fatal cardiovascular complications postoperatively. Interestingly, 30-day postoperative myocardial infarction and atrial fibrillation were lower in the metoprolol group, however, the mortality, incidences of hypotension, bradycardia and postoperative stroke were higher. The vast majority of strokes in the metoprolol group were ischaemic, which might be explained by the increased likelihood of “clinically-significant” hypotension. In POISE, the metoprolol dosage was 200 mg daily (100 mg extended-release form, twice a day) and started 4 hours preoperatively. It is widely believed, that in the absence of definite evidence-based answers, the key factors for determining suitability for optimal perioperative beta blockade are the risk profile of patients, dosage, duration and the timing of administration.

Regarding AAA expansion, propranolol was the only beta blocker studied, and it appeared to have a small, but non-significant effect of limiting AAA expansion, and was poorly tolerated by patients [34]. Currently, beta blockers are not recommended to prevent AAA expansion or

progression [113].

1.1.9.2.4 Anti-hypertensives

An important factor in reducing cardiovascular morbidity for patients with small AAAs is adequate blood pressure control. It is recommended that a target blood pressure of less than 140/90 mmHg be maintained during surveillance [97].

Many trials are now underway investigating the effect of anti-hypertensive agents such as angiotensin converting enzyme inhibitors (ACEIs) on AAA expansion, as observations made in animal studies suggested that angiotensin II-mediated aneurysm wall inflammation and proteolysis represent two potential factors in aneurysm formation. Conflicting results, however, emerged from different studies, particularly when ACEIs were studied as opposed to angiotensin receptor blockers (ARBs). One case-controlled study linked the use of ACEIs in AAA patients to a reduced likelihood of aneurysm rupture [114]. An NIHR HTA funded, multicentre, randomised controlled trial (the AARDVARK Trial) analysing the effects of ACEi on AAA expansion has now completed recruitment, and is due to report within the next 12 months.

In summary, there is currently no sufficient evidence to clarify the potential role of ACEIs or ARBs in AAA disease and further research is underway.

1.1.9.3 Surgical Management of AAA

There are generally two interventions for the repair of non-ruptured abdominal aortic aneurysms: open repair, or the less invasive endovascular repair, first described in the late 80s. Laparoscopic repair is another option, but it is less commonly used despite reports in the literature indicating it has relatively low complication rates, and can therefore be considered a safe and feasible option [115]. The EVAR 1 trial [116], answered many queries regarding the newly adopted, less invasive, endovascular technique. The trial demonstrated a significant reduction in 30-day mortality with EVAR in comparison to open repair, however, this benefit was lost at 12 months.

It is worth mentioning that both interventions should be considered as intermediate-to- high risk, particularly in the patient with cardiac risk factors, as coronary artery disease remains the most common cause of early and late death in this patient population. Some studies that showed cardiac morbidities can be as high following EVAR as it is following open repair [117]. Aneurysm repair should be deferred in patients with significant cardiac morbidities until this is optimised [97].

1.1.9.3.1 Open repair

Open aneurysm repair (OAR) is considered a major surgical procedure, and therefore, perioperative management is an important cornerstone in

aiming to minimise morbidity and mortality. OAR is performed under general anaesthesia and involves a laparotomy (via a transverse or a longitudinal midline incision (Figure 10), or a via a retroperitoneal approach) with cross-clamping of the abdominal aorta for a minimum of 30 minutes. The aneurysmal aortic segment is replaced with a prosthetic graft, usually made of Dacron (knitted or woven) or polytetrafluoroethylene (PTFE), which maybe configured as a tube or a bifurcated shape, according to need or preference. As aneurysms can extend proximally to the origins of one or both renal arteries and distally to involve the common iliac arteries, the procedure can be considerably more complex and time-consuming. Supra-renal clamp placement and an increased operative duration can be associated with higher rate of complications [118].

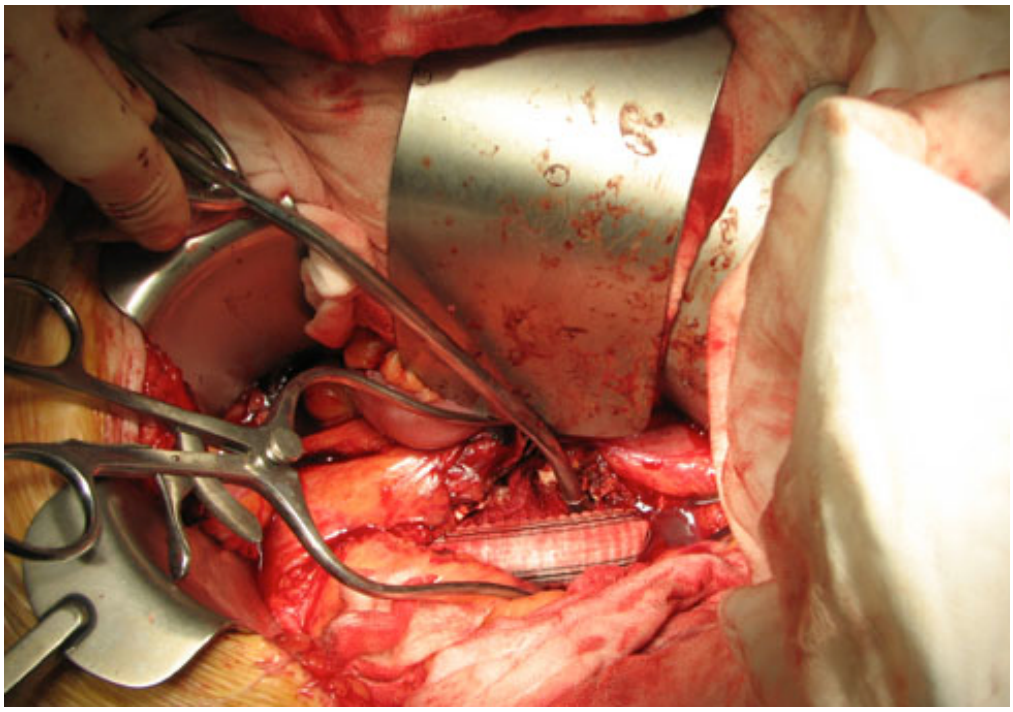


Figure 10: Open tube-graft repair of AAA, access through a laparotomy incision

During the procedure, some important measures are taken to minimise the surgical insult, for example:

- To minimise the risk of wound or graft infection, a single dose of prophylactic antibiotic is usually given at induction of anaesthesia [97].

- The risk of hypothermia is minimised by monitoring core body temperature and using warming blankets, humidified gas and warmed intravenous fluids.

- Intraoperative fluid management is another crucially important measure. Crystalloids, colloids and blood transfusion are all commonly used to compensate for the high fluid loss, which may average up to 1 litre per hour during surgery due to blood loss and tissue oedema.

It is essential to communicate effectively with the anaesthetic team throughout these procedures, especially at the time of clamping and de-clamping the abdominal aorta, which may result in haemodynamic disturbances that should be anticipated and promptly managed.

Open repair of non-ruptured AAA has an associated 30-day mortality in the range of 2-8 % [119-123], with a high incidence of postoperative complications. In most cases, the outcome depends on the patient's recovery during the early postoperative period; therefore, patients undergoing open repair should be managed in the critical care setting for the immediate postoperative period. This allows for optimal monitoring and early management of postoperative complications [124]. Invasive

monitoring, inotropic support, in addition to any other organ support facilities are usually available.

1.1.9.3.2 Endovascular repair

This is the minimally invasive option for AAA repair. It involves less pain, reduced operative time and reduced hospital stay. There is also less blood loss, a shorter duration of aortic occlusion and critical care is not routinely needed for all patients [116,117,125]. EVAR can also be performed under local anaesthetic [126].

EVAR involves the insertion of a stent graft (Figure 11) inside the aortic aneurysm, excluding it from the circulation by adequate proximal and distal sealing and fixation. This is delivered via femoral access and involves exposure to radiation and contrast material.

Figure 11: Stent grafts used for EVAR

The disadvantages of EVAR are mainly related to technical challenges in achieving a durable seal between the stent graft system and the vessel walls in order to prevent blood leaking back into the aneurysmal sack; a phenomenon known as an endoleak. Patients undergoing EVAR will therefore be subjected to repeated imaging postoperatively. In addition, this technology is limited by anatomic suitability, which is assessed by detailed preoperative imaging to plan the intervention, however, graft designs have improved in recent years and grafts are now commercially available to accommodate for anatomically challenging aneurysms, e.g. para-renal aneurysms, iliac aneurysms and presence of accessory renal arteries.

The preoperative risk assessment and postoperative complications for both interventions will be discussed in dedicated sections in the remainder of this chapter.

1.2 Preoperative risk management

Most surgeons base their decisions for intervening in AAA depending on two factors:

1- The balance between the risk of aneurysm rupture and operative mortality for individual patients.
2- The diameter of the aneurysm and its rate of expansion, or the associated symptoms.

Risk assessment in the perioperative period is mainly an evaluation of basic organ functions and co-morbidities in AAA patients. Cardiac causes, especially coronary artery disease, are the most common causes for early and late mortality and morbidity following vascular surgery [127-129] and the general agreement is that cardiac function should be evaluated in these patients to detect for silent dysfunction as well as apparent coronary arterial disease or functional abnormalities. Equally, the evaluation of pulmonary and other body functions is important in determining fitness for intervention.

The advent of EVAR, which is associated with lower short-term morbidity and mortality, gradually meant that patients who might have been considered unfit for open repair can be offered EVAR. However, the EVAR-2 randomised clinical trial demonstrated that in patients who are unfit for open repair and undergo an EVAR, early postoperative mortality is higher than anticipated and there was no difference in overall survival

compared to patients who had no intervention at all [125]. This highlights the importance of preoperative risk assessment also in subjects undergoing EVAR.

In order to understand the importance of perioperative assessment and surgical risk management, it is necessary to discuss the physiological changes and the stress responses associated with operative interventions for AAA.

1.2.1 The physiological responses to AAA repair

In general, the stress of surgical interventions is dependant on the extent of the procedure and its total duration, both resulting in a marked increase in oxygen demand. Major intra-abdominal surgery, such as open AAA repair results in an increase of oxygen demand that can exceed 40% [130]. Healthy cardiovascular and pulmonary systems are needed to compensate for this by an increase in cardiac output and oxygen delivery to tissues. If the metabolic and neuroendocrine responses are unable to maintain essential organ functions perioperatively, the likelihood of postoperative complications and organ failure rises dramatically. This is especially true in subjects likely to have multiple co-morbidities such as AAA patients. Pre-existing myocardial ischaemia, left ventricular dysfunction or the presence of respiratory illness should therefore be highlighted preoperatively and optimised to minimise these risks.

1.2.1.1 Haemodynamic changes during surgery

In the case of open repair, aortic cross-clamping is associated with a range of haemodynamic changes which might lead to myocardial stress [131]. These include a decrease in cardiac index (cardiac output in litres per minute per square metre body surface area) with an increase in afterload (or systemic vascular resistance). In addition, cross-clamping can cause an increase in preload and in pulmonary artery wedge pressure (PAWP). The end result being, a pronounced rise in arterial pressure, with or without changes in heart rate. Because of an increase in both preload and afterload, an increase in myocardial oxygen demand ensues and requires healthy coronary arteries to provide the extra supply. These changes are obviously, proximal to the clamp site, while the circulation distal to that demonstrates an overall decrease in blood flow and a decrease in arterial and, subsequently capillary pressure with associated end organ ischaemia [131].

Cross-clamping has a variable effect on cardiac output. This depends on the level of the clamp, its overall duration and the presence of collateral circulation. Pre-existing cardiac dysfunction can mask a potential change in cardiac output, as will the anaesthetic technique and the intravenous fluid status.

Clamp release is associated with further drop in cardiac index and a rapid decrease of systemic vascular resistance, and as a result, a drop in

arterial blood pressure. The changes in cardiac output are variable, but left ventricular end-diastolic pressure will decrease, while myocardial blood flow increases again. The end result is central hypovolaemia that is usually compensated for rapidly. It is important to note, that blood flow through the carotid arteries will also decrease at clamp release [131].

Despite the fact that aortic occlusion is sometimes needed, EVAR is associated with generally less profound haemodynamic changes, which is one of the main factors for it to be considered a less invasive procedure associated with lower incidences of short term cardiac complications and early mortality [132].

1.2.1.2 Metabolic and neuroendocrine changes during surgery

As explained above, aortic cross-clamping is the main haemodynamic insult during open surgery. In addition to its haemodynamic effects, it is associated with metabolic changes in the form of acidosis (a decrease in pH, HCO_3^{-1}, and an increase in base deficit) as a result of increased lactate production [133]. Clamp release will result in an initial worsening of the lactic academia and increased carbon dioxide release, which can aggravate the vasodilation and hypotension, but this will be usually balanced rapidly.

The levels of plasma catecholamines usually increase with surgical interventions for AAA. This is greater with open repair as concentrations of cortisol, epinephrine and norepinephrine remain relatively high throughout surgery and contribute to the regulation of the haemodynamic changes mentioned before [133].

It is also worth mentioning, that the levels of prostaglandins, cytokines, oxygen free radicals and inflammatory markers are subject to significant changes during aortic surgery, this is especially true in relation to aortic clamping [131]. The generation of oxygen free radicals and inflammatory markers is less with EVAR [133].

1.2.2 Preoperative co-morbidities

The main objective of preoperative risk assessments in planning repair of AAAs is to identify patients at a higher risk of morbidity and mortality. Extensive research therefore aimed at identifying predictors of morbidity and inferior survival by means of preoperative clinical biomarkers, functional assessment measures and mathematical scoring systems. Cardiac, pulmonary and renal causes account for the main postoperative complications and can be optimised. These will be discussed separately in this section. The focus here will be on patient-specific parameters related to inferior short-term postoperative outcomes.

Advanced age, is a recognised, non-modifiable risk factor that is associated with higher early mortality in most reports in the literature. It is usually an essential component of the risk-scoring systems used to stratify preoperative risk in vascular surgery [134-136]. However, the independent role of advanced age as a predictor is only moderate on early mortality [137]. So, elderly patients should not be denied surgery on the basis of age alone, as physiological age is the important predictor and this relates to subject's functional capacity, which can potentially be modified in the preoperative period.

Another non-modifiable, controversial predictor of inferior outcome is female gender. Some studies showed a higher risk of early mortality in women [137,138], while others failed to confirm this [139]. Giles et al, in a study using data from the US Medicare population that included more than 22 000 repairs between open and EVAR, demonstrated that female gender is an independent predictor of mortality [135]. The reasons behind this are not clear, but maybe related to the observation that females tend to present later in life and be generally frail to withstand the insults of surgery and recovery.

The presence of organ-specific diseases, most commonly chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), chronic renal failure and cerebrovascular disease are consistent predictors of inferior short term outcomes and long term survival following AAA repair [135,137,140,141]. Preoperative low forced expiratory volume in 1 second

(FEV1) and elevated creatinine levels are both independent, strong predictors of higher postoperative mortality [139]. Changes on renal function postoperatively are also known predictors of poor short-term outcomes [141], this should be emphasised early and managed aggressively in these patients.

1.2.3 Plasma N-terminal pro-brain natriuretic peptide (NT pro-BNP)

Initially discovered in porcine brain tissue, NT pro-BNP is a recognised biomarker used in the preoperative assessment of survival and cardiac risk.

BNP is secreted by the left ventricular tissue in response to stress. It is initially synthesized as a pro-hormone: pro-BNP and then cleaved into the N-terminal end and the bioactive BNP. NT pro-BNP was generally used as a cardiac biomarker of left ventricular dysfunction, severity of heart failure and as a generic risk biomarker for patients following acute coronary syndrome (ACS) [142,143].

Recently, it has been suggested that identifying those at risk of left ventricular dysfunction or heart failure before peripheral vascular surgical

procedures would be useful to direct their perioperative optimization and monitoring. This is especially useful in patients with asymptomatic heart failure, who are at a high risk of cardiac morbidity.

A study that included 190 patients undergoing surgery showed that preoperative NT pro-BNP measurement is useful for predicting cardiac morbidities. A level above 450 ng/L predicted cardiac complications with 100% sensitivity [144]. Thirty of the190 patients underwent vascular surgical procedures. Feringa and colleagues investigated the value of a preoperative NT pro-BNP measurement in vascular patients undergoing AAA repair or lower limb arterial bypass procedures and found similar results [145]. Eleven (42%) of 26 patients with a preoperative NT pro-BNP level above 533 ng/L suffered postoperative cardiac complications compared to 2 in 114 patients with a level below this threshold. Complications were especially likely in patients who also had a positive stress-induced myocardial ischaemia at dobutamine-stress echocardiography.

Furthermore, Rajagopalan and colleagues investigated the role of assessing preoperative NT pro-BNP in predicting myocardial damage, measured by periodic Troponin-I levels postoperatively [146]. They found that NT pro-BNP levels ≥380 pg/mL were predictive of myocardial damage. This study was interesting as the incidence of myocardial damage was high at 20%, but without any apparent electrocardiographic (ECG) changes. ‘Sub-clinical’ damage correlated well with short and long

term survival [147-149].

More recently, Goei et al showed that serial measurements of NT pro-BNP are useful in predicting postoperative survival after major vascular surgery. An increase in NT pro-BNP level was an excellent predictor of cardiovascular morbidity and long term survival, more so than an isolated elevation of preoperative levels [150].

A meta-analysis that included 16 publications showed that elevated preoperative levels of BNP and NT pro-BNP identifies a proportion of patients at higher risks of all-cause mortality, cardiac mortality and major cardiac events in subjects undergoing non-cardiac surgery [151]. These findings make both BNP and NT pro-BNP exciting biomarkers to investigate specifically for elective AAA interventions in larger prospective studies.

1.2.4 Functional capacity

The functional capacity of any patient determines their ability to support the perioperative demand of increased oxygen consumption and cardiac output. This is very important in AAA repair; a procedure that involves a range of perioperative haemodynamic changes and stress responses.

The assessment of functional capacity has been historically considered important in determining preoperative fitness and patient's ability to withstand the stress of major surgery. However, most surgeons did this by simply enquiring about patients' exercise tolerance, and so, relied on patient-reported fitness levels during pre-operative risk assessment. This self-rated physical status was generally well related to long term outcomes [152]. Failure to complete simple tasks, such as climbing two flights of stairs, for example, can be valuable in identifying those at an increased risk of postoperative complications in the early post-operative period [153]. This is even more important if cardiac symptoms limit exercise capacity.

A more objective approach would be to assess the patient's ability to perform a specific exercise, while observed by a clinician or a healthcare professional, who can note the level of exertion, time consumption in addition to overall ability. A stair-climbing test is an example of such assessment. The Duke Activity Status Index (DASI) 12-item questionnaire that utilized self-reported physical work capacity to estimate peak metabolic equivalents (METs) and has been shown to be a valid measurement of functional capacity. The 6- minute walk test (6MWT), incremental shuttle walk test (ISWT) are other examples. These tests estimate the maximum oxygen consumption. More interest, however, is now on evaluating objective tools to quantify functional capacity, or more specifically, measure aerobic fitness. Cardiopulmonary exercise testing (CPET) is now a very popular tool for this purpose and considered by

many the gold standard. This test was initially developed to assess athletes and monitor their progress with training. Over the last few decades, CPET gradually found use in clinical practice and today aerobic fitness parameters measured by CPET are considered extremely useful indicators of functional capacity. CPET is considered superior to stair climbing, DASI, 6MWT and ISWT, as it is a direct measurement of the maximum oxygen consumption and provides a wide variety of other useful physiological parameters.

1.2.4.1 Stair-climbing test

This is a cost-effective, safe and simple assessment to do, with a moderate level of exertion, which is enough to stimulate an increase in oxygen demand by the patient's body, matched by increases in heart and respiratory rates during the assessment.

This test, originally described in 1955 [154], has been used by surgeons for assessing exercise tolerance objectively for the last few decades in the process of perioperative outcome evaluation [153,155]. It has been shown that a poor stair climbing test, i.e. inability to climb two flights of stairs has a positive predictive value of 82% for postoperative cardiac and pulmonary complications or early death following major non-cardiac surgery [156].

The test itself is easy to perform. Patients are brought to a staircase, consisting of a number of flights, each with a similar number of steps. The numbers of steps, along with the height of each step vary according to where the test is being conducted, but need to be defined in advance if they are to be used for the purpose of preoperative assessment in a group of patients. Subjects are then instructed to climb up the stairs as far as they can, at their own pace, using the hand railing only for balance when needed. They are instructed to stop if they need to report symptoms such as severe dyspnoea, chest pain or exhaustion. The time should be recorded from the start till the test ends. The number of stairs and flights is noted along with the degree of exhaustion, usually on a predetermined specific scale.

These types of tests do have limitations; patients with disabling arthritis or weak lower limb muscles cannot perform a stair-climbing test. Similarly those with multiple co-morbidities (e.g. cardiac failure, COPD) will prefer not to try such exertion knowing their ability is severely limited.

Stair-climbing assessments have shown excellent correlation with some parameters of lung function [157], and so, found value in predicting pulmonary complications following thoracic surgery. This is not necessarily applicable to abdominal surgeries. It is also worth noting that there are no reports in the literature assessing the use of stair-climbing tests specifically for the preoperative assessment in AAA patients.

1.2.4.2 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a tool that now offers an objective, non-invasive method for assessing functional capacity. During the last decade, the use of CPET has gained popularity in a variety of clinical settings, including assessing the functional reserve in patients with cardiac, pulmonary or malignant disease [158-161], and importantly in the assessment of preoperative patient fitness [162,163].

CPET offers clinicians the ability to perform a controlled exercise test over a defined period of time, in a safe environment. It involves the measurement of a number or physiological and respiratory parameters, along with continuous electrocardiographic and blood pressure monitoring. It can be performed safely in different groups of patients provided trained staff are present and resuscitation equipment readily available.

The basic principle is the continuous measurement of basic physiological variables that characterise the cardiopulmonary and metabolic responses to exercise. It is essentially a measure of the efficiency and capacity of the oxygen-transport system, which is important to withstand the stress of major surgery as explained in previous sections. CPET also examines the pattern of an individual's ability to exercise and the cardiovascular response to variable levels of exertion, and is therefore, very useful in monitoring the progress achieved by exercise training in individuals.

1.2.4.2.1 The physiological basis for CPET interpretation

The energy immediately required by muscle at the initiation of exercise comes from the stored phosphocreatine. As exercise ensues, an increase in blood flow to muscle is met by an increase in cardiac output. This is principally due to the muscle's need for extra oxygen to facilitate the next, and most efficient way of energy production: aerobic metabolism. Here, glucose is metabolised to produce energy; where each molecule of glucose produces 37 Adenosine Triphosphate (ATP) molecules. As exercising muscles increase their workload, this is matched by an increase in blood flow and oxygen delivery for the first few minutes. During this stage energy continues to be produced aerobically as oxygen demand is being matched by increased lung ventilation and cardiac output.

At a certain point during continuous exercise, the supply of oxygen will not be adequate to match the demand by the large contracting skeletal muscle groups. At the cellular level, skeletal muscle cells will start using an additional source of energy: anaerobic metabolism; where only 3 ATP molecules are produced per glucose molecule. Glucose is metabolised to lactic acid during anaerobic metabolism, which is a highly unstable acid that dissociates to lactate and hydrogen ions (H^+) resulting in acidosis. Venous lactate concentrations will gradually begin to rise, this point is called the Lactate Anaerobic Threshold (LAT).

As subjects start incremental exercise, their expired minute volume (V_E) increases linearly along with their oxygen consumption (VO_2) and carbon dioxide production (VCO_2). The H^+ is being buffered by bicarbonate (HCO_3^-) producing more carbon dioxide (CO_2), which is washed out by the lungs and will be increasingly measurable as CO_2 in expired air. Here, VCO_2 increases out of proportion to VO_2, which allows the clinician to determine the point nearest to LAT by respiratory measurement. The rise of CO_2 at LAT, stimulates the carotid bodies to increase minute ventilation to wash out this excess, this is the point commonly referred to as Ventilatory Anaerobic Threshold (VAT) [164]. At this point, V_E increases in proportion to VCO_2 and the ratio between them (V_E/VCO_2) remains constant. The rate of rise of V_E exceeds that of VO_2, and so V_E/VO_2 starts to increase. This aids as a method of determining VAT, where V_E/VO_2 increases in relation to the constant V_E/VCO_2.

The terms LAT, VAT and AT are commonly used interchangeably, but as explained they represent different entities. To measure LAT, the examiner must assess for changes in the level of lactate in the blood by measuring it at different points during exercise. VAT, on the other hand, is estimated commonly by measuring the changes in gas exchange at the level of the mouth during exercise. AT is used to describe either of these two.

A common method used for determining VAT is to plot VCO_2 against VO_2 during an incremental exercise CPET. Linear regression lines are drawn through the lower and upper parts of the curve, the point of intersection

will represent the point at which VCO_2 increased out of proportion and can indicate the VO_2 at which this happened, i.e. VAT or AT. This is called the V-slope method (Figure 12).

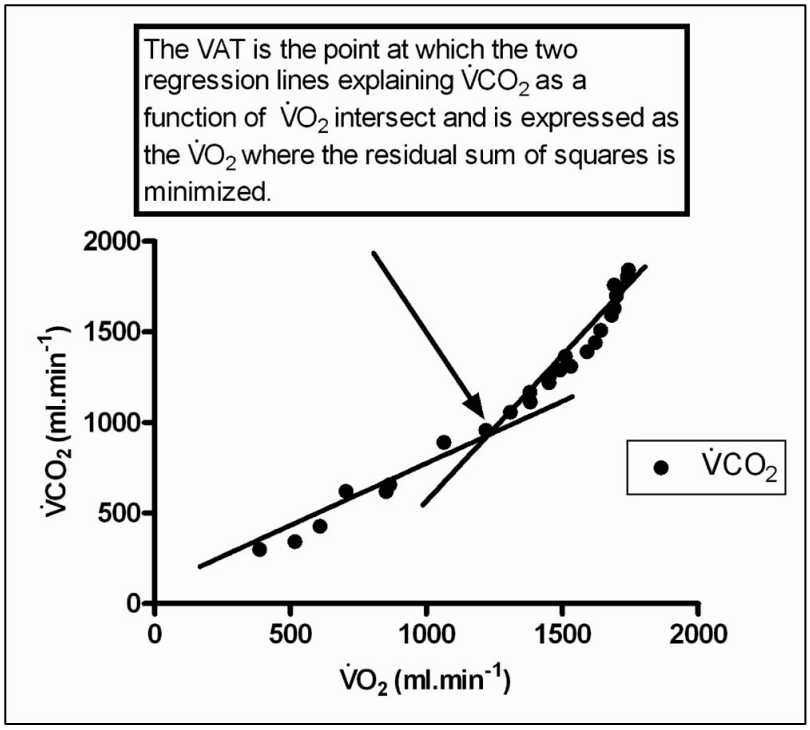


Figure 12: The V-Slope method of determining AT

The body's maximum oxygen uptake is referred to as VO_2max, and is measured by volume of oxygen consumed according to body weight per minute, given by ml O_2/kg/min. Oxygen uptake is given at CPET breath-by-breath, so VO_2max, or VO_2 peak (the maximum oxygen uptake at the highest level of exercise) are easily obtained. VO_2 max, is an excellent mark of exercise tolerance and is seen at the maximum point when the subject's VO_2 is observed increasing up to reaching a plateau with the increasing workload. If this plateau was not reached, VO_2 peak is the

reading achieved by testing. AT occurs usually at 47-64% of VO_2max in healthy individuals. The main advantage of AT measurement is that, unlike VO_2 peak (or VO_2 max) it is not effort dependent, and is therefore considered a more representative assessment of aerobic fitness in comparison in subjects with chronic diseases or multiple co-morbidities.

1.2.4.2.2 The indications for CPET in clinical practice

The American Thoracic Society/American College of Chest Physician Statement on CPET in 2003 provided an outline for the indications for CPET as follows [165]:

1. Evaluation of exercise tolerance:

   To objectively evaluate functional impairment and functional capacity.

   To determine exercise-limiting factors and pathophysiologic mechanisms.
2. Evaluation of undiagnosed exercise intolerance:

   To assess the role of cardiopulmonary aetiology in coexisting disease.

   To assess the symptoms disproportionate to resting cardiopulmonary tests.

   To assess dyspnoea when initial cardiopulmonary testing is not diagnostic.
3. Evaluation of patients with cardiovascular disease:

To assess prognosis and functional capacity in patients with heart failure.

To aid patient selection for cardiac transplantation.

4. Exercise prescription and monitoring the effect of training in cardiac rehabilitation
5. Evaluation of patients with respiratory disease:

   To assess functional impairment.

   In the assessment of patients with COPD.
6. Establishing exercise limitations and assessing other potential contributing factors such as occult cardiac ischaemia

   To determine the magnitude of hypoxemia and aid O_2 prescription.

   To determine is therapeutic intervention is necessary.
7. Evaluation of patients with interstitial lung diseases:

   To detect early gas exchange abnormalities.

   To assess and monitor pulmonary gas exchange.

   To determine the magnitude of hypoxemia and aid O_2 prescription.

   To determine potential exercise-limiting factors.

   To document the therapeutic response to potentially toxic therapy.

   To assess pulmonary vascular disease.

   To assess subjects Cystic fibrosis.

   To assess for the presence of exercise-induced bronchospasm
8. Preoperative evaluation for:

   Lung resection surgery

   Major abdominal surgery in elderly subjects
9. Exercise evaluation and prescription for pulmonary rehabilitation

10. Evaluation for impairment–disability
11. Evaluation of cardiopulmonary capacity for lung, heart–lung transplantation in subjects with coexisting disease.

1.2.4.2.3 The clinical applications of CPET in AAA patients

The value of CPET as a preoperative assessment tool in AAA repair is highlighted by many studies in the literature. Hartley and colleagues prospectively studied over 400 AAA patients analysing the value of the main CPET parameters (VO_2 peak, AT, V_E/VO_2 and V_E/VCO_2) in predicting early postoperative mortality following EVAR and open repair [166]. The majority of patients in this study underwent EVAR, and the 30-day mortality rates were: 2.2% following EVAR and 5.5% following open repair. The 90-day mortality was 4.1% following EVAR and remained at 5.5% following open repair. An AT below 10.2 ml O_2/kg/min and a VO_2 peak below 15 ml O_2/kg/min (threshold values predetermined by previous reports in literature) were found to be independent predictors of 30-day and 90-day mortality. Also, patients with any two CPET parameters outside pre-defined thresholds had an increased risk of death.

However, the short-term mortality following elective AAA intervention has decreased in most recent years in the UK. Prentis et al demonstrated that CPET has a value in predicting postoperative morbidity and length of hospital stay, two significant indicators of postoperative recovery. In this prospective study, EVAR patients were separately analysed from those

undergoing open repair. AT predicted postoperative morbidity following open repair only, and length of hospital stay following both types of repair, [167]. The authors concluded that CPET could be valuable in directing postoperative care planning in AAA patients. A cut-off value of 10 ml O_2/kg/min identified the subgroup of patients likely to occupy hospital and critical care beds for longer.

The two abovementioned studies supported the value of CPET in risk stratification of patients undergoing AAA repair which was particularly important after a systematic review failed to demonstrate similar benefits of CPET in patients undergoing surgery for peripheral vascular disease [168].

Nugent et al were amongst the first to investigate the value of VO_2peak, as measured during CPET, in identifying those at risk of post-operative complications following open AAA repair [169]. Carlisle and colleagues showed that CPET is useful in predicting survival, in particular AT and V_E/VCO_2 [170]. V_E/VCO_2 predicted 30-day and midterm survival. Others also found that AT appears to have good value in predicting outcomes after AAA repair [171].

1.2.5 Risk scoring systems

Mathematical models have been used to aid preoperative risk stratification as they incorporate scores for a variety of relevant risk factors. Vascular-

specific and AAA-specific scoring systems are available and are continuously revalidated, the two most commonly used are the Glasgow Aneurysm Score (GAS) [172] and the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) score [173]. The Acute Physiology And Chronic Health Evaluation (APACHE) systems [174,175], the Revised Cardiac Risk Index (RCRI) and the Detsky scoring system [176] are also widely used and incorporate different criteria.

Factors that are taken into account when using these scoring systems are:

1. Accuracy and satisfactory risk prediction.
2. Continuous validation of risk scoring models, especially with new emerging techniques and changes in criteria of patient selection for interventions.
3. Ease of use and applicability in real life.

1.2.5.1 The Glasgow Aneurysm Score

The GAS was first developed and validated in 1994 using data on 500 AAA patients. It incorporates the patient's age, the presence of: preoperative shock, myocardial, renal and cerebrovascular disease, and it assigns a score for the presence of each or any of these significant factors [172] (Figure 13).

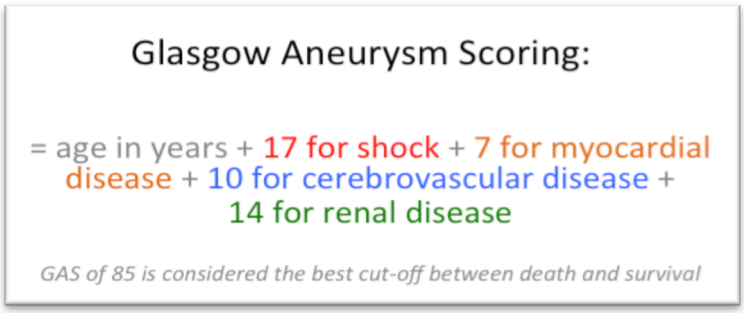


Figure 13: Calculating the Glasgow Aneurysm Score

The same group then revalidated the GAS to confirm its applicability for elective and emergency AAA repair [177]. Two further revalidation exercises were performed, the first included 403 patients from a single centre and showed a satisfactory predictive power [178], while the second, using the Finnvasc database demonstrated the predictive power to be lower than previously suggested [179]. Two later studies confirmed a reasonable accuracy between predicted and observed short-term mortality for the GAS following AAA repair [180,181].

The evidence supporting the accuracy of GAS in predicting outcomes following EVAR is conflicting. In a series of 266 consecutive patients, GAS only achieved borderline significance in predicting mortality following EVAR, with low accuracy represented by a 0.68 Area Under the Curve (AUC) in Receiver Operating Characteristic analysis (ROC). Using data from the EUROSTAR registry for EVAR patients, the GAS showed slightly better accuracy (AUC of 0.70) and the authors recognised it still has a valuable role in identifying those at high risk [182]. GAS appeared to be a

good predictor of long-term survival in this study. Interestingly, GAS has been useful in predicting 30-day and 2-year death in the Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial, more so, when patients are fit for both procedures it was a better predictor for EVAR patients [181].

The advantages of GAS are its simplicity, its relative common usage, its constant revalidation and its “broad brush accuracy in predicting mortality. The disadvantages are: it compares poorly to more modern models, it is inaccurate in predicting morbidity, and it is not very reliable in identifying high-risk individuals due to a low positive predictive value [182].

1.2.5.2 POSSUM models

The first POSSUM score was created for use in surgical audit in 1991 [173]. It included scores for physiological as well as operative components and therefore contained more variables (Figures 14 and 15). POSSUM can be used preoperatively only if the physiological component was used [183,184].

These original POSSUM equations over-predicted mortality, and underwent modification to produce the more accurate P-POSSUM [185]. The Vascular Society of Great Britain and Ireland then reviewed the use of POSSUM, based on the P-POSSUM methodology [186,187], to show that they can be accurate predictors of mortality. They were then called the

V-POSSUM models, and they similarly incorporate 12 physiological and 6 operative parameters.

Overall, the POSSUM models are considered useful and simple to use. In Vascular, as is the case in many surgical specialities, web-based platforms exist to simplify the risk prediction model by using POSSUM for clinicians.

	Score			
	1	2	4	8
Age	≤60	60-70	≥71	
Cardiac signs Chest radiograph	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral oedema, warfarin therapy, borderline cardiomegally	Raised Jugular venous pressure, Cardiomegally
Respiratory history Chest radiograph	No dyspnea	Dyspnea on exertion Mild COAD	Limiting dyspnea (1 flight) Moderate COAD	Dyspnea at rest (RR >30/min) Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110-130	131-170 100-109	≥171 90-99	- ≤89
Pulse (beats/min)	50-80	81-100 40-49	101-120	≥121 ≤39
Glasgow coma score	15	12-14	9-11	≤8
Haemoglobin (g/100ml)	13-16	11.5-12.9 16.1-17.0	10.0-11.4 17.1-18.0	≥18.1
White cell count (x10 ^{12}/l)	4-10	10.1-20.0 3.1-4.0	≥20.1 ≤3.0	
Urea(mmol/l)	≤7.5	7.6-10.0	10.1-15.0	≥15.1
Sodium (mmol/l)	≥136	131-135	126-130	≤125
Potassium (mmol/l)	3.5-5.0	3.2-3.4 5.1-5.3	2.9-3.1 5.4-5.9	≤2.8 ≥6.0
Electrocardiogram	Normal		Atrial Fibrillation rate 60-90	Any other abnormal rhythm, ≥5 ectopics/min, Q wave or ST/T wave changes

Figure 14: Physiological component of the original POSSUM score

	Score			
	1	2	4	8
Operative Severity	Minor	Moderate	Major	Major +
Multiple procedures	1		2	3
Total blood loss (ml)	≤100	101-500	501-999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation for more than 2 hrs Operation < 24h since admission	Emergency, immediate surgery < 2h

Figure 15: Operative component of the original POSSUM score

1.2.5.3 APACHE models

Morbidity and mortality outcomes following major surgery, including AAA repair, are largely related to the very early postoperative course. AAA patients are routinely managed in higher levels of care during the first few postoperative hours, especially those undergoing open repair. It is thought that risk prediction models can prove useful in assessing the severity of disease and in directing further care, in addition to predicting adverse events. Scores recorded based on initial critical care parameters can be equally important.

The APACHE scoring system differs from the other two systems discussed previously. It is a prognostic system that attempts to predict adverse events in hospitalized patients, usually to guide further care. In relation to AAA interventions, the APACHE scoring models used most frequently are: APACHE II [174], APACHE III [188] and APACHE-AAA [175]. These are all simple

modifications on the original APACHE system [189]. Calculating the APACHE II score, for example is shown in Figure 16.

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6		
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1
Glasgow Coma Score (GCS) Score = 15 minus actual GCS									
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6									
C. Chronic Health Points (see below)									
Total APACHE II Score (add together the points from A+B+C)									

Figure 16: APACHE II scoring system

APACHE is especially useful for AAA patients as operative urgency is integrated within the calculated score. APACHE II was also useful in predicting mortality for those undergoing surgery for ruptured AAA (190). When compared to other scoring systems, APACHE II is more specific to the critical care setting and so is suited better to assess the impact of

higher levels of care. APACHE-AAA was developed from the original APACHE II, and it demonstrated better accuracy (AUC 0.845 vs 0.813) in relation to elective and emergency AAA repairs. APACHE-AAA was internally validated by the same group of investigators who originally described it [175].

However, the available evidence to specifically assess the value of APACHE systems as predictors of survival following elective AAA repair is scarce. Kabbani et al, in a prospective series that included more than 400 elective open AAA repairs, found that APACHE III, recorded on intensive care admission, accurately predicted survival even though patients in this report had a lower mortality rate than the cohorts on which the APACHE models were initially evaluated [191].

1.2.5.4 Revised Cardiac Risk Index (RCRI)

This is a simple tool that incorporates a number of preoperative patient variables in assessing preoperative cardiac risk. The RCRI was described in 1999 [192], and has been widely used since. It assigns points to the type of surgery, the presence of cardiovascular comorbidities (ischaemic heart disease, heart failure, cerebrovascular disease), diabetes and preoperative renal function (serum creatinine above 177 umol/L) in the equation that produces a calculated percentage risk of cardiac morbidity. Lee and colleagues first developed and validated this index in a study that included more than 8000 patients. A significant proportion of these

underwent vascular surgical interventions. Despite that, it was later found at meta-analysis that it is not a good predictor of cardiac events in vascular surgical patients [193]. The studies included in this analysis varied widely in terms of overall quality and in how they defined postoperative cardiac events. The authors recommended further prospective research to ascertain RCRI's value in this patient population.

1.2.6 Cardiac risk assessment and optimisation

A high proportion of patients with AAA have co-existing coronary artery disease. The primary aim of preoperative evaluation of cardiac function is to identify patients with significant silent or apparent coronary disease who are at risk of early death and cardiac complications.

The starting point is with a detailed medical history, with focus on prior cardiovascular events including MI, angina or associated coronary interventions. A history of diabetes, previous cerebrovascular events and cigarette smoking is also significant. Subsequent physical examination and an electrocardiogram may also contribute to the diagnosis. More detailed tests are needed to accurately classify patients into low-, medium- or high-risk of cardiac morbidity. Patients requiring further optimisation should be referred to the cardiology service for further management preoperatively [194].

The measurement of left ventricular ejection fraction (LVEF) is considered a valuable assessment tool in preoperative evaluation of cardiac function. LVEF measurement provides functional and prognostic information and aids in monitoring the response to potential treatments that can be offered during the preoperative period. LVEF can be measured using a variety of non-invasive methods including: Echocardiography, radionuclide ventriculography and myocardial perfusion scintigraphy. The predictive value of such tests can be improved by the addition of 'stress'; either by exercise, or pharmacologically using dipyridamole or dobutamine [195,196].

The measurement of LVEF has been recognised as an important assessment of acquired heart disease and myocardial dysfunction, and is an important prognostic parameter in subjects with coronary artery disease. In the perioperative setting, dobutamine-stress echocardiography (DSE) is considered a useful, safe and valid test for evaluating cardiac function [197]. DSE has a good ability to correctly identify those with no functional myocardial dysfunction preoperatively, and those are least likely to develop cardiac events subsequently.

An alternative to DSE is radionuclide ventriculography using multigated acquisition (MUGA) scanning; which is also a widely used test for estimating LVEF. We [198], and others [199,200] have studied the role of LVEF measured using MUGA as a perioperative risk assessment tool. A retrospective series from our centre showed that LVEF independently predicted long-term survival in a cohort of patients undergoing elective

open AAA repair [198]. However, limited data is available to show the value of LVEF in assessing for short-term postoperative cardiac events, and more research is needed to ascertain this value and to compare the value of LVEF as a tool in comparison to novel methods of perioperative risk assessment.

Coronary revascularisation or new pharmacotherapies may be necessary prior to AAA repair according to the degree of myocardial dysfunction and ischaemia. However, there is no clear evidence to support the role of prophylactic coronary revascularisation immediately prior to AAA repair [201,202]. A large multi-centre randomised study including more than 5000 patients undergoing elective vascular surgery showed that there is no advantage of preoperative coronary revascularisation on both short-term morbidity and long-term survival. Another study later showed that even higher-risk subjects (with more than 3 risk factors and demonstrating stress-induced ischaemia at DSE) will not benefit in the short-term or up to 1 year of follow-up from preoperative coronary revascularisation. The lack of benefit maybe due to 2 main factors: the theory that further delay in treatment increased morbidity and mortality from peripheral vascular disease (e.g. AAA rupture), and the theory that postoperative myocardial infarction has a slightly different aetiology. There is increasing evidence that MI in the postoperative period is more likely to result due to progressive stenosis and prolonged ischaemia in coronary vessels with minimal stenosis at baseline, rather than an acute thrombosis due to plaque rupture [203,204].

1.2.7 Pulmonary risk assessment and optimisation

Chronic respiratory disease is associated with aneurysm expansion, risk of rupture and inferior operative outcomes [205]. Spirometry is useful in the preoperative assessment of patients with AAA. FEV1 in particular is correlated with surgical outcomes [35,139,177].

Cardiopulmonary exercise testing (CPET) is increasingly popular as an objective measure of aerobic capacity in patients undergoing major surgery [162,163].

The initial step, however, in assessing and optimising pulmonary function is smoking cessation. This can improve overall lung function even in the short term by decreasing secretions and improving ventilation. Furthermore, physiotherapy and exercise programmes have the potential to improve lung function and overall outcomes [35].

1.2.8 Renal risk assessment and optimisation

Renal function is an important determinant of outcomes following AAA repair [134,139,177,206]. Serum creatinine and creatinine clearance should be estimated preoperatively on a routine basis and a referral to a nephrologist is recommended if they are significantly abnormal.

Patients should be well-hydrated perioperatively, especially when the use of intravenous contrast material is anticipated. Renal function should be continuously assessed during the postoperative hospital stay and AAA repair should generally only be undertaken at a centre able to provide haemofiltration, dialysis and advanced renal support.

EVAR, despite being the less invasive option with less haemodynamic disturbance, still involves the use of contrast agents, which can cause contrast-induced nephropathy (CIN). This, in addition to the risks of embolic debris dislodgement with the use of wires and catheters, and the potential arterial occlusion due to graft positioning makes the risk of renal damage higher than anticipated. Intravenous and oral hydration perioperatively are encouraged as appropriate, and the use of non-ionic, low- or iso-osmolar contrast material is recommended in patients with preoperative abnormalities in renal function [97]. Administration of the antioxidant oral medication N-acetyl-cysteine, in combination with sodium bicarbonate may also provide extra renal protection, although the supporting evidence is not conclusive [207].

1.3 Preoperative supervised exercise interventions

1.3.1 History

Exercise is defined as a subset of physical activities that are structured and purposeful with the main objective being an overall improvement or maintenance of physical fitness, which includes cardiopulmonary fitness, body composition and strength.

Exercise tolerance and functional capacity represent important predictors of postoperative morbidity and mortality following a variety of major surgical interventions. Higher preoperative fitness levels, assessed with an exercise tolerance test, are associated with a lower cardiovascular mortality. The positive effect of perioperative rehabilitation is well documented following a variety of interventions [208,209]. In specific circumstances, preoperative exercise interventions are associated with improved postoperative outcomes, for example; a reduction in hospital and intensive care stay, and an overall improvement in quality of life was also noted in patients awaiting coronary artery bypass surgery (CABG) who underwent preoperative exercise training [210].

Much of the research on preoperative exercise training interventions involved orthopaedic patients awaiting joint replacement surgeries [211,212], investigating potential functional improvements on mobility and hospital stay. Overall, it appears that exercise interventions carry much promise in reducing hospital stay and the incidence of postoperative complications [213].

1.3.2 The effects of exercise interventions

1.3.2.1 Effects on Cardiovascular function

One of the well-known uses of physical rehabilitation in healthcare is for the prevention of ischaemic heart disease and as a major therapeutic component following myocardial infarction or CABG.

The relationship between exercise and long-term cardiovascular outcomes is a positive one [214]. A significant reduction in cardiovascular mortality is seen in patients undertaking rehabilitation programmes when compared to control subjects [215].

The main mechanism behind the cardiovascular benefits of exercise is risk factor modification. Regular exercise has a beneficial effect on blood pressure, lipid profile, glucose metabolism, insulin sensitivity in addition to

platelet and endothelial functions [214]. It also modifies lifestyle and reduces stress. A short period of regular exercise training at moderate intensity improves peak fitness levels amongst patients with cardiac disease as much as it improves it in healthy subjects [216].

There is also evidence that regular exercise reduces the progression of atherosclerotic lesions and can even result in their regression [217,218], but this is probably more evident in long-term exercise training, i.e. lasting more than one year. Exercise also improves myocardial perfusion, which appears to be significantly associated with clinical outcomes [219].

Improvement in muscle strength, apparent through better coordinated movements and muscle hypertrophy can be achieved through appropriate resistance exercises and ultimately results in an improvement in peak cardiac performance.

The other direct benefits of exercise on cardiovascular functions are:

1. Slowing of resting heartbeat; possibly through alterations in autonomic nervous balance and an increase in stroke volume. Benefits of this are an improvement in functional capacity as a result of an increase in cardiac reserve, a longer diastole phase and so, increased myocardial perfusion.
2. Reduction of blood pressure.

3. An increase in peripheral venous tone, resulting in an increased central blood volume and ventricular preload, which in turn helps increase the stroke volume.
4. Increased myocardial contractility, resulting form an increase in preload (by increased peripheral venous tone and plasma volume expansion) and a reduction in afterload (strengthened skeletal muscle and reduced systolic blood pressure).

1.3.2.2 Effects on Pulmonary function

There is little evidence to specifically demonstrate a benefit for preoperative exercise interventions in improving pulmonary functions in the elderly patient population. However, the general consensus is that exercise programmes containing aerobic and resistance training have the potential to improve aerobic fitness [220-222].

Several studies showed that preoperative inspiratory muscle training can be an effective strategy to reduce postoperative pulmonary complications, especially in patients undergoing thoracic and upper abdominal operations [223,224]. This is likely to be due to a more rapid postoperative recovery of inspiratory muscles and lung function postoperatively. Upper abdominal surgery is associated with a noticeable drop in functional residual capacity (FRC), this together with pain and immobility limit the overall lung function and predisposes to atelectasis and subsequent

infection. The reduction in forced vital capacity (FVC) and the peak expiratory flow rate (PEFR) associated with abdominal surgery, is less in subjects receiving preoperative chest physiotherapy [225].

Intensive exercise programmes with a mixture of resistance, aerobic and inspiratory muscle training showed some potential to improve respiratory function in preoperative patients. Many studies are limited by small patient numbers and so, are not adequately powered to detect clinical improvements. Shorter term exercise (approximately 6 weeks) of moderate intensity improves innate immune functions and potentially reduces the incidence of upper respiratory infections [226].

The advantages of exercise for the purposes of weight loss and lifestyle modification is also likely to have a positive influence on overall respiratory function, and the majority of exercise programmes administered within the healthcare environment are delivered in conjunction with smoking cessation advice, this can result in significant improvement in ciliary function and a reduction in postoperative upper and lower respiratory infection rates.

1.3.2.3 Effects on the musculoskeletal system

Exercise interventions are promising in terms of an improvement in overall functional abilities, which is particularly true as the positive effects of exercise are noticeable on the musculoskeletal system. Therefore, it is anticipated, that balanced preoperative exercise interventions can help in achieving earlier postoperative mobility and return to normal functions in subjects undergoing major surgeries.

Exercise has multiple effects on the musculoskeletal function in older patients, including:

1. Improvement in muscle strength; this appears to be due to muscular hypertrophy achieved through the recruitment of extra fibers and is especially evident with resistance exercises, as is the noted increase in neuromuscular coordination. In general, exercise of variable intensities, even if for short periods of time, has been shown to improve muscle strength and enhance neuromuscular performance [227].

2. Improvement in gait and balance [228]; resulting from stronger peri-articular muscles, improved subject's confidence and cognitive function [229].

3. Improved mobility and a reduction in the common limiting bodily pain, e.g. low back pain [230].

4. Improved bone mineral density in subjects at high risk of osteoporosis [231].

5. Reduced incidence of falls, which is thought to be primarily due to the improved strength and balance, and the enhanced reactions associated with exercise.

1.3.2.4 Effects on quality of life measures

It is important to consider the effects of exercise interventions on quality of life in older patients along with its effects on general health as explained above.

It appears that the feelings of 'well-being' among elderly subjects are related to the quality of physical functioning and dependence [232]. A better physical function is also a predictor of healthier social life in adults [233]. Additionally, there is evidence to suggest that older adults are less likely to experience depressive symptoms if they are physically active [234]. These are important factors that correlate closely with quality of life.

Specific analysis shows that general quality of life measures are expected to improve in patients undergoing exercise training. This improvement is more obvious among the physical aspects of the quality of life parameters in contrast to the psychological aspects. Changes in psychological parameters appear to be related to the primary reason subjects are undertaking an exercise intervention. Patients exercising as part of management of their chronic illness (e.g. COPD, multiple sclerosis) appear to report a deterioration in psychological parameters [235] . This might be related to not achieving an anticipated positive effect with training. Psychological aspects of quality of life measures can also be related to the intensity of training, where lighter exercise regimes appear to be associated with better outcome [235].

1.3.3 Effects on aerobic fitness

The previous sections described the benefits of exercise training on the cardiovascular, pulmonary and musculoskeletal systems. The overall change associated with exercise include: increases in maximum heart rate at peak levels of stroke volume, increased cardiac output, larger arterial-venous oxygen difference and increased skeletal muscle blood flow. These changes are likely to be due to an improvement in endothelial function, skeletal muscle oxidative function, in addition to an attenuation of sympathetic activation and an increase in chronotropic responsiveness.

CPET parameters of fitness such as VO_2 peak are determined by central (heart rate, stroke volume, cardiac output) and peripheral (muscle oxygen extraction) components, all of which seem to respond favorably to exercise training in most individuals. Most studies that investigate the effect of exercise on VO_2 peak show an improvement in this clinically important parameter. However, these improvements can also be due to random variation, learning effect with training, changes in the natural history of a specific disease, changes in subject activity pattern or drug regimens, and therefore it needs to be matched with favorable changes in other parameters.

Many studies show that AT improves with appropriate exercise training [236-238]. As AT is independent of patient efforts, it has been considered a superior measure of aerobic fitness in patients with chronic illness, and a more reliable parameter to help tailor exercise prescription. AT usually occurs at 45-65% of VO_2 max in healthy untrained individuals, and probably at lower percentages in sedentary subjects or those with chronic disease. Three different studies showed that AT can improve with exercise training in subjects with AAA disease [222,239,240]. In one of these, Kothmann and colleagues defined the clinically important improvement in AT as an increase of 2 ml O_2/Kg/min. Arguably, this is a reasonable estimate, as AT was found to have acceptable reliability upon retesting, however, there are no studies in the literature that further examine this in subjects with AAA disease.

In order to achieve relevant benefits in aerobic fitness, exercise volume (intensity, frequency and duration) has to be appropriately determined and prescribed. Higher relative intensities are associated with larger benefits on aerobic fitness in sedentary, otherwise healthy subjects [237]. In patients with cardiovascular risk factors, high-intensity interval exercise training has also been shown to be superior to moderate exercise in improving fitness and as a cardio-protective intervention [241,242].

In addition, it is important to consider the duration of training if exercise is to be practical in the preoperative setting. The timescale of intervention has to be balanced in order to achieve clinically important benefits and to avoid delays on important surgical interventions. A period between 4-8 weeks is ideal. The intensity and frequency of exercise classes has to be optimized to be as effective as possible within this period of time.

Exercise interventions in clinical practice are generally considered safe and feasible [243,244]. However, patient motivation plays a key role in participation, compliance and so, health benefits. Hospital- based exercise sessions are not expensive to conduct as most hospitals do have facilities for simple aerobic and resistance exercises that are used for physiotherapy, cardiac rehabilitation and other clinical utilities. Home, or community-based exercises can sometimes be more suitable for patients, and in theory, could result with better compliance, however, in patients with intermittent claudication, for example, hospital-based exercise was more the more effective [245,246], which probably reflects the superiority of

supervised exercise in groups in maintaining proper exercise participation, intensity and motivation.

It must be clarified that in patients with large AAA, there isn't enough evidence to demonstrate the safety and efficacy of high-intensity or interval exercise training. Similarly no studies established the safety of home-based exercise in this patient population, therefore, early research should be conducted in a safe environment (i.e. hospital with vascular surgical 24 hour service, and under medical supervision).

1.4 Postoperative complications

The literature is rich in reports on the postoperative morbidity and mortality rates following open and endovascular interventions for AAA. The reported 30-day mortality following open repair ranges between 1 and 8 per cent [119-121,140,247,248], compared to only 0.5 to1.7 per cent following EVAR [116,117].

Ischaemic heart disease remains the leading cause of early and late mortality following AAA repair and risk factors such as chronic lung disease, renal disease and diabetes mellitus are important risk factors for postoperative morbidity and mortality, as is advanced age.

Endovascular repair is associated with lower postoperative morbidity, owing to reduced trauma, operative time, blood loss, transfusion requirements, duration of mechanical ventilation and length of hospital and critical care stay [249]. However, there are additional risks of technical and device related complications, and the increased exposure to radiation. The risk of re-intervention following EVAR is also significantly higher than that following open repair [250,251].

A summary of the main systematic complications following AAA repair is given in Table 1.

Systematic postoperative complication	Reported incidence in OAR[119,140,262]	Reported incidence in EVAR [250, 251]
Cardiac complications: Arrhythmias Ischaemic cardiac: myocardial infarction Congestive cardiac failure	5.4-15.1% 3.0 – 10.5% 1.4- 5.2 % 1.0-8.9 %	5.3% (1.8% - severe cardiac complications)
Pulmonary complications: Pneumonia Respiratory failure (re-intubation for ventilation) Adult Respiratory Distress Syndrome (ARDS) Pulmonary Embolism (PE)	4.2 – 25.0% 3.0 – 15.0% 8.4% 1% 0.2 – 5%	2.9% (1.2% - severe
Renal complications: Acute kidney injury (AKI) Renal insufficiency requiring dialysis	 5.4-10.9% 0.6%	 1.2-5.5% 0.4%
Severe infections: Sepsis	 0.7-1.0%	
Cerebrovascular complications: Stroke	 0.5-0.6%	
Bleeding: Postoperative –requiring transfusion Postoperative –requiring re-operation	 2.3% 1.4%	

Table 1: A summary of the main postoperative complications reported following elective repair of abdominal aortic aneurysms

1.4.1 Cardiac complications

More than 60% of in-hospital deaths following AAA repair are directly caused by cardiac complications [140,252]. These complications are more commonly seen in the elderly, and in patients with predisposing risk factors such as previous history of coronary artery disease or cardiac failure.

Cardiac events following vascular surgery are precipitated by intraoperative myocardial stress and ischaemia [253]. However, a sustained level of perioperative myocardial stress results from an increase in oxygen demand by both the myocardium and the peripheral tissues as a result of the systemic haemodynamic response to surgical trauma. More importantly, a significant proportion of vascular surgical patients have a degree of occult or clinically evident coronary artery disease, and are therefore at an increased risk of cardiac events.

Postoperative pain, hypoxia, anaemia as well as coronary artery disease will exacerbate myocardial ischaemia and are all more pronounced with more invasive interventions. One of the most important factors in relation to open aortic surgery is the intraoperative process of aortic cross-clamping and declamping, which introduces ischaemic tissues into the circulation. Aortic cross-clamping can decrease the cardiac index and stroke volume by 35% and increase systemic vascular resistance (SVR)

by up to 40%, with a significant increase in mean arterial pressure (MAP) [254,255].

Arrhythmia or acute ischaemic events (myocardial infarction with electrocardiographic changes and/or elevated cardiac enzyme levels) are the common cardiac complications. These complications can be further classified according to severity, where severe cardiac events can lead to cardiorespiratory arrest and are usually fatal.

1.4.1.1 Cardiac arrhythmias

Postoperative cardiac arrhythmias are common following AAA surgery, and can be of a new onset (i.e. developing acutely), or present as an exacerbation of a preexisting arrhythmia. Atrial arrhythmias are associated with acute MI, CHF and respiratory failure in the postoperative period. Similarly, ventricular arrhythmias are commonly associated with ischaemic events and CHF. New postoperative arrhythmias are also more commonly seen in patients with pre-existing angina pectoris or COPD [140].

The incidence of postoperative cardiac arrhythmia is higher in patients having open repair compared to EVAR [132].

1.4.1.2 Acute myocardial infarction

Acute myocardial infarction (MI) is commonly a fatal complication amongst patients undergoing major vascular surgery. There appears to be two different patterns with regards to the extent and timing of these coronary events [256]; early and delayed MI. Early MI occurring within 24 hours of surgery and seems to have a pathophysiology which resembles that of a MI occurring in nonsurgical patients (i.e. an acute plaque rupture resulting in coronary artery occlusion. However, in delayed MI (occurring more than 24 hours) there appears to be a period of silent progressive myocardial damage preceding the actual event, which is likely to be precipitated by the stress of surgery, increased myocardial tissue demands, thrombogenicity, sympathetic activity and the levels of circulating inflammatory markers. The mortality following early and delayed postoperative MI is similar and significant (> 20%) [256]. Monitoring myocardial enzyme levels is a useful measure to identify those at increased risk postoperatively [257]. However, the most important step is to identify those at risk preoperatively and to manage significant coronary artery disease prior to AAA repair in the elective setting.

1.4.2 Pulmonary complications

This umbrella-term includes postoperative atelectasis, pneumonia, acute respiratory distress syndrome (ARDS) and respiratory failure are commonly classified as pulmonary complications [258]. Amongst upper abdominal surgeries, patients undergoing open repair of AAA are considered at higher risk of severe postoperative pulmonary complications [259].

As atelectasis and pneumonia are predominantly clinical diagnoses, they are usually identified by clinical and radiological features and treated with chest physiotherapy and systematic antibiotics, if indicated. The predisposing factors are advanced age, smoking, poor functional capacity, obesity, co-existing cardiopulmonary disease and renal disease. In the postoperative setting, pain and opioid analgesics can inhibit efficient breathing, and the site of the surgical incision plays an important role. Chest physiotherapy, adequate pain control and early mobilization are usually beneficial.

The feared complication is postoperative respiratory failure; defined as prolonged postoperative intubation (or re-intubation) for more than 48 hours. This is seen in up to 8% of open AAA repairs [259].

It is possible to identify patients at increased risk of severe pulmonary complications, so that management of modifiable risk factors can be started early and clinical care planned in advance. In addition to the risk factors mentioned above, malnutrition, represented by low albumin levels can be corrected and is a known risk factor for postoperative respiratory failure. Pulmonary rehabilitation, optimization of COPD and smoking cessation are important interventions that should also be considered in the high-risk group.

1.4.3 Renal complications

Acute renal failure following AAA repair occurs in 2-10% of patients and is an independent predictor of mortality and morbidity [119,140]. Renal hypoperfusion as a result of cross-clamping and haemorrhage are recognized risk factors with open repair, and nephrotoxic contrast, embolic dislodgement with the use of wires and catheters, and renovascular occlusion by the stent devices are risk factors associated EVAR. Renal replacement therapy will be required in 0.2-5.0% of patients undergoing elective AAA repair and is associated with a hospital mortality of 25-66%. The incidence of renal complications is reported to be similar between OAR and EVAR [117], although recent data show significant reduction of renal complications with EVAR [260].

The use of non-ionic, low- or iso-osmolar contrast medium in addition to perioperative oral and intravenous fluids are encouraged following EVAR

to prevent the occurrence of contrast-induced nephropathy [97]. This is especially true in cases of pre-existent renal insufficiency. Creatinine is monitored throughout the postoperative course in all AAA patients.

1.4.4 Other complications

Table 2 summarizes the other common postoperative complications encountered following both OAR and EVAR.

Complications following OAR	Complications following EVAR
- **Gastrointestinal:** Prolonged ileus Diarrhea Ischaemic Colitis	- **Gastrointestinal:** Colon ischaemia
- **Graft related:** Anastomotic pseudoaneurysm Thrombosis Infection	- **Graft related: Endoleak** Type I – Graft attachment Type II – Retrograde Type III – Graft defect Type IV – Graft porosity Type V – Endotension
- **Wound related:** Superficial infection Deep infection Wound dehiscence	- **Wound related:** Groin wound infection Bleeding
- **Other vascular:** Distal (lower limb ischaemia) Deep venous thrombosis Pulmonary embolism	- **Other vascular:** Ischaemic limb complications and distal embolization
- **Others:** Erectile dysfuncion	- **Others:** Post implantation syndrome

Table 2: A summary of other postoperative complications that can occur following elective repair of abdominal aortic aneurysms

1.5 Aims, hypothesis and study design

When the research towards this thesis was initiated, there was no evidence to demonstrate that preoperative exercise can influence postoperative outcomes following elective AAA repair. By the time this project was completed, there were still no studies that evaluated this, however, some investigators in the UK [222] and North America [240,261] have investigated the role of exercise in patients under surveillance for 'small' AAAs (under 5.5 cm in maximum diameter) and demonstrated that exercise of appropriate intensity, frequency and duration, has the potential to improve aerobic fitness parameters, as measured by CPET. Furthermore, many reports emerged during the last few years to support the use of CPET in patients undergoing elective AAA repair. CPET was considered a useful, objective preoperative assessment tool that predicted postoperative mortality [166,170,171]. Fewer studies however, investigated the predictive value of CPET, or other risk assessment tools on postoperative morbidity and organ-specific complications following elective AAA repair [167]. This, and national recommendations such as those made by the UK Abdominal Aortic Aneurysm Quality Improvement Programme (AAAQIP) and the EVAR-2 trial [125] to investigate interventions that can improve surgical outcomes in AAA patients, encouraged us to pursue the research leading to this thesis.

The main hypothesis of this research was that a period of perioperative exercise training can improve functional capacity, and reduce the incidence of major postoperative complications in patients awaiting elective repair of AAAs.

Based on this, the main questions to answer were:

1. Can preoperative exercise training improve the measurable parameters of aerobic fitness in patients awaiting AAA repair?

2. Will a preoperative medically supervised exercise intervention reduce the incidence of cardiac, pulmonary and renal complications in patients undergoing elective repair of AAA?

3. What value do CPET parameters and other commonly used risk assessment tools have in predicting postoperative complications?

In this thesis:
Study 1; is a prospective, randomised controlled trial to assess the effect of a locally developed exercise intervention on clinical outcomes following elective AAA repair.

Study 2; is a sub-group study that included patients from Study 1 who consented to undergo two rather than one preoperative CPETs to assess

for improvement in preoperative fitness following exercise.

Study 3; an evaluation of the predictive values of the preoperative risk assessment tools was carried out at the end of data collection.

The methodologies of the 3 studies are explained in greater detail in the next chapter.

So, to summarise, the aims of the three studies incorporated within this project were:

Study 1: To determine whether a medically supervised, 6-week exercise programme improves post-operative outcomes in patients undergoing elective AAA repair, when compared to standard treatment.

Study 2: To determine whether preoperative exercise improves the CPET-measured parameters of aerobic fitness in patients awaiting elective AAA repair.

Study 3: To undertake a comprehensive assessment of objective pre-operative assessment techniques as potential predictors for postoperative outcomes and assess the accuracy of CPET in predicting organ-specific complications.

CHAPTER 2:
PATIENTS
AND METHODS

Study 1; A Randomised Controlled Trial to Assess the Effect of Preoperative Supervised Exercise on Outcomes Following Elective Abdominal Aortic Aneurysm Repair

2.1 Patients

The setting for this randomised controlled trial was at a tertiary vascular referral centre (The Department of Vascular Surgery - Hull and East Yorkshire NHS Trust) offering highly specialised interventions and perioperative care to patients with aortic disease, covering a population of more than 1.2 million across the region of East Yorkshire and Northern Lincolnshire, United Kingdom.

Consecutive patients planned for interventions for AAA by the vascular surgical consultants at Hull Royal Infirmary between September 2009 and January 2014 were approached. These patients were usually referred directly to the chief investigator from the outpatient clinics when seen by their supervising consultant, or when decisions regarding the type and date of repair were made at our weekly local multi-disciplinary team meetings. Occasionally, patients were directly approached as they were identified via the hospital's theatre waiting lists.

At Hull, the decision to intervene for AAAs is usually based on: the aneurysm size as it reaches an appropriate threshold (5.5 - 6.0 cm in

maximum diameter), and on patient fitness or suitability for intervention.

Patients were contacted directly and if interested provided with an information sheet and booked in for their first visit. The chief investigator was always contactable to answer and explain any queries. Those declining participation were politely asked to give their reasons in order to give us insight on future limitations. In those patients willing to take part, an explanation of the intervention (exercise programme) was given with details on the duration, location and intensity of exercise.

All patients were supplied with a detailed information sheet to read in advance. They were then invited for their first visit; the aims of which were to assess their eligibility for inclusion, to randomly allocate them into the study groups and to establish a baseline risk profile for each participant. Once the main criteria were satisfied, patients were randomised into one of the two study groups (exercise and control) and clinically assessed as explained in detail in this chapter, all at the same visit. The aims of the trial were explained to all participants, in addition to the nature of their group allocation following randomisation. Patients were reassured that ethical approval has been provided, along with contact details of the study's chief investigator and the research centre for any enquiries at any time during their participation in the trial. The participant information sheet and consent forms are available in Appendix 1.

2.1.1 Inclusion criteria

Patients were included only if they satisfy the following criteria:

1. Patients undergoing open repair or EVAR for an asymptomatic abdominal aortic aneurysm.
2. Able to comply with the study protocol.
3. Able to provide written informed consent.
4. Able to communicate in English language.

2.1.2 Exclusion criteria

Patients were excluded if they:

1. Had severe disabling disorders limiting their mobility, for example severe osteoarthritis or limiting back pain.
2. Were undergoing urgent or emergency repair of an abdominal aortic aneurysm.
3. A diagnosis of thoraco-abdominal aneurysm.

2.2 Randomisation

Following informed written consent, eligible patients were randomised into one of two groups:

Exercise (intervention) group:

Patients receiving standard planned operative management for AAA, with all preoperative assessments and a period of 6 weeks of medically supervised, hospital-based exercise programme.

Control group:

Patients receiving standard operative management for AAA, with all the preoperative assessments but no preoperative interventions. These patients were clearly instructed to continue with their normal life-style, including their day-to-day activities. They were discouraged from undertaking any additional exercises without medical supervision.

Simple randomisation was performed into two parallel-groups. The groups were: the exercise (intervention) group and the control group. Randomisation was done via a sealed envelope system. Patients were instructed to pull an opaque, sealed envelope according to their study identification number from a group of exactly similar, sequenced envelopes and opened it under supervision. The sequence was generated

using a computer-based, online, sequence generator, and prepared by an independent research fellow.

The processes of informed consent and randomisation were witnessed by an independent professional when available. Clinicians (consultant surgeons, anaesthetists, interventional radiologists) were blinded to individual patient group allocation at all times during the study.

2.3 Sample size

A sample size calculation was performed based on the composite of primary outcome measures (incidence of postoperative cardiac, pulmonary and/or renal complications, see section 2.7). This was informed by data from the literature [119,140,153,262], giving an estimated postoperative cardiac, pulmonary and renal complication rate of 30 per cent.

The sample size was determined using *nQuery statistical software, (nQuery Advisor™ Version 6.1, USA)* and calculated by an independent medical statistician at the Hull York Medical School – University of Hull.

Based on a complication rate of 30 % for standard group, a two-group χ^2 test with a 5 % significance level will have a power of 80 % to detect a fall in the complication rate from 30 % to 10 % when the sample size in each group is 62 patients. This reduction was deemed the most suitable to use in order to conduct this trial effectively as the clinical benefit would be appropriate and the sample size required would be realistic for a single-centre trial.

The loss to follow-up was estimated at 10 %, therefore increasing the number of patients needed to 136, (68 patients in each group).

2.4 Preoperative assessments

2.4.1 Baseline assessment

All patients underwent a detailed history and clinical examination at the first visit. This specifically included enquiring about a history of pre-existing cardiac, pulmonary, renal disease or other co-morbidities. In addition, a record was made of each patient's current medications, allergies and any relevant past surgical history.

A physical examination followed, and this included an estimation of every patient's body mass index, measurement of vital signs, pulse oximetry, and a thorough examination of the cardiopulmonary systems, the abdomen and the peripheral vascular system including measurement of ankle-brachial pressure indices (ABPI).

During the baseline visit, a risk profile was determined for each individual participant. All patients underwent a treadmill CPET followed by a period of rest, and then a stair-climbing exercise assessment, unless contra-indicated. A blood sample was taken following patient approval for:

1. A full blood count.
2. A biochemical profile (including renal and liver functions, serum c-reactive protein [CRP] levels and a lipid profile).
3. A coagulation screen.

4. Serum NT pro-BNP levels.

At a second visit, patients underwent radionuclide ventriculography via a multigated acquisition (MUGA) scan at the nuclear medicine department within the trust. Preoperative GAS, V-POSSUM, RCRI and Detsky scores and a baseline quality of life assessment were also completed for all patients during this stage of assessment.

2.4.2 Cardiopulmonary exercise testing

Prior to all CPET, possible contra-indications for the test were excluded by general clinical assessment, blood pressure measurement and ECG at rest.

A treadmill CPET was then carried out for all patients using MedGraphics Cardio-Ultima™ (Medical Graphics, St Paul, Minnesota, USA) or Cosmed Quark-CPET™ (Cosmed, Srl, Rome, Italy) equipment. The gas exchange analysis software used was the BreezeSuite™ software (Medical Graphics, St Paul, Minnesota, USA).

Patients were instructed to walk on a treadmill with a soft, fitted face mask to provide adequate seal around the nose and mouth and permit the best gas exchange assessment. Twelve-lead ECG with ST segment analysis was performed before the start and throughout the test (Figure 17), until

the patients completed the recovery and rest periods and the heart rates returned to resting pre-exercise value. ECG was done using the Mortara mobile ECG system (Medical Graphics™, St Paul, Minnesota, USA).

Figure 17: ST segment monitoring during exercise ECG (red box) at CPET

The CPET involved walking on the treadmill according to the modified Bruce protocol:

1. The first 3 minutes involved walking at 0% inclination at a speed of 1.7 mph (Stage 1 of 4).
2. Over the next 3 minutes the inclination increased to 5% (Stage 2 of 4).
3. Over the next 3 minutes the inclination increased to 10% (Stage 3 of 4).
4. Over the last 3 minutes speed increased to 2.5 mph, and the inclination increased to 12.5% (Stage 4 of 4).

Patients then entered the recovery, or cool-down stage.

A decision to terminate the test was made if the patient reported distress, exhaustion, alarming clinical symptoms (chest tightness, chest pain, severe dyspnoea, abdominal pain or unusual headache, dizziness or other significant symptoms), or developed ≥ 2mm ST depression in any lead. The test was also terminated if any unusual observations were noted on the monitors such as irregularities in heart rate or blood pressure by the attending examiners. All tests were performed with trained medical staff in attendance and resuscitation equipment immediately available.

The modified V-slope method was used to determine the AT (Figure 18) [263].

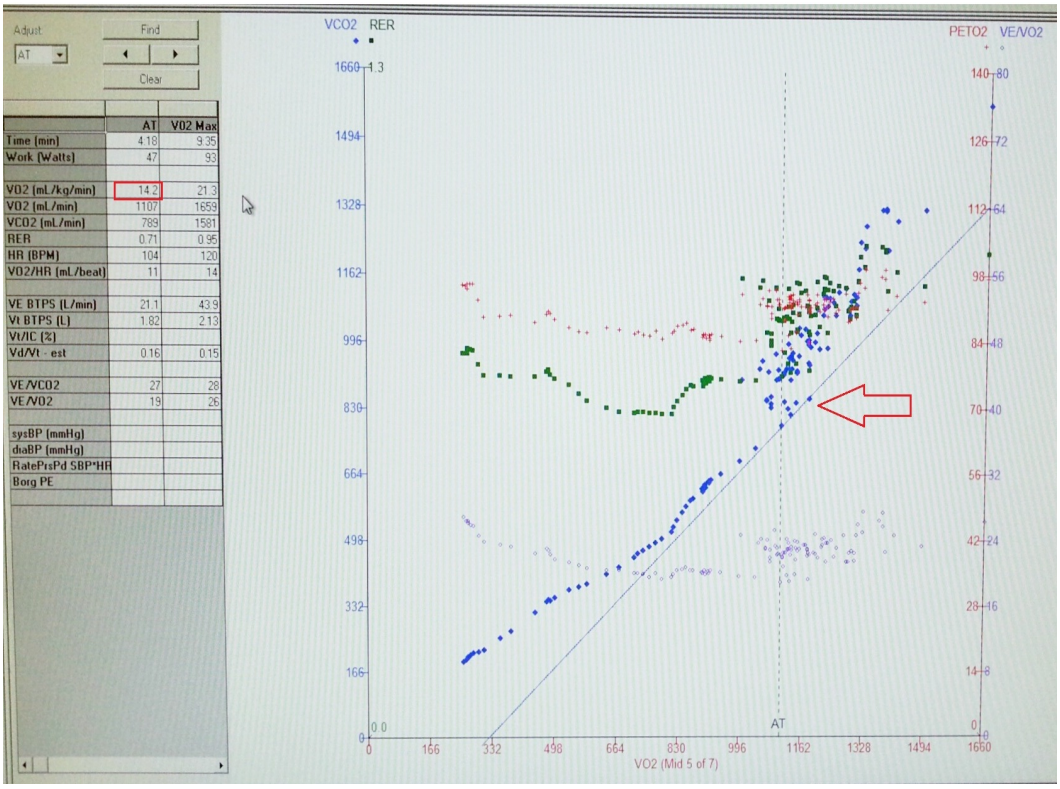


Figure 18: The modified V-Slope method to ascertain the ventilatory anaerobic threshold; the breakpoint is determined by visual inspection at breath-by-breath values of VCO_2 and VO_2

An independent, blinded, trained medical professional later validated these measurements. When the two AT values (from each observer) differed, the midpoint (sum of the two divided by 2) was used as the AT value recorded.

The following parameters were obtained following the completion of CPET (Figure 19):

1. Peak oxygen consumption: VO_2 peak in ml O_2/kg/min
2. AT in ml O_2/kg/min
3. Total time of exercise
4. Time at which peak values were obtained
5. Time at which AT was achieved
6. Ventilatory equivalents for both oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2) at AT

	Rest	AT	V02 Max	Pred
Time (min)	0:44	4:18	9:35	
Ex Time (min)		3:29	8:46	
---- WORK ----				
Speed (MPH)		1.7	1.7	
Grade (%)		5.0	10.0	
---- VENTILATION ----				
Vt BTPS (L)	0.65	1.82	2.13	
RR (br/min)	11	12	21	
VE BTPS (L/min)	6.9	21.1	43.9	113.0
---- O2 CONSUMPTION ----				
VO2 (mL/kg/min)	3.3	14.2	21.3	31.6
VO2 (mL/min)	256	1107	1659	2466
VCO2 (mL/min)	193	789	1581	2984
RER	0.76	0.71	0.95	
METS	0.9	4.1	6.1	9.0
---- CARDIAC ----				
HR (BPM)	68	104	120	152
VO2/HR (mL/beat)	4	11	14	16
---- V/Q ----				
VE/VO2	27	19	26	32
VE/VCO2	36	27	28	27
PETO2 (mmHg)	96	82	97	
PETCO2 (mmHg)	37	42	42	

Figure 19: A typical CPET report that includes the main recorded parameters

2.4.3 Stair climbing assessment

A thorough explanation was provided to patients prior to obtaining a verbal consent. Patients were then brought to a staircase within the hospital and instructed to climb as far as possible at their own pace using the railing only for balance. This assessment was done at the baseline visit only.

The staircase used had a maximum of four floors (4 flights); each flight of stairs had 28 steps with a small platform after 14 steps. Each step measured 6 inches in height. This staircase was chosen because of safety

reasons after discussion with the local physiotherapy department.

Patients were instructed to stop, once they can climb no more. Chairs were placed at each level if they wanted to sit down and rest. The investigator accompanied patients as they climbed the stairs step by step to ensure their safety. Time to climb stairs was noted and documented (in seconds) as well as the number of stairs climbed or flights completed. Standard cardiopulmonary markers (pulse, blood pressure, respiratory rate and oxygen saturations) and ECG were performed prior to & after the stair climbing test where indicated. Borg scale (1 to 10) was used to ascertain every patient's rate of perceived exertion (RPE) at the end of the test.

For the purposes of classifying the outcomes, the test was considered abnormal if:

1. Patients did not complete the 4 flights in 2 minutes.
2. Patients reported an RPE of 5 or more on the Borg 1-10 scale.
3. Patients reported significant limiting symptoms.

2.4.4 NT pro-BNP measurement

A blood sample was taken for plasma NT pro-BNP analysis at the baseline visit. Samples were taken in EDTA vacutainers and analysed using Elecys 2010 analyser (Roche diagnostics) at the trust's local laboratories. Values

were expressed as ng/L.

2.4.5 Radionuclide ventriculography

Radionuclide ventriculography were used to estimate LVEF by means of a MUGA scan done at the trust's nuclear medicine department.

MUGA scans were performed using a standard ECG-gated technique: Following venous cannulation, a blood sample was withdrawn and red blood cells were labelled with Technetium-99m in vivo after stannous pyrophosphate priming. A three-lead ECG was then used to give distinct R-wave trace to enable the gated acquisition cycle. Imaging was done in 2 planes. Using an Infinia® (General Electric) Gamma camera, a left anterior oblique 40 degree projection was taken for 7 minutes followed by a 70 degree projection also for 7 minutes producing 32 frames per each R-R gated cycle. The global LVEF was computed using the Xelenis® functional imaging locally developed software (General Electric) which enables the interpreter to hand mark the region of interest, i.e. left ventricle. LVEF was determined in the usual manner by subtracting end-systolic from end-diastolic counts and dividing this by end-diastolic counts. Using this method the LVEF was considered normal when it was ≥ 40%.

It is worth mentioning, that at the department of nuclear medicine, the locally developed software was vigorously tested to show excellent inter-

observer and intra-observer reproducibility. Based on the MUGA scan interpretation; which was provided by the same nuclear cardiologist, high cardiac risk patients were referred for cardiology consultation and any further cardiac interventions were decided by the cardiologists.

2.4.6 Risk scoring systems

The following risk scoring system were prospectively recorded for each patient during their initial clinical assessment visit:

1. Glasgow Aneurysm Score (GAS)
2. Vascular POSSUM score (physiologic)
3. Revised Cardiac Risk Index (RCRI)
4. Detsky's modified cardiac risk index

In addition, the V-POSSUM (operative) score was calculated for each patient using intraoperative data and the APACHE II scores were calculated upon admission to critical care directly following intervention (within 6 hours following operative interventions).

The scoring calculators used for some of the abovementioned risk scoring systems can be found in Appendix 2.

2.4.7 Blood samples

Venous blood samples were taken from each participant following completion of clinical assessment during the first visit. The following samples were taken:

1. Flood blood count: 4 ml EDTA (lavender) vacutainer.
2. Biochemical profile (including urea and electrolytes, liver enzymes and albumin): 4 ml clotting accelerator and separator gel (yellow) vacutainer.
3. Clotting screen: 3.5 ml Trisodium citrate (blue) vacutainer.
4. Lipid profile and C-reactive protein: 4 ml clotting accelerator and separator gel (yellow) vacutainer.

These samples were sent directly to the local lab at Hull and East Yorkshire NHS Trust to be analysed along with the sample collected for measuring NT-pro BNP. The results were recorded for each patient under their specific study ID by the chief investigator when available.

2.4.8 Quality of life assessment

All patients completed their questionnaires independently prior to their clinical assessment at baseline and at 3 months postoperatively. The questionnaires were then assessed for completeness, and in the presence

of missing responses patients were prompted to complete these sections. The investigator was present to address any queries patients had during questionnaire completion but without influencing patients' responses.

The questionnaires used were the generic:

1. Short Form (SF) 8 ©QualityMetric
2. EuroQol (EQ-5D) ©EuroQol Group

(Both questionnaires are available in Appendix 3)

2.5 Preoperative exercise intervention

Patients recruited in the intervention arm of the trial were provided with instructions and a timetable to join the exercise classes, ideally for 6 weeks immediately before their operative dates. In the event of a delay of intervention for any reason, participants were instructed to continue exercising as scheduled and their attendances were recorded as 100% or 18 out of 18 classes.

These exercise classes were done each Monday, Wednesday and Friday starting from 4 p.m. at the physiotherapy department within the hospital premises. All classes were supervised by one or more trained medical professional(s), with available resuscitation equipment for immediate use when needed. Attendance was recorded for all patients and documented at the end as the number and the percentage of all the classes they were scheduled to attend.

Each exercise session started with a 5-minute warm-up routine that was done at the beginning (Figure 20), and the session was then comprised of closed-circuit training on 6 stations each lasting for 2 min, with 2 min of brisk walking around the gym or on a treadmill between each station. The session lasted for a total of 45 minutes to 1 hour. The main exercises were:

1. Cycle ergometer, (Figure 21).
2. Heel raises (calf muscles), (Figure 22).
3. Resistance knee extensions, (Figure 23).
4. Knee flexions, (Figure 24).
5. Biceps curls (dumbbell exercises), (Figure 25).
6. Step-ups or lunges, (Figure 26).

Figure 20: Stretching and warm-up at the start and end of each class

Figure 21: Cycle ergometer training

Figure 22: Heel raises

Figure 23: Knee extension - resistance exercise

Figure 24: Knee bends exercise

Figure 25: Biceps (arm) curls

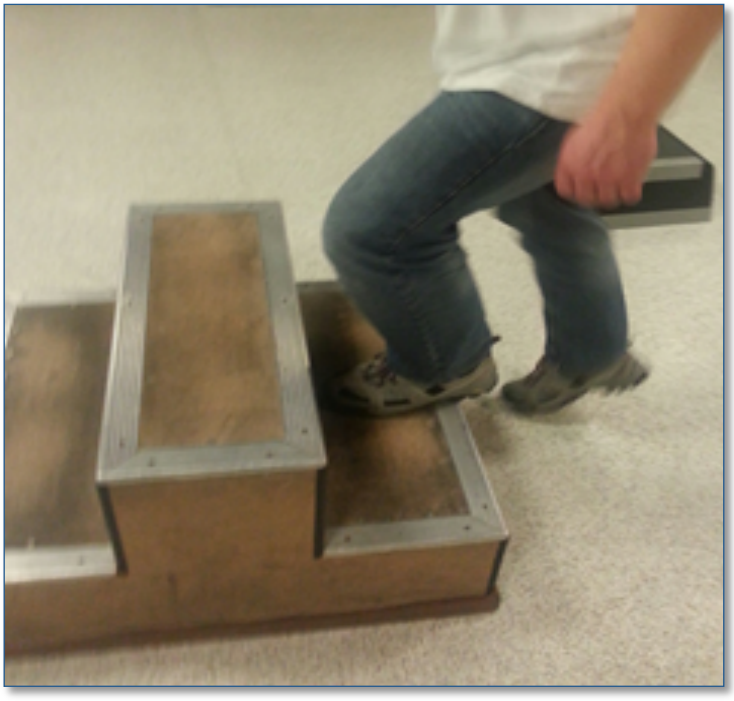


Figure 26: Step-ups exercise

2.6 Operative interventions

Surgical interventions for AAAs are either open repair or EVAR. Consultant vascular surgeons and interventional radiologists performed all interventions at Hull Royal Infirmary. All patients were admitted the night before the scheduled intervention, and transferred postoperatively to either high-dependency unit (HDU) or intensive therapy units (ITU) where they stayed for their first postoperative day as per the trust's practice guidelines. Only a few participants were deemed clinically well enough postoperatively (following EVAR only) for immediate care on the vascular surgical ward.

For each individual patient, a number of operative variables will be recorded, as follows:

- American Society of Anaesthesia (ASA) scores
- Duration of intervention
- The volume of intravenous fluids used
- The volume of blood given via the cell saver
- The use of intraoperative inotropes
- Any other unplanned or additional intraoperative details
- Presence of peritoneal contamination

These variables were primarily used to record the V-POSSUM operative severity scores.

2.7 Outcome measures

2.7.1 Primary outcome measures

The primary endpoint was a composite of cardiac, pulmonary and renal complications. The occurrence of any of these organ-specific complications defined below was scored as a primary endpoint:

A- Cardiac complications defined as**:**

1. Myocardial Infarction (2 out of following 3 criteria)
    i. Characteristic ischemic symptoms lasting > 20 min.
    ii. ECG changes: ST elevation, new persistent T wave inversion, LBBB or new ST segment depression which persists >24 hr.
    iii. A positive Troponin T, i.e. >0.10ng/ml.
2. New onset prolonged (>1 hour) arrhythmia or requiring therapy.
3. Congestive heart failure as defined as both clinical and radiological changes.
4. Use of inotropic support for at least 12 hours.
5. The development of unstable angina defined as worsening angina or angina at rest.

B- Pulmonary complications, defined as:

1. Pneumonia defined as an appropriate clinical history with either a positive sputum culture or infiltrate seen on chest radiograph).
2. Mechanical ventilation in the post-operative period (>48 hours).

3. Unplanned re-intubation after surgery.
4. Pulmonary embolism as determined by a positive CT pulmonary angiogram.

C- Renal complications, defined as:

1. Acute renal failure, requiring dialysis or ultrafiltration post op only.
2. Renal insufficiency, a >20% decrease in Creatinine Clearance post operatively.

If patients sustained one or more of the abovementioned complication(s), they will be scored as having had a complication, or having had an 'endpoint'. The reported 'endpoint' refers to a patient sustaining one, or more, of the abovementioned organ-specific complications. Patients sustaining more than one of the abovementioned complications were recorded as 1 endpoint.

2.7.2 Secondary outcome measures

These include:

1. Length of hospital stay (in days).
2. Length of critical care stay (in days), i.e. in-patient stay postoperatively on ITU and/or HDU.
3. Apache II scores on HDU or ITU admission (within 6 hours postoperatively).
4. Criteria of systemic inflammatory response syndrome (SIRS), at least two of the following:
   - Temperature >38°C or <36°C
   - Heart rate >90

- Respiratory rate >20
- WBC >12 or <4

5. The need for re-operation.
6. Quality of life scores (SF8 and Euroqol).
7. Postoperative bleeding; requiring re-operation, or a transfusion of more than 4 units of blood products within 72 hours postoperatively.
8. Death within 30 days of surgery.

2.8 Patient follow-up

Patients were reviewed on a daily basis during their hospital stay to record the occurrence of any of the abovementioned endpoints and to monitor their progress to recovery.

Patients underwent a final assessment 3 months after their surgery date. Postoperative outcome measures were actively sought and recorded during hospital stay, and then patients were specifically questioned during follow-up as to whether they sustained any complication postoperatively following their discharge and up to the end of follow-up. The quality of life questionnaires were also re-assessed at the final visit.

In an attempt to ensure completeness of follow-up, any patients who could not attend their final follow-up visit were contacted by telephone to ensure no further clinical concerns remained, and to enquire about their general health status and whether or not a re-admission or a visit to their doctor was warranted for any reason. Their general practitioner was also contacted if more clinical information were required. Quality of life questionnaires were sent via the post with a prepaid return envelope for completion and patients were encouraged to contact the trial investigators if they had any future concerns.

2.9 Data and statistical considerations

The trial's data was recorded and transcribed in a dedicated database (Microsoft Excel, Redmond, WA, USA). This database was password-protected at all times and stored only on a secured, hospital-based, computer drive.

A Statistical Package for the Social Sciences Program (SPSS) version 20 for Mackintosh (SPSS Inc. Chicago, IL) was used for statistical analysis. This analysis was performed according to a standardized, prospectively determined protocol, using an intention to treat analysis. No assumptions were made at any time as to the direction of any relationships and no imputation of missing data was attempted. Any key assumptions of the statistical techniques used were tested appropriately.

2.9.1 Continuous data:

Descriptive statistics:

Normally distributed data was quoted as mean (± standard deviation).

Data that was not normally distributed was quoted as median (inter-quartile range).

Analysis:

Simple histogram analysis, and where needed, the Kolmogorov-Smirnov statistic were used to explore whether data were normally distributed or not prior to any statistical analysis. In this test, a non-significant P value of > 0.050 indicated normality.

Hypothesis testing was performed comparing groups according to the nature of data distribution and whether data was paired or unpaired. The quoted p values represent the probability values of having observed the data if the null hypotheses were true (i.e. where there are no significant differences between the data). P values are quoted to three decimal places and a value of less than 0.050 is regarded as significant, leading to the rejection of the null hypothesis.

Comparisons between the study groups at baseline were performed using the unpaired Student's t-test for parametric variables (normally distributed data) and the Mann-Whitney U test for non-parametric variables (non-normally distributed data). This also applies to comparing the secondary outcomes: length of hospital stay and length of critical care stay.

2.9.2 Categorical data:

Descriptive statistics:

Categorical data is presented as percentages (x/y) where x represents the number of cases in a category and y represents the total number of cases under consideration. Where required, relative risk reduction (RRR), absolute risk reduction (ARR) or the number needed to treat (NNT) are also reported. These were calculated using the following equations:

RRR = CER – EER/CER

ARR = CER – EER

NNT = 1 / ARR

(CER = control [control group] event rate, EER= experimental [exercise group] event rate)

Analysis:

The primary hypothesis test used in categorical analysis is Pearson's Chi-square test (X^2 test). If greater than 20% of expected frequencies are less than 5 or any are below 1, then Fisher's exact test (FET) was used. This applies to all the categorical primary and secondary outcome measures in this study.

Study 2; A Sub-group Study Within a Prospective Randomised Controlled Trial to Assess the Effect of Exercise on Aerobic Fitness in Patients Awaiting Elective Abdominal Aortic Aneurysm Repair

2.10 Patients

This study was undertaken under the same settings described for *Study 1* at The Department of Vascular Surgery at Hull and East Yorkshire NHS Trust.

Patients scheduled for elective AAA repair (OAR and EVAR) were identified via the vascular outpatient clinics, multi-disciplinary weekly meetings or the waiting lists for theatre bookings. They were then directly contacted. Each patient who expressed interest was then invited for participation in this study, and an appointment for their first, or baseline visit was scheduled.

At the initial visit, patients were all assessed for eligibility for participation according to the following inclusion and exclusion criteria:

Inclusion criteria:

1. Patients with an AAA of 5.5 cm or more in maximum diameter, and being assessed for an elective open or endovascular repair.

2. Patient willing to participate in exercise training for 6 weeks.

3. Ability to give informed written consent.

4. Ability to communicate fully in English.

Exclusion criteria:

1. Any contraindication to undergo CPET.
2. Inability to adequately exercise due to any cause.
3. Inability to give an informed consent

The contraindications to undergo CPET were adopted from the international guidelines published by the American College of Cardiology/American Heart Association Task Force [264].

2.11 Randomisation

The description for randomisation in *Study 2* is identical to that described for Study 1 (section 2.2). Between November 2011 and November 2013, patients recruited and randomised into the large randomised controlled trial described under *Study 1* were invited to participate in this sub-study (*Study 2*), which involved undergoing two rather than one preoperative CPETs; the first at baseline (CPET 1), and a second following completion of 6 weeks of exercise, or the day immediately prior to surgery (CPET 2), dependant upon their group allocation.

Eligible patients who agreed for an additional CPET were randomised into one of two groups:

Exercise (intervention) group:

Patients receiving preoperative CPET assessments for elective AAA repair in addition to a period of 6 weeks of medically supervised, hospital-based exercise programme.

Control group:

Patients receiving preoperative CPET assessments for elective AAA repair but no preoperative interventions. These patients were clearly instructed to continue with their normal life-style and discouraged from undertaking any unsupervised exercises.

2.12 Assessments

2.12.1 CPET assessments

Following a complete history, a thorough clinical examination, assessment for eligibility and randomisation, all patients underwent their baseline CPET assessment (CPET 1) at the first visit as described for *Study 1*. This was a treadmill CPET. A measurement of patient's height and weight for estimation of their body mass index (BMI) was performed before the test.

The repeat treadmill CPET assessments (CPET 2) were performed following completion of the scheduled exercise training in those randomised to the exercise group, or on the day prior to surgery in the control group. CPET 2 assessments were performed under identical settings to that of CPET 1 assessments: during daytime, using the same software and system calibration and by the same investigator. These tests also followed a detailed clinical examination including a resting ECG and an assessment of patient blood pressure prior to the test. A new measurement of each patient's body mass index was performed prior to exercise testing to ascertain for any change in weight that might have took place over the period between the two CPET assessments.

2.13 Interventions

Participants in the exercise group of this study underwent a scheduled, consecutive 6 weeks of exercise training according to the provided instructions as described in section 2.5.

2.14 Outcome measures

The primary outcome measure in *Study 2* was the change in aerobic fitness assessed by the following CPET parameters:

1. VO_2 peak
2. AT
3. Time for achieving AT
4. Total exercise time on the treadmill
5. V_E/VO_2
6. V_E/VCO_2

These parameters were recorded for each patient, in either study group at CPET 1 and CPET 2.

The secondary outcome measure was the effect of exercise attendance on the magnitude of change on the clinically relevant CPET parameters within the exercise group of this study.

2.15 Statistical analysis

Data was recorded and transcribed in a dedicated database (Microsoft Excel, Redmond, WA, USA) which was password-protected at all times and stored only on a secured, hospital-based, computer drive.

A Statistical Package for the Social Sciences Program (SPSS) version 20 for Mackintosh (SPSS Inc. Chicago, IL) was used for statistical analysis.

2.15.1 Continuous data:

Normally distributed data was quoted as mean (± standard deviation [SD]). Data that was not normally distributed was quoted as median (inter-quartile range [IQR]). Simple histogram analysis, and where needed, the Kolmogorov - Smirnov statistic were used to ascertain whether data was normally distributed or not prior to any statistical analysis. In the Kolmogorov - Smirnov test, a non-significant P value of > 0.050 indicated normality of distribution.

Comparisons between study groups for co-morbidities and demographics at baseline were performed using the unpaired Student's t-test for parametric variables (normally distributed data) and the Mann-Whitney U test for non-parametric variables (non-normally distributed data).

The intragroup comparisons featured the analysis of paired data (i.e. before and after, for the same patient) and the comparisons between the values of the CPET parameters between CPET 1 and CPET 2 were carried out using the non-parametric Wilcoxon-Rank test for all variables.

A P value of < 0.050 was considered statistically significant.

2.15.2 Categorical data:

Categorical data is presented as percentages (x/y) where x represents the number of cases in a category and y represents the total number of cases under consideration.

For comparisons between study groups at baseline, the primary test used was the Pearson's Chi-square test. If greater than 20% of expected frequencies are less than 5 or any are below, then Fisher's exact test was used.

Study 3; The Value of Different Preoperative Assessment Tools in Predicting Postoperative Complications Following Elective Abdominal Aortic Aneurysm Repair

2.16 Patients

The setting for this observational study was the same tertiary vascular centre featured in *Study 1*. The data from all study participants was utilised.

Patients were recruited as explained in section 2.1 for *Study 1*. The inclusion and exclusion criteria were also the same to those of *Study 1*.

2.17 Assessments

As explained in section 2.4, at the baseline visit, all patients would undergo a detailed history and clinical examination. A record was specifically made for all co-morbidities, current medications, allergies and the relevant past medical and surgical history. At physical examination, every patient's body mass index and ABPIs were recorded. The outcomes from the stair climbing assessments, GAS, RCRI, Detsky score and the V-POSSUM physiological score were also recorded at this stage. In addition, the CPET parameters: VO_2 peak, AT, V_E/VO_2, V_E/VCO_2 were recorded.

If CPET was repeated again preoperatively (CPET 2), then the parameters recorded at CPET 2 were also recorded, and the new measured parameters were used in the analysis described for *Study 3*. Further records were also made for:

1. A full blood count results
2. A biochemical profile (including renal and liver functions, serum CRP levels and a lipid profile)
3. A coagulation screen
4. Serum NT pro-BNP levels.
5. LVEF measured by MUGA scans.

Postoperatively, APACHE II scores and the operative components of V-POSSUM scores were recorded.

2.18 Outcome measures

The primary outcome measure for this study was similar to the one stated for *Study 1*, i.e. the composite endpoint postoperative cardiac, pulmonary and/or renal complications as defined in section 2.7.

Patients who sustained any one or more of these complications were recorded as having had a complication, and patients who did not sustain any of these were counted as having not had a complication.

The secondary outcome measures were the isolated occurrence of a:

- Cardiac complication
- Pulmonary complication
- Renal complication

as defined in section 2.7.

All complications were actively sought and prospectively recorded for each patient within the first three postoperative months.

2.19 Statistical analysis

Data was recorded and transcribed in a dedicated database (Microsoft Excel, Redmond, WA, USA). This database was password-protected at all times and stored only on a secured, hospital-based, computer drive.

A Statistical Package for the Social Sciences Program (SPSS) version 20 for Mackintosh (SPSS Inc. Chicago, IL) was used for statistical analysis. This analysis was done according to a standardized, prospectively determined protocol, with an intention to treat analysis. No assumptions were made at any time as to the direction of any relationships and no imputation of missing data was attempted. Any key assumptions of the statistical techniques used were tested appropriately.

2.19.1 Continuous data:

Descriptive statistics:

Normally distributed data was quoted as mean (± standard deviation).

Data that was not normally distributed was quoted as median (inter-quartile range).

Analysis:

Simple histogram analysis, and where needed the Kolmogorov - Smirnov statistic were used to explore whether data were normally distributed or not prior to any statistical analysis. For the Kolmogorov – Smirnov test, a non-significant p value of > 0.050 indicated normality of distribution.

Hypothesis testing was performed comparing groups according to the nature of data distribution. The quoted p values represent the probability values of having observed the data if the null hypotheses were true (i.e. where there are no significant differences between the data). P values are quoted to three decimal places and a value of less than 0.05 is considered significant, leading to the rejection of the null hypothesis.

Univariate analysis

Comparisons between two groups: those sustaining a postoperative complication, and those who did not, were performed using the unpaired Student's t-test for parametric variables (normally distributed data) and the Mann-Whitney U test for non-parametric variables (non-normally distributed data).

2.19.2 Categorical data:

Descriptive statistics:

Categorical data is presented as percentages (x/y) where x represents the number of cases in a category and y represents the total number of cases under consideration.

Analysis:

The primary hypothesis test used in categorical analysis is Pearson's Chi-square test (X^2 test). If greater than 20% of expected frequencies are less than 5 or any are below 1, then Fisher's exact test (FET) was used. This applies to the primary and secondary outcome measures in this study.

Univariate analysis:

A comparison between the study participants who developed postoperative complications and those who did not was done to explore the potential variables that can predict postoperative complications. Similarly, comparisons were carried out using unpaired t-test for

parametric variables and Mann-Whitney U test for non-parametric variables, X^2 test and Fisher's exact probability test were used for categorical variables as appropriate.

Logistic Regression Analysis:

Logistic regression analysis was used to identify factors that independently predicted the occurrence of postoperative complications. Only variables with $p<0.050$ in the univariate analysis were included in the regression model as the primary variables of interest.

The same model was done 4 times with the dependent variables being set as follows:

1. The primary outcome measure of cardiac, pulmonary and/or renal postoperative complications (composite endpoint: binary variable; 1: Present, 0: Absent)
2. The secondary outcome: occurrence of postoperative cardiac complications (binary variable; 1: Present, 0: Absent)
3. The secondary outcome: occurrence of postoperative pulmonary complications (binary variable; 1: Present, 0: Absent)
4. The secondary outcome: occurrence of postoperative renal complications (binary variable; 1: Present, 0: Absent)

The statistical significance was set at a p value less than 0.050. Regression analysis outcomes were reported with regression coefficients, p values, odds ratios and 95 per cent confidence intervals (95% C.I.).

Receiver operator characteristics (ROC) curve analyses

ROC curve analyses were performed to establish the prognostic accuracy of CPET parameters in predicting postoperative complications.

ROC curves were constructed using the same statistical software (SPSS v.20 Mackintosh). These were constructed first by tabulating and then plotting the sensitivity and specificity of CPET parameters if they independently predicted postoperative cardiac, pulmonary or renal complications. ROC curves were also used to compare the accuracy of the same parameters for both types of AAA repair (open and EVAR).

The area under the curve (AUC) was then calculated to quantify the overall prognostic discrimination for the endpoint in question as follows:

1. Composite endpoint: cardiac, pulmonary or renal complications. This was performed separately for both types of aneurysm repair (EVAR and Open) to establish whether different cut-off values will have different accuracies.
2. Cardiac complications
3. Pulmonary complications

In terms of predictive accuracy, AUC values are usually classified as follows:

1. 0.5 to 0.6 – No predictive accuracy
2. 0.6 t0 0.7 – Poor predictive accuracy
3. 0.7 to 0.8 – Fair predictive accuracy
4. 0.8 to 0.9 – Excellent predictive accuracy
5. 0.9 to 1 – Outstanding predictive accuracy

AUC is presented with 95% CIs and p values.

2.20 Ethical considerations

The conduct of the three studies, and all the included analyses, along with the dissemination of findings and writing this thesis has been performed in accordance with the principles of the declaration of Helsinki. Patient's safety, satisfaction and best interest were the primary concern of each individual who was involved in this project, and all investigators had undergone formal *Good Clinical Practice* training, and had valid certification at all times.

Operative repairs were always mutually agreed interventions that followed thorough explanation and discussions with patients and primary carers. Multidisciplinary team decisions are the only way an AAA repair is planned and agreed at our centre; where decisions regarding patient fitness, anatomical suitability and best interest are usually decided on an individual basis. An informed written consent was given for patients who took part in this study prior to AAA repair. Similarly, radiological imaging, assessments for fitness or organ function were always done following informed consent by patients taking part at each step of this research. The exercise classes were always medically supervised and patients were given the opportunity to enquire about any issue during their involvement in this study.

After all, the principal aim of this research project was to improve patient care and outcomes by exploring the clinical benefit of this exercise intervention.

The study protocol, with the final versions of the patient information sheet, consent form and other documents were all designed primarily to conform to the best standards of care. Approval was prospectively secured from both an independent regional ethical committee and the trust research and development review board. The trial was then registered and made available as recommended. Progress reports and notifications of adverse events were provided to the Ethics Committee according to the regional regulations and guidelines. The study was also monitored in accordance with the Hull and East Yorkshire NHS Trust's research and development department standard operating protocols.

All study participants were included if they fitted the inclusion/exclusion criteria defined earlier in this chapter. Patients were informed that they had the right to withdraw from this study at any point in time without providing any explanation. They were reassured their standard clinical care would not be affected by withdrawal from the study. Study participants were regularly contacted to ensure their wellbeing and general satisfaction with the care provided and they were always invited to enquire or express any concern as they were given direct telephone contact numbers for the trial investigators.

All information collected about the trial participants were collated using unique patient identity numbers to ensure optimum confidentiality. Patient names and details were always anonymised and were never available in accessible, open data sets or any other reports. All data were

electronically kept in a password-protected dataset on a private folder accessible by the chief investigator on a secured, trust-based hard drive accessible only to researchers within the Academic Vascular Surgical Unit at Hull Royal Infirmary. This data has an identified Caldicott guardian and has not been disseminated in any way that risked the identification of individual patient's details. Hard copies of individual patient's data and other related documents were held in a locked room at the Academic Vascular Surgical Unit and will be securely stored in locked cabinets for the next five years within specially labelled, secure boxes that state the date after which the documents can be destroyed. The chief investigator held the responsibility for data collection, recording and maintenance of its quality at all times during this trial.

CHAPTER 3: RESULTS

Study 1; A Randomised Controlled Trial to Assess the Effect of Preoperative Supervised Exercise on Outcomes Following Elective Abdominal Aortic Aneurysm Repair

3.1 Study population and baseline analysis

A total of 293 patients were assessed for eligibility. 136 patients were randomised in the two study groups between September 2009 and January 2014. Figure 27 outlines the study recruitment process and includes the number of patients who withdrew or were lost to follow-up.

The two study groups were compared in terms of age, gender, baseline co-morbidities and medications, baseline aerobic fitness parameters measured by CPET, LVEF assessed by MUGA scanning and serum NT pro-BNP measurements.

Out of 68 patients randomised in the exercise group, 6 patients dropped out before starting exercise: 3 declared their desire to withdraw from the study, 1 patient had a CTA and his aneurysm was smaller than the measurement by ultrasound scanning, so he was referred back to the surveillance programme for follow-up, 1 patient had an urgent laparoscopic cholecystectomy and her aortic surgery was delayed and 1 was declared unfit for open surgery and later, anatomically not suitable for EVAR, this individual died of metastatic lung cancer shortly after.

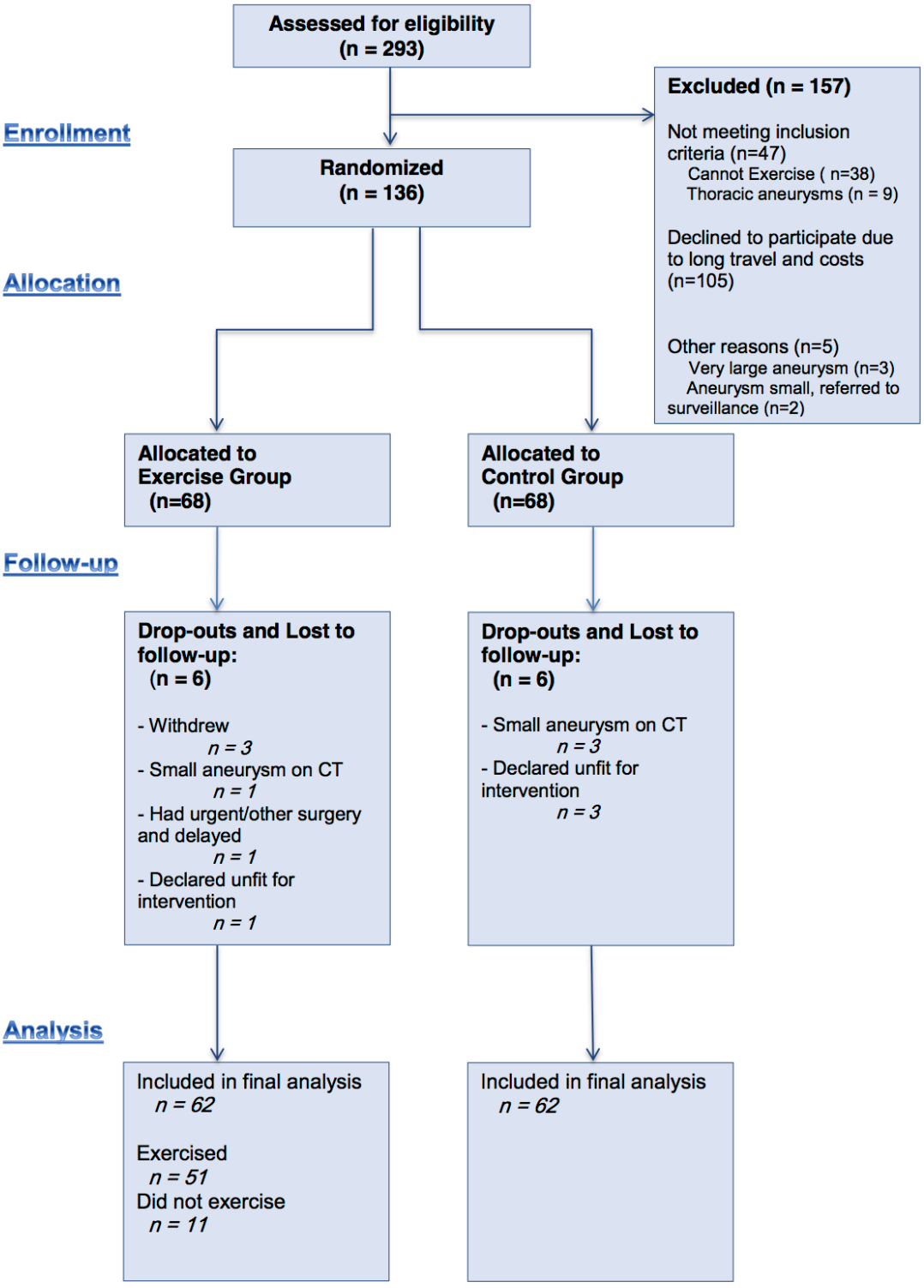


Figure 27: Consort diagram for *Study 1*

In the exercise group, 62 patients were included in the analyses with no further loss to follow-up. Fifty-one patients attended their exercise training as scheduled, the remaining 11 did not attend the exercise class; 7 of these patients had their operative interventions expedited and did not consider a short period of exercise worthwhile. The other 4 patients declared that difficulties in travelling to the hospital three afternoons a week were the main reason for not participating. These patients did not declare any desire to withdraw from the study.

Of the 68 patients randomised to the control group, 3 patients were found to have smaller aneurysms on CTA and were referred back to the local AAA surveillance programme, and 3 were later declared unfit for open repair and were not anatomically suitable for EVAR and had no interventions by the end of the study. Sixty two patients in the control group were included in the analysis with no further loss to follow-up. Approximately 90% of participants are male patients with a history of cigarette smoking in the vast majority.

Table 3 also illustrates that there were no significant differences between the two study groups in terms of the baseline characteristics, aerobic capacity parameters and preoperative NT-pro BNP or LVEF.

Variable	Total (n=124)	Exercise group (n=62)	Control group (n=62)	P value
Age [a]	73.4 (7.2)	73.8 (6.5)	72.9 (7.9)	0.519*
Females [c]	13 (10.5%)	6 (9.7%)	7 (11.3%)	0.769‡
EVAR [c]	46 (37.1%)	23 (37.1%)	23 (37.1%)	1.000‡
Hypertension [c]	88 (71.0%)	45 (72.6%)	43 (69.4%)	0.692‡
CAD [c]	47 (37.9%)	24 (38.7%)	23 (37.1%)	0.853‡
Hyperlipidaemia [c]	52 (41.9%)	27 (43.5%)	25 (40.3%)	0.716‡
History of smoking [c]	117 (94.4%)	60 (96.8%)	57 (91.9%)	0.243‡
Current smokers [c]	39 (31.5%)	18 (29.0%)	21 (33.9%)	0.562‡
Previous smokers [c]	78 (62.9%)	42 (67.7%)	36 (51.1%)	0.309‡
Never smoked [c]	7 (5.6%)	2 (3.2%)	5 (8.1%)	0.272§
Diabetes [c]	13 (10.5%)	4 (6.5%)	9 (14.5%)	0.143‡
Cerebrovascular disease [c]	21 (16.9%)	10 (16.1%)	11 (17.7%)	0.811‡
COPD [c]	41 (33.1%)	18 (29.0%)	23 (37.1%)	0.340‡
High serum creatinine [c]	25 (20.2%)	15 (24.2%)	10 (16.1%)	0.263‡
Statin use [c]	102 (82.3%)	52 (83.9%)	50 (80.6%)	0.638‡
Antiplatelet use [c]	76 (61.3%)	37 (59.7%)	39 (62.9%)	0.719‡
Beta blocker therapy [c]	30 (24.2%)	16 (25.8%)	14 (22.6%)	0.417‡
AAA diameter [a]	6.2 (0.8)	6.0 (0.7)	6.3 (0.9)	0.111*
Body Mass Index [a]	27.0 (3.9)	26.7 (3.5)	27.4 (4.2)	0.281
VO_2 peak [a]	17.5 (4.5)	17.8 (4.2)	17.2 (4.8)	0.471*
AT [a]	12.5 (3.9)	12.3 (3.4)	12.6 (4.3)	0.699*
V_E/VO_2 [b]	28.0 (25.0-32.0)	28.0 (25.0-32.0)	28.0 (24.3-31.8)	0.653†
V_E/VCO_2 [b]	32.0 (27.3-36.0)	33.0 (29.2-36.0)	31.0 (21.9-36.2)	0.125†
NT-pro BNP [b]	153.0 (72.0-258.0)	158.5 (62.5-304.8)	135.0 (85.0-251.0)	0.541†
LVEF [b]	40.0 (36.8-46.3)	41.5 (36.0-50.0)	40.0 (37.0-44.0)	0.285†

Table 3: Baseline characteristics of Study 1 participants
[a] mean (±SD) , [b] median (IQR), [c] n (%). CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease. *Unpaired t-test, †Mann Whitney U Test, ‡Chi Square test, § Fisher's exact test

3.2 Primary outcome measure: Postoperative complications

The primary outcome measure was the composite endpoint of cardiac, pulmonary and/or renal postoperative complications, compared between the two study groups.

An intention to treat analysis showed a reduction in the study's primary endpoint of postoperative complications in the exercise group:

26 endpoints were recorded in the control group (41.9%) versus 14 endpoint in the exercise group (22.6%), *p*=0.021.
The relative risk reduction (RRR) for postoperative complications was 46.1% and the NNT was 5 (95% C.I. 3 to 35).

Of this total of 40 complications; 19 (15.3%) were cardiac as defined in the study protocol. All cardiac complications occurred within the first postoperative month and were distributed amongst the study groups as follows:

14 complication (22.6%) in the control group and 5 complications (8.1%) in the exercise group; *p*=0.025.
RRR was 64.3% for cardiac complications and the NNT was 7 (95% C.I. 4 to 58). Two of the 19 cardiac complications were fatal; both occurring in the control group.

A total of 20 (16.1%) pulmonary complications were recorded as follows: 13 complications (21.0%) in the control group and 7 (11.3%) in the exercise group, p=0.143.
RRR was 46.2% for pulmonary complications, and NNT was 10 (95% C.I. -29 to 4). Only one of these complications was a fatal complication; a multi-organ failure as a consequence of a severe response to aspiration pneumonia.

A total of 17 (13.7%) renal complications were recorded as follows: 13 (21.0%) in the control group and 4 (6.5%) in the exercise group; p=0.019.
RRR was 69.2% for renal complications, and NNT was 7 (95% C.I. 4 to 44). None of these complications was a direct cause of early mortality, however, one patient had a multi-organ failure and an established severe renal insufficiency, and died shortly following his surgery.

A summary of the cardiac, pulmonary and renal postoperative complications is presented in Table 4.

Complications	Total	Exercise group	Control Group
Cardiac	19 (15.3%)	5 (8.1%)	14 (22.6%)
	5 – Myocardial Infarction (2 fatal) 5 – prolonged inotropic support 5 – new onset arrhythmia (without evidence of myocardial damage or ischaemia) 3 – New onset arrhythmia with elevated Troponin-T levels 1 – Unstable angina with Troponin level of 0.05		
Pulmonary	20 (16.1%)	7 (11.3%)	13 (21.0%)
	14 – Postoperative pneumonia 3 – Severe postoperative pneumonia resulting in re-intubation or respiratory support 1 – Postoperative pneumonia and an exacerbation of COPD 1 – Unplanned re-intubation 1 – Re-intubation and aspiration pneumonia (fatal)		
Renal	17 (13.7%)	4 (6.5%)	13 (21.0%)
	15 – More than 20% decrease in creatinine clearance 2 – Renal insufficiency postoperatively requiring hemodialysis/haemofiltration		

Table 4: Summary of the cardiac, pulmonary and renal complications in the two study groups

3.2.1 Exercise attendance and postoperative outcomes

Within the exercise group, 51 patients attended the exercise class, and 11 did not attend. Out of the 51 patients: 18 patients attended all classes in six weeks (100%), 3 of these exercised for more than 6 weeks as their operative dates were delayed. The attendance rates were categorized in three subgroups (subgroups 1, 2 and 3) and are summarized along with the number of recorded endpoints (postoperative cardiac, pulmonary or renal complications) in Table 5.

Subgroup	Classes attended	Number of participants	Number of complications recorded
1	13-18 classes	32	3 (9.4%)
2	6-12 classes	19	7 (36.9%)
3	Did not attend	11	4 (36.4%)

Table 5: Exercise attendance rates and the number of postoperative complications recorded in each subgroup

Patients in subgroup 1 were less likely to sustain a postoperative complication in comparison to subjects in subgroup 2 ($p = 0.020$) or in subgroup 3 ($p=0.036$). On the other hand, there was no statistical significance between the incidences of postoperative complications observed for subjects in subgroups 2 and 3.

3.3 Secondary outcome measures

3.3.1 Length of hospital stay

The median duration of hospital stay for all patients was 7.0 (5.0-9.0) days. 28 patients stayed for more than 10 days in hospital postoperatively; only 4 of these had an EVAR.

Only 4 of 28 patients who stayed in hospital for more than 10 days did not sustain a cardiac, pulmonary or renal complication. However, two of them sustained a postoperative ileus, 1 was struggling with mobility and had a wound infection, and 1 did fairly well but was slow to progress following open repair.

Duration of hospital stay was significantly shorter for patients in the exercise than in patients in the control group: median 7.0 (5.0-9.0) days versus 8.0 (6.0-12.3) days; p = 0.025. Those who died in-hospital (n=3) were excluded from this analysis.

3.3.2 Length of critical care stay

At the study centre, it is routine for all patients to be admitted to critical care: usually the high dependency unit following open repair or EVAR.

All but 5 patients who underwent EVAR were admitted to the high dependency unit postoperatively. These 5 patients were admitted for routine care and observations to the ward as they were clinically suitable. On the other hand, 6 patients were admitted to the intensive care unit (ICU) following open repair for more invasive monitoring and organ support. These were all included in this analysis.

The median (IQR) duration of critical care stay in days for the study population was 1.0 (1.0-2.0) day.

There was no statistically significant difference between the two study groups in terms of the duration of critical care stay: the median duration of critical care stay in the exercise group was 1.0 (1.0-2.0) day versus 2.0 (1.0-2.0) days in the control group; p = 0.845.

3.3.3 APACHE II scores on HDU/ITU admission

APACHE II scores were prospectively recorded based on vital signs, blood tests and observations made upon admission to ITU or HDU postoperatively.

The median (IQR) APACHE II score for the whole study population was 10.0 (8.0 – 14.0). The difference in APACHE II scores between the study

groups was not statistically significant: 9.0 (7.0-13.3) in the exercise group versus 11.0 (8.0-15.0) in the control group; p=0.256.

3.3.4 Criteria of SIRS during hospital stay

The presence or absence of the criteria of SIRS during hospital stay was recorded for all patients.

101 (81.5%) patients had a record of SIRS criteria postoperatively;
50 (80.6%) in the exercise group versus 51 (82.3%) in the control group; p= 0.817.

3.3.5 The need for re-operation

A total of 5 patients had a re-operation (4.0%). All of them had an open repair. 2 patients had a postoperative bleed and underwent another laparotomy and revision. One had ischaemic colon and had to undergo resection, one was diagnosed with a postoperative abdominal compartment syndrome and one had a lower limb peripheral arterial occlusion and was taken back to theatre for embolectomies and subsequent fasciotomies.

2 (3.2%) patients from the exercise group had a re-operation compared to 3 (4.8%) from the control group; p=1.000.

3.3.6 Postoperative bleeding

The presence or absence of significant postoperative bleeding that required either a reoperation for control or a transfusion more than 4 units of blood within 72 hours was recorded in 11 patients (8.9%); 4 (6.5%) in the exercise group versus 7 (11.3%) in the control group; p=0.343.

3.3.7 Death within 30 days of surgery

Four patients (3.2%) died within thirty day of surgery in this study. Three of these died in-hospital and one patient died following discharge from a massive stroke; this patient was frail and had a pre-existing end-stage renal disease. He underwent EVAR and was discharged on day 8 postoperatively as he had dialysis as an in-patient twice and was slow to make progress. Two of the patients who died in-hospital had a significant myocardial infarction and one suffered severe consequences of aspiration pneumonia.

Two (3.2%) patients died with 30 days postoperatively from each of the study groups; p=1.000.

3.3.8 Quality of life scores

There were no statistically significant changes on the quality of life scores (EQ-5D and SF-8) from baseline till the end of follow-up at three months, when compared between the two study groups. These are summarized in Table 6.

	Baseline		Change at 3 months		P value
	Exercise	Control	Exercise	Control	
E5-QD score[a]:	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.004	-0.008	0.596[*]
SF-8 scores:					
PF[a]	48 (40-54)	48 (40-54)	0.2	-2.3	0.194[*]
RP[a]	47 (39-54)	54 (39-54)	-1.5	-3.5	0.315[*]
BP[a]	53 (48-61)	53 (48-61)	-0.7	-0.6	0.987[*]
GH[a]	46 (38-53)	46 (38-53)	1.8	-0.8	0.070[*]
VT[a]	56 (45-56)	45 (45-56)	-0.7	0.2	0.313[*]
SF[a]	55 (50-55)	50 (40-55)	-1.8	-0.3	0.728[*]
RE[a]	52 (46-52)	52 (46-52)	-0.5	-0.8	0.677[*]
MH[a]	50 (48-57)	50 (44-57)	2.5	2.5	0.842[*]
PCS[a]	51 (42-55)	52 (44-55)	-1.5	-3.5	0.307[*]
MCS[a]	53 (48-58)	51 (46-56)	1.2	2.5	0.510

Table 6: Summary of EQ-5D and SF8 changes from baseline compared between the two study groups. [a] median (IRQ). [*] Mann Whitney U test.
PF: Physical functioning, RP: Role physical, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social function, RE: Role emotional, MH: Mental health, PCS: Physical component summary, MCS: Mental component summary

Study 2; A Sub-group Study Within a Prospective Randomised Controlled Trial to Assess the Effect of Exercise on Aerobic Fitness in Patients Awaiting Elective Abdominal Aortic Aneurysm Repair

3.4 Study population and baseline analysis

Forty eight patients were recruited in total to *Study 2*. All participants completed their two CPET assessments: 33 patients in the exercise group, and 15 in the control group. The two study groups were generally comparable at baseline in terms of age, gender, co-morbidities and medications. Hypertension, diabetes and antiplatelet use were significantly more common in the control group. This is presented in Table 7.

No adverse events were recorded during exercise training or CPET testing.

	Total (n=48)	Exercise (n =33)	Control (n=15)	P value
Age [a]	71.7 (7.2)	72.6 (7.2)	69.7 (7.2)	0.206*
Females [c]	6 (12.5%)	5 (15.2%)	1 (6.7%)	0.410‡
Hypertension [c]	36 (75.0%)	22 (66.7%)	14 (93.3%)	0.048‡
CAD [c]	19 (36.9%)	13 (39.4%)	6 (40.0%)	0.968‡
Hyperlipidaemia [c]	24 (50.0%)	15 (45.5%)	9 (60.0%)	0.350‡
History of smoking [c]	45 (93.8%)	32 (97.0%)	13 (86.7%)	0.172‡
Diabetes [c]	5 (10.4%)	1 (3.0%)	4 (26.7%)	0.028§
Cerebrovascular disease [c]	10 (20.8%)	6 (18.2%)	4 (26.7%)	0.502‡
COPD [c]	15 (31.2%)	10 (30.3%)	5 (33.3%)	0.834‡
High serum creatinine [c]	5 (10.4%)	4 (12.1%)	1 (6.7%)	1.000§
Statin use [c]	39 (81.2%)	26 (78.8%)	13 (86.7%)	0.517‡
Antiplatelet use [c]	31 (64.6%)	18 (54.5%)	13 (86.7%)	0.031‡
Beta blocker therapy [c]	17 (35.4%)	11 (33.3%)	6 (40.0%)	0.654‡
BMI [a]	27.5 (3.8)	27.2 (3.4)	28.0 (4.7)	0.473*

Table 7: Baseline characteristics and parameters of aerobic fitness for Study 2 patients compared between the two study groups
[a] mean (±SD) , [b] median (IQR), [c] n (%). CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease.
***Unpaired t-test, †Mann Whitney U Test, ‡Chi Square test, § Fisher's exact test**

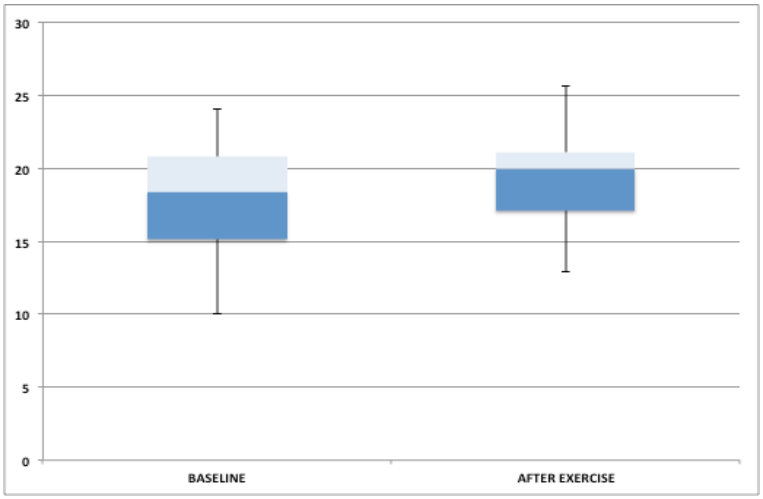
3.5 The effect of exercise training on CPET parameters

Intra group analysis

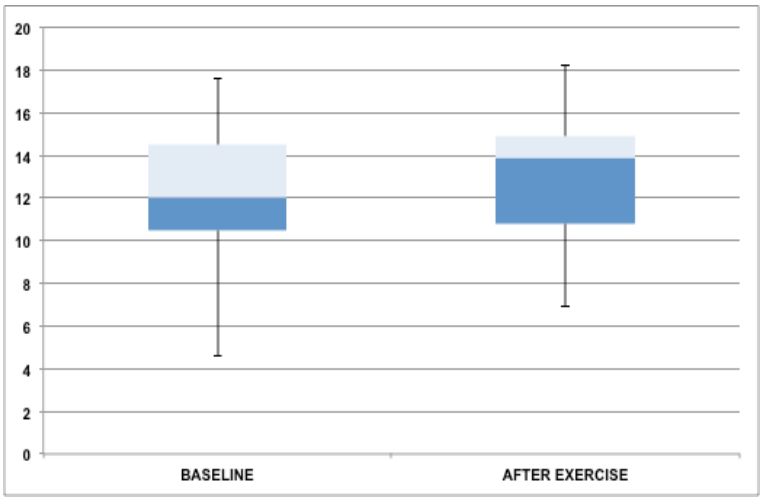
Statistically significant changes between the parameters of aerobic fitness were seen in the 33 patients who exercised, these are presented in Table 8 and Figure 28.

Aerobic fitness parameter	Baseline (CPET 1)	After Exercise (CPET 2)	P value
VO_2 peak [a] (ml O2/kg/min)	18.4 (15.0-20.9)	20.0 (16.9-21.3)	0.004*
AT [a] (ml O2/kg/min)	12.0 (10.4-14.5)	13.9 (10.6-15.1)	0.012*
Time for achieving AT [a] (seconds)	136.0 (79.0-226.0)	165.8 (113.0-442.0)	0.003*
Total exercise time [a] (seconds)	412.0 (219.0-613.0)	577.0 (398.0-705.0)	<0.001*
V_E/VO_2 [a]	28.0 (26.0-32.5)	27.0 (25.5-32.0)	0.026*
V_E/VCO_2 [a]	32.0 (30.0-37.0)	32.0 (29.0-36.5)	0.090*

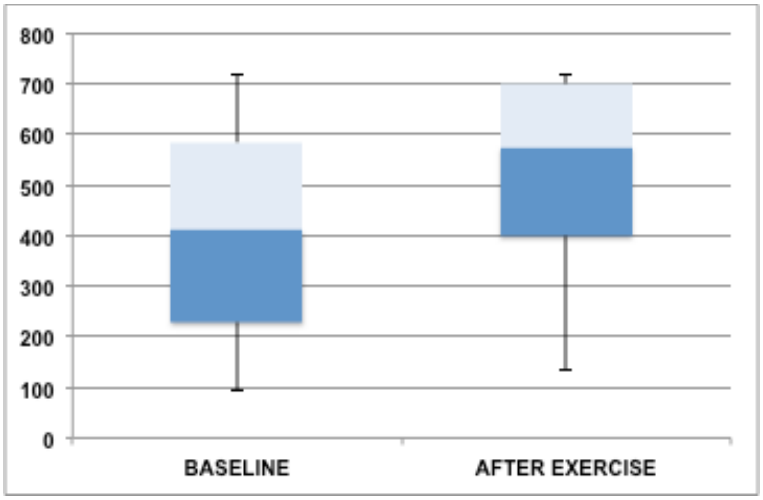
Table 8: The changes in the main CPET-measured parameters following exercise [a] median (IQR). * Wilcoxon rank test



(A) Changes in VO_2 peak after exercise



(B) Changes in AT after exercise



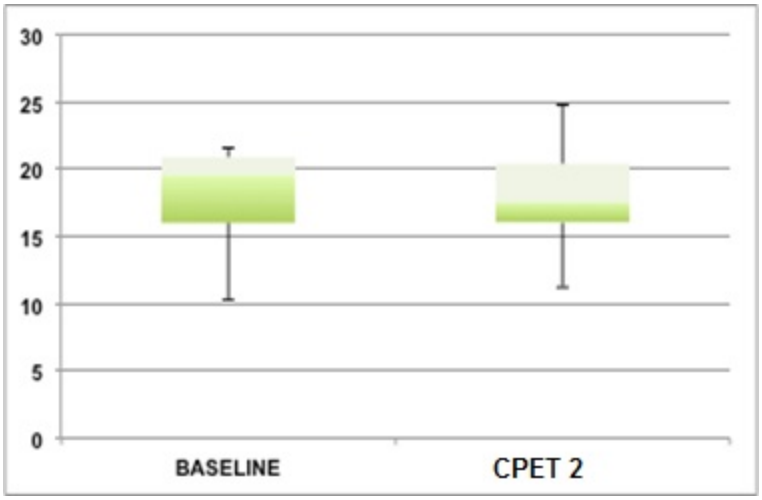
(C) Changes in total treadmill exercise time after exercise

Figure 28: Box-whisker presentation of the changes in VO_2 peak (A), AT (B) and Total exercise time (C) between baseline (CPET 1) and after exercise (CPET 2)

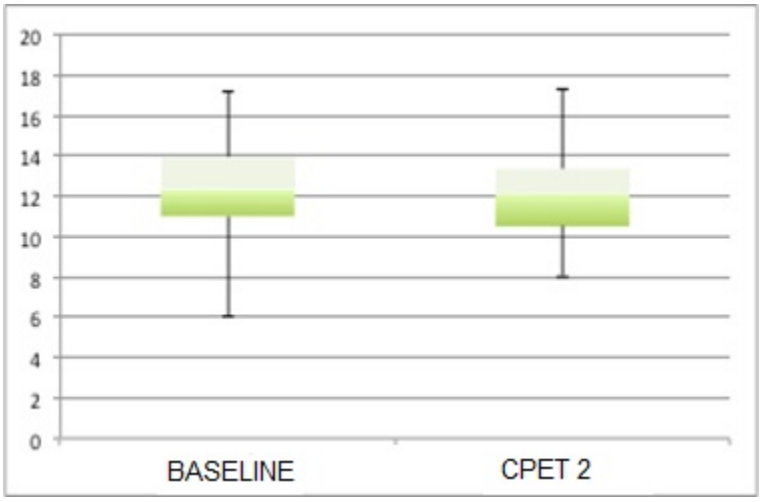
The changes between the parameters of fitness between baseline and the day prior to surgery in the 15 patients from the control group who did not exercise were not statistically significant, and are summarized in Table 9 and Figure 29.

Aerobic fitness parameter	Baseline (CPET 1)	Day prior to surgery (CPET 2)	P value
VO_2 peak [a] (ml O2/kg/min)	19.6 (15.4-21.3)	18.4 (15.9-20.7)	0.609*
AT [a] (ml O2/kg/min)	12.3 (10.7-14.4)	12.1 (10.2-14.3)	0.532*
Time for achieving AT [a] (seconds)	164.0 (99.0-232.0)	160.0 (104.0-206.0)	0.629*
Total exercise time [a](seconds)	519.0 (323.0-624.0)	533.0 (290.0-673.0)	0.191*
V_E/VO_2 [a]	25.0 (24.0-30.0)	28.0 (24.0-33.0)	0.268*
V_E/VCO_2 [a]	32.0 (29.0-36.0)	33.0 (30.0-36.5)	0.507*

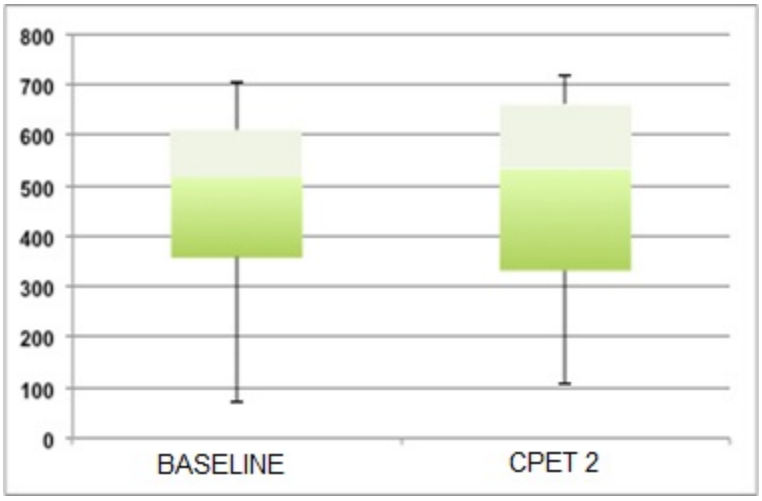
Table 9: The changes in CPET-measured parameters from baseline in the control subgroup
[a] median (IQR). * Wilcoxon rank test



(A) Changes in VO_2 PEAK from baseline and the last preoperative day



(B) Changes in AT between baseline and the last preoperative day



(C) Changes in the Total exercise time between baseline and the last preoperative day

Figure 29: Box-whisker presentation of the changes in VO_2 peak (A), AT (B) and Total exercise time (C) between CPET1 and CPET2

Inter group analysis

A comparison between both groups in *Study 2* in terms of the CPET parameters is presented in Table 10 for CPET 1 (baseline) and Table 11 for CPET 2 (after exercise, or on the day prior to surgery).

CPET 1 Parameters	Total (n=48)	Exercise (n=33)	Control (n=15)	P value
VO_2 peak [a] (ml O2/kg/min)	18.8 (15.4-20.9)	18.4 (15.0-20.9)	19.6 (15.4-21.3)	0.504[†]
AT [a] (ml O2/kg/min)	12.2 (10.6-14.5)	12.0 (10.4-14.5)	12.3 (10.7-14.4)	0.490[†]
Time for achieving AT [a] (seconds)	139.5 (85.0-226.3)	136.0 (79.0-226.0)	164.0 (99.0-232.0)	0.553[†]
Total exercise time [a] (seconds)	453.0 (231.0-616.8)	412.0 (219.0-613.0)	519.0 (323.0-624.0)	0.477[†]
V_E/VO_2 [a]	27.5 (25.0-31.8)	28.0 (26.0-32.5)	25.0 (24.0-30.0)	0.115[†]
V_E/VCO_2 [a]	32.0 (30.0-36.8)	32.0 (30.0-37.0)	32.0 (29.0-36.0)	0.746[†]

Table 10: CPET 1 (baseline) parameters compared between the two study groups [a] Median (IQR). [†] Mann Whitney U Test

CPET 2 Parameters	Total (n=48)	Exercise (n=33)	Control (n=15)	P value
VO_2 peak [a] (ml O2/kg/min)	18.9 (17.0-21.1)	20.0 (17.1-21.1)	17.6 (16.1-20.4)	0.251[†]
AT [a] (ml O2/kg/min)	12.4 (10.7-14.8)	13.9 (10.8-14.9)	12.1 (10.5-13.4)	0.261[†]
Time for achieving AT [a] (seconds)	186.5 (110.5-298.3)	189.0 (117.0-426.0)	160.0 (107.5-204.0)	0.367[†]
Total exercise time [a] (seconds)	555.5 (389.0-686.8)	577.0 (402.0-700.0)	533.0 (332.0-662.5)	0.414[†]
V_E/VO_2 [a]	27.0 (25.0-30.8)	27.0 (26.0-30.0)	28.0 (24.5-31.5)	0.965[†]
V_E/VCO_2 [a]	32.0 (29.8-36.0)	32.0 (29.0-36.0)	33.0 (30.0-36.0)	0.466[†]

Table 11: CPET 2 (after exercise or on the day prior to surgery) parameters compared between the two study groups

[a] Median (IQR). [†] Mann Whitney U Test

Within the exercise group, 25 of the 33 patients attended more than 13 out of possible 18 classes (subgroup 1); which includes 12 patients who attended all of their 18 scheduled classes. The other 8 patients attended between 6 and 12 classes (subgroup 2). An improvement in the main aerobic fitness parameters was more noticeable in subgroup 1 compared to subgroup 2. Table 12.

In subgroup 1, median (IQR) VO_2 peak improved from 18.7 (16.2-21.0) ml O_2/kg/min before exercise to 20.2 (17.4-22.3) ml O_2/kg/min after exercise; p=0.013, and AT improved from 12.6 (10.7-14.7) ml O_2/kg/min to 14.4 (11.8-15.8) ml O_2/kg/min, p=0.013.

In subgroup 2, VO_2 peak improved from 16.4 (13.5-20.0) ml O_2/kg/min to 17.6 (13.1-20.5) ml O_2/kg/min; p=0.075, and AT improved from 10.2 (8.6-11.1) ml O_2/kg/min to 10.7 (9.7-11.8) ml O_2/kg/min, p=0.889. (Table 12)

Subgroup	Classes attended	Number of participants	Median improvement in VO_2 peak	Median improvement in AT	P value
1	13-18 classes	25	1.5	1.8	0.013
2	6-12 classes	8	1.2	0.5	0.889

Table 12: The improvement in VO_2 peak and AT classified according to exercise attendance

Study 3; The Value of Different Preoperative Assessment Tools in Predicting Postoperative Complications Following Elective Abdominal Aortic Aneurysm Repair

3.6 Predictors of postoperative complications

A total of forty postoperative complications from cardiac, pulmonary and/or renal sources were identified in 124 patients.

A univariable analysis comparing patients who developed postoperative complications to those who did not, is summarized in Tables 13 and 14.

This shows that patients who had renal disease, a poor stair climbing assessment, a Detsky score higher than 10, a low VO_2 peak, a low AT, a high V_E/VCO_2 and a high POSSUM scores, were more likely to develop complications. These variables were then entered in a multivariable logistic regression analysis to identify which were actually predictive of postoperative complications. The results of the multivariate regression are presented in Table 15.

Variable	All (n=124)	Complications (n=40)	No Complications (n=84)	P Value
Age [a]	73.4 (7.2)	73.1 (7.0)	73.5 (7.3)	0.808*
Female gender [b]	13 (10.5%)	3 (7.5%)	10 (11.9%)	0.454†
Body mass index [a]	27.0 (3.9)	27.0 (4.1)	27.1 (3.8)	0.888*
Hypertension [b]	88 (71.0%)	33 (82.5%)	55 (65.5%)	0.051†
Hypercholesterolaemia [b]	52 (41.9%)	20 (50.0%)	32 (38.1%)	0.209†
Smoking history [b]	117 (94.4%)	40 (100.0%)	77 (91.7%)	0.060†
Current smokers [b]	39 (31.5%)	15 (27.5%)	24 (28.6%)	0.317†
Diabetic [b]	13 (10.5%)	5 (12.5%)	8 (9.5%)	0.613†
Cerebrovascular disease [b]	21 (16.9%)	6 (15.0%)	15 (17.9%)	0.692†
COPD [b]	41 (33.1%)	18 (45.0%)	23 (27.4%)	0.051†
CAD [b]	47 (37.9%)	18 (45.0%)	29 (34.5%)	0.261†
Renal disease [b]	25 (20.2%)	13 (32.5%)	12 (14.3%)	0.018†
Statins [b]	102 (82.3%)	35 (87.5%)	67 (79.8%)	0.292†
Antiplatelets [b]	76 (61.3%)	29 (72.5%)	47 (56.0%)	0.077†
Beta blockers [b]	30 (24.2%)	11 (27.5%)	19 (22.6%)	0.553†
ACE inhibitors [b]	53 (42.7%)	19 (47.5%)	34 (40.5%)	0.460†

Table 13: Comparison between subjects who sustained a postoperative complication and those who did not in terms of the baseline characteristics [a] mean (±SD) , [b] n (%). CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease. *Unpaired t-test, †Chi Square test

Variable	All (n=124)	Complications (n=40)	No Complications (n=84)	P Value
Abnormal ABPI measurement [c]	27 (21.8%)	10 (25.0%)	17 (20.2%)	0.494
Abnormal Stair Climbing assessment [c]	**35 out of 116 (30.2%)**	**18 out of 37(48.6%)**	**17 out of 79 (21.5%)**	**0.003**
GAS [b]	78.0 (72.0-85.0)	79.5 (72.5-86.5)	78.0 (71.3-84.0)	0.454
V-POSSUM; physiologic [b]	17.0 (15.0-19.0)	19.5 (16.0-22.5)	16.0 (15.0-17.0)	<0.001
V- POSSUM; operative [b]	10.0 (7.0-12.0)	12.0 (10.0-12.0)	10.0 (7.0-12.0)	0.001
Detsky > 10 [c]	22 (17.7%)	11 (27.5%)	11 (13.1%)	0.050
RCRI > 2 [c]	10 (8.1%)	5 (12.5%)	5 (6.0%)	0.211
LVEF <40% [c]	43%	50%	39.3%	0.339
NT-proBNP level [b]	153.0 (72.0-258.0)	169.0 (88.0-262.0)	135.0 (59.3-253.8)	0.289
VO_2 peak [a]	**17.5 (4.5)**	**15.6 (4.7)**	**18.5 (4.1)**	**0.002**
AT [a]	**12.5 (3.9)**	**11.2 (4.1)**	**13.3 (3.4)**	**0.005**
V_E/VO_2 [b]	28.0 (25.0-32.0)	28.5 (26.0-35.0)	27.0 (25.0-31.0)	0.075
V_E/VCO_2 [a]	**33.4 (5.7)**	**36.1 (6.3)**	**32.3 (5.1)**	**0.001**

Table 14: Comparison between subjects who sustained a postoperative complication and those who did not in terms of the baseline clinical and functional assessments, and risk scores
[a] mean (±SD) , [b] median (IQR), [c] number (%). CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease. *Unpaired t-test, [†]Mann Whitney U Test, [‡]Chi Square test , [§] Fisher's exact test

In the multivariate analysis model, only AT and POSSUM scores were predictive of the main endpoint: the occurrence of a cardiac, pulmonary or renal postoperative complication. Table 15.

Variable	Regression coefficient	P value	OR	95% confidence intervals
VO_2 peak	0.122	0.376	1.129	0.863 - 1.479
AT	**-0.535**	**0.014**	**0.586**	**0.382 - 0.899**
V_E/VCO_2	0.026	0.716	1.026	0.893 - 1.180
V-POSSUM scores*	**0.353**	**0.001**	**1.423**	**1.159 - 1.749**
Abnormal Stair Climbing assessment	0.993	0.261	2.700	0.478 - 15.269
Renal disease	0.030	0.970	1.031	0.209 - 5.083

Table 15 Multivariate logistic regression analysis to identify the predictors of postoperative cardiac, pulmonary and renal complication in the study population
***V-POSSUM variables included in this analysis are the sum of both the physiological and the operative scores**

ROC curve analysis for AT as the test variable, and the primary endpoint of the study (cardiac, pulmonary and renal complications) as the state variable identified an AT value of 11.4 mlO_2/kg/min as the best cutoff point in identifying subjects at risk, with a sensitivity of 71% and specificity of 75% (Area Under Curve 0.77, 95% confidence intervals 0.67 to 0.87) (Figure 30).

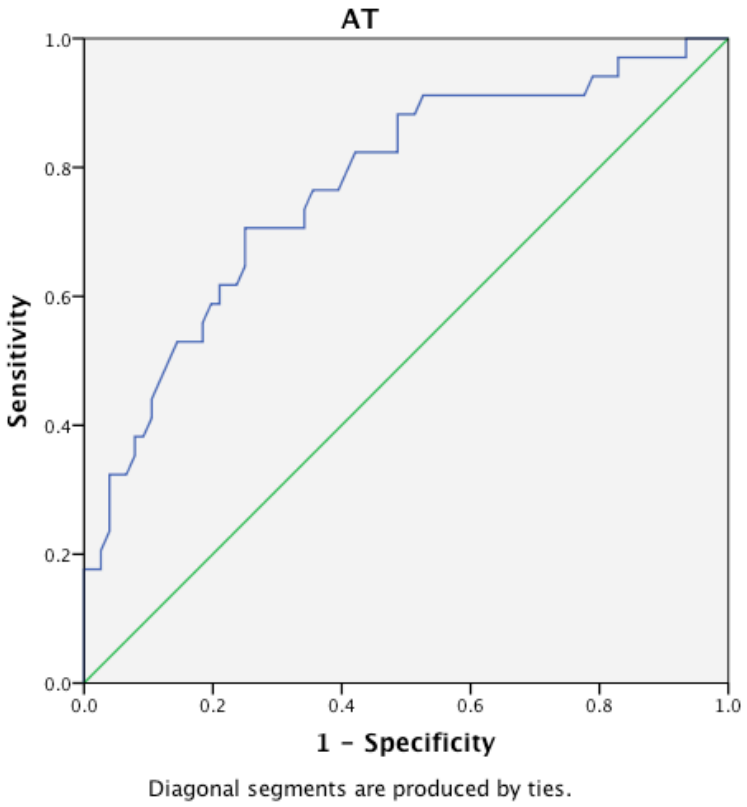


Figure 30: ROC curve analysis. The accuracy of AT in predicting postoperative complications

The prognostic accuracy of AT was further analysed separately for both types of aneurysm repair (Open and EVAR):

In open repair, a cutoff value of 11.4 ml O_2/kg/min had a sensitivity of 67% and a specificity of 75% in identifying those at risk of postoperative cardiac, pulmonary and renal complications (Area under curve: 0.73, 95% confidence interval 0.60 to 0.86). In EVAR, a different cutoff value of 9.9 ml O_2/kg/min, had a sensitivity of 70% and a specificity of 91% in identifying those at risk of postoperative cardiac, pulmonary and renal complications (Area under curve: 0.87, 95% confidence interval 0.74 to 0.99) (Figure 31).

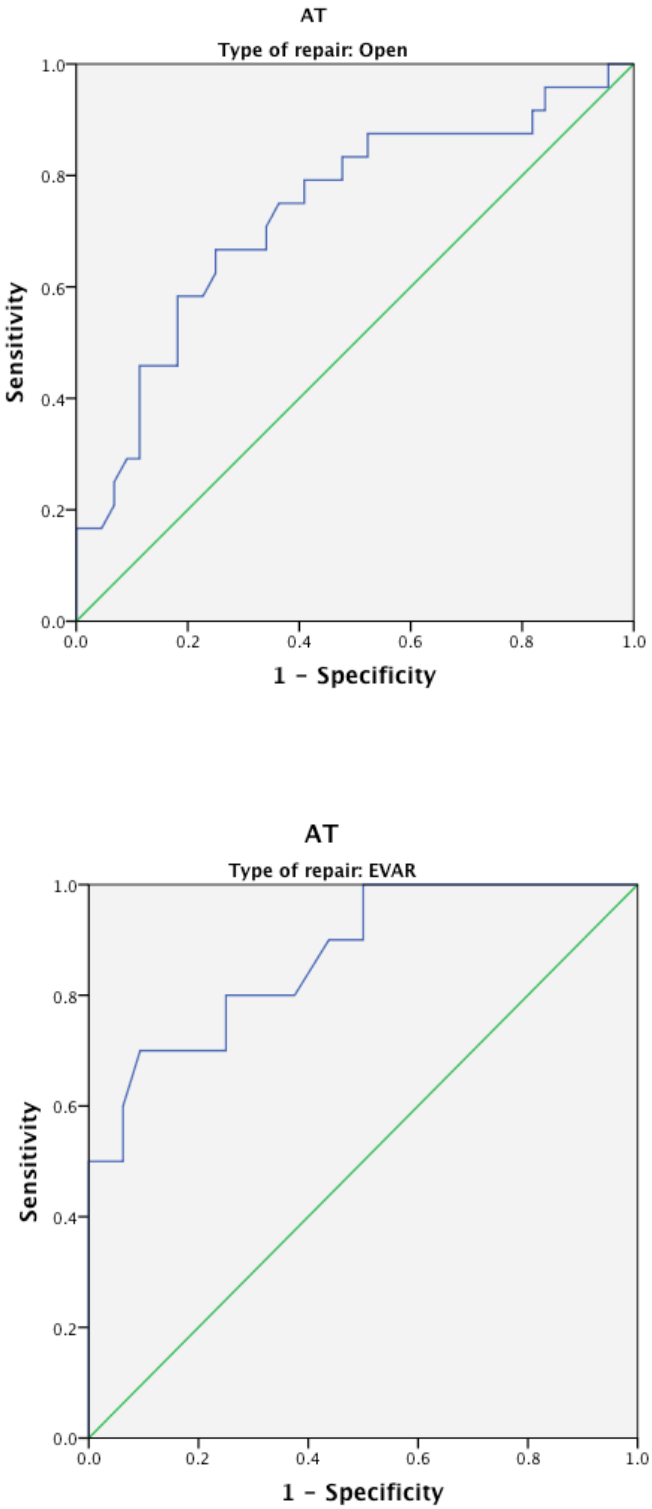


Figure 31: ROC curves used to determine the accuracy of AT in predicting postoperative complications in open repair (top) and EVAR (bottom)

3.6.1 Predictors of cardiac complications

The multivariate logistic regression identified a low AT, and a high V-POSSUM score as independent predictors of postoperative cardiac complications, Table16.

Variable	Regression coefficient	P value	OR	95% confidence intervals
VO_2 peak	0.208	0.230	1.232	0.876 - 1.731
AT	**-0.531**	**0.034**	**0.588**	**0.360 - 0.960**
V_E/VCO_2	0.013	0.876	1.013	0.864 - 1.187
V-POSSUM scores*	**0.317**	**0.001**	**1.373**	**1.134 - 1.662**
Abnormal Stair Climbing assessment	-1.647	0.163	0.193	0.019 - 1.950
Renal disease	0.140	0.144	1.150	0.178 - 7.437

Table 16: Multivariable logistic regression with the dependent variable of postoperative cardiac complications
***V-POSSUM variables included in this analysis are the sum of both the physiological and the operative scores**

ROC curve analysis identified the optimum AT level of 11.35 ml O2/kg/min for predicting cardiac complications (AUC 0.75, 95% C.I. 0.64 to 0.85), with a sensitivity of 81% and a specificity of 68%. (Figure 32).

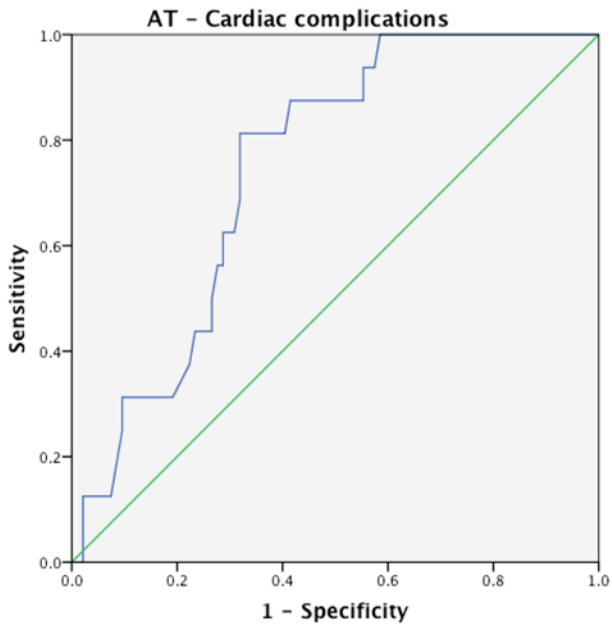


Figure 32: ROC curve analysis to assess the predictive accuracy of V_E/VCO_2 for postoperative pulmonary complications

3.6.2 Predictors of pulmonary complications

The multivariate logistic regression identified a high V_E/VCO_2 and a high V-POSSUM score as independent predictors of postoperative pulmonary complications, Table17.

Variable	Regression coefficient	P value	OR	95% confidence intervals
VO_2 peak	-0.202	0.384	0.817	0.519 - 1.288
AT	0.286	0.346	1.332	0.734 - 2.417
V_E/VCO_2	**0.219**	**0.027**	**1.244**	**1.025 - 1.511**
V-POSSUM scores*	**0.200**	**0.023**	**1.221**	**1.028 - 1.449**
Abnormal stair climbing assessment	1.639	0.093	5.149	0.760 - 34.872
Renal disease	-0.908	0.399	0.403	0.049 - 3.332

Table 17: Multivariable logistic regression with the dependent variable of postoperative pulmonary complications
***V-POSSUM variables included in this analysis are the sum of both the physiological and the operative scores**

ROC curve analysis identified the optimum V_E/VCO_2 level of 36 for predicting pulmonary complications (AUC 0.75, 95% C.I. 0.59 to 0.91), with a sensitivity of 67% and a specificity of 79%. (Figure 33).

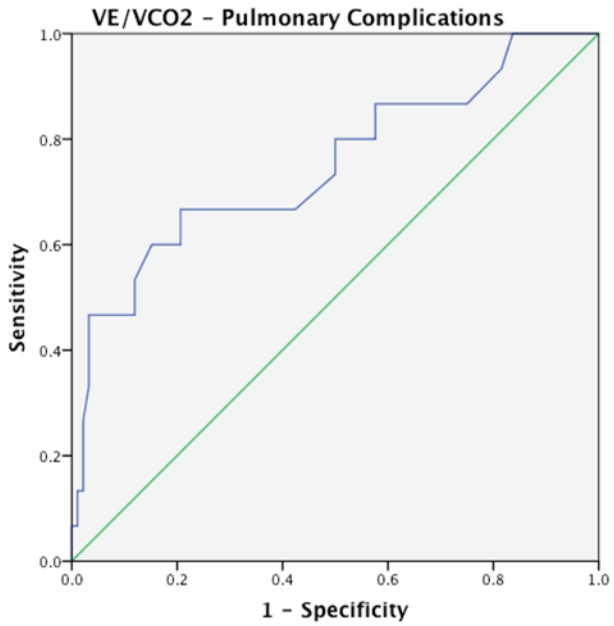


Figure 33: ROC curve analysis to assess the predictive accuracy of V_E/VCO_2 for postoperative pulmonary complications

3.6.3 Predictors of renal complications

The multivariate logistic regression identified a high V-POSSUM score as the only independent predictor of postoperative renal complications, Table18.

Variable	Regression coefficient	P value	OR	95% confidence intervals
VO_2 peak	0.268	0.145	1.307	0.912 - 1.874
AT	-0.110	0.616	0.896	0.582 - 1.377
V_E/VCO_2	0.090	0.301	1.094	0.922 - 1.298
V-POSSUM scores*	**0.258**	**0.006**	**1.294**	**1.076 - 1.555**
Abnormal Stair Climbing assessment	1.792	0.090	6.004	0.756 - 47.689
Renal disease	0.100	0.923	1.105	0.146 - 8.389

Table 18: Multivariable logistic regression with the dependent variable of postoperative renal complications
***V-POSSUM variables included in this analysis are the sum of both the physiological and the operative scores**

3.7 Adverse Events

Throughout this research, some patients underwent one or more CPET assessments, and participants in the exercise group underwent preoperative regular exercise under medical supervision. Participants underwent clinical examination at each visit. There were no adverse events during the CPET assessments or during exercise training. No training programme-related injuries were observed in 51 patients attending the exercise class, although some reported mild to moderate muscle aches at the start of their participation in the programme.

Two patients developed a significant ST segment depression during exercise testing, they were referred to the cardiology services were one of them had a coronary artery bypass graft and a year later was reviewed, reassessed, and was among the patients who exercised prior to an open AAA repair within this study. Another patient had an angioplasty but opted to withdraw from the study before starting exercise. Another patient developed fast AF during exercise, with no significant symptoms or haemodynamic changes. He was also referred to cardiology assessment and started on a beta blocker. He took part in the study as planned and was originally allocated to the control group.

CHAPTER 4: DISCUSSION

4.1 Overview

The research presented within this thesis comprehensively assessed the effects of preoperative exercise in patients prior to elective AAA repair. We hypothesized that a well-structured, medically supervised exercise programme will reduce the main morbidities following this surgical intervention as a result of an improvement in preoperative aerobic fitness.

To our knowledge, the randomised controlled trial presented as *Study 1* in this thesis, provides the only high-level of evidence available to date, which clearly demonstrates the significant clinical benefits of preoperative exercise on postoperative outcomes in patients undergoing elective open or endovascular AAA repair.

The original design and implementation of this research was stimulated by the growing need to improve surgical outcomes in vascular surgery. The current environment of surgical practice in the UK requires researchers to actively explore potential interventions that improve morbidity and mortality following major surgical interventions. Quality improvement programmes were introduced to implement evidence-based perioperative risk management guidelines, and to monitor outcomes on a national scale. The AAAQIP, by promoting the implementation of such activities in patients undergoing elective AAA repair in the UK over the last few years, has contributed to a notable reduction in mortality rates [265]. Our research, therefore, maybe viewed as a progressive step beyond the work being

done on a national level, to investigate interventions that can further improve patient experience and operative outcomes.

Study 1 was a randomised controlled trial that specifically assessed the effect of a defined exercise intervention prior to AAA repair. The significant clinical benefits included: a reduction in postoperative complication rates and overall hospital stay. These findings suggest that preoperative supervised exercise programmes should become routine as part of preoperative surgical care for AAA patients. In addition, future research to investigate the value of exercise interventions in other groups of surgical patients maybe worthwhile.

In *Study 2*; we explored the potential mechanism responsible for the significant clinical effects of a preoperative supervised exercise programme, namely, the effect on aerobic fitness in a patient population who usually have a range of cardiopulmonary co-morbidities. Only three previous studies, in patients under surveillance for small AAA (maximum diameter < 5 cm) demonstrated that parameters of aerobic fitness can be improved with exercise training [222,239,240]. *Study 2* supported such observation, with similar improvements in aerobic fitness with exercise in the preoperative setting, prior to operative repair for larger aneurysms. This was especially true for the sub-group of patients who complied better with exercise; with significantly superior improvements in aerobic fitness.

CPET appears to be a valuable objective preoperative risk assessment tool in non-cardiac surgery [162,163]. However, the perioperative role of CPET in patients undergoing vascular surgery is still controversial and its value as a standard assessment tool is debated [168]. In *Study 3*, we demonstrated the value of CPET in predicting organ-specific complications following elective AAA repair, and showed its accuracy in stratifying patients at risk before either endovascular or open aneurysm repair.

4.2 Main findings

Within this thesis, *Studies 1* and *2* complemented each other by proposing a mechanism by which a specific exercise intervention can be clinically relevant in patients undergoing elective AAA repair. The theory was that exercise-associated improvements in cardiorespiratory function would enhance patients' ability to withstand the perioperative stress associated with AAA repair, reducing complications and facilitating more rapid recovery. In this section, the suggested mechanisms by which exercise can improve clinical outcomes following elective AAA repair are discussed, along with a review of the benefits of perioperative exercise in surgical patients, and a discussion of the value of CPET in preoperative risk assessment.

4.2.1 Suggested mechanisms of action

Evidence suggests that CPET-measured aerobic fitness parameters can be improved with the appropriate exercise interventions in the elderly population [237,238,266]. These parameters have been consistently linked with postoperative outcomes in AAA patients [166,167,170]. This lead us to hypothesize that improving such parameters has the potential of improving outcomes following surgery.

In *Study 2*, the improvements of parameters such as VO_2 peak and AT with exercise were similar to those observed by previous researchers. Three different studies demonstrated the value of exercise training on aerobic fitness in patients with small (<5.5 cm) AAAs [222,239,261]. Kothmann and colleagues conducted a small, randomised, pilot study on patients under surveillance for AAA disease to show an improvement in AT in patients who exercised [222]. The exercise intervention was of similar duration but different frequency and intensity than that implemented in our current research. Tue et al investigated the role of a relatively longer exercise period (12 weeks) in patients with small AAAs [239]. The improvement in AT was more noticeable (mean of 2.5 ml O_2/kg/min) and their findings were boosted by the high compliance with training. These investigators also noted an associated improvement in inflammatory markers such as C-reactive protein and systolic blood pressure in subjects who exercised. More recently, Myers and colleagues reported the results of a randomised trial that included 140 patients. In this trial, they compared the CPET responses in a group of patients who exercised against a control group who had usual care. Those patients were also under surveillance for small AAAs, and the average duration of exercise exceeded 20 months. Although this trial aimed primarily at assessing for changes on the rates of aneurysm expansion, the investigators noted improvements in aerobic fitness parameters, namely: VO_2 peak, AT, treadmill exercise time and other measures of energy expenditure. In addition, they reported another favorable observation, which is a reduction in submaximal heart rate in the subgroup of patients who exercised [240].

Therefore, the research carried out so far, adequately quantified the benefits of exercise on the parameters of fitness in patients with small AAA. We felt it was essential to formally assess whether improvements in fitness parameters were mirrored by clinical benefits by investigating the effects of a preoperative exercise on outcomes after elective AAA repair. And this was the primary aim of *Study 1*. In *Study 2*, we investigated the potential influence our specific exercise intervention would have on aerobic fitness parameters in patients awaiting AAA repair, i.e. with aneurysms > 5.5 cm in diameter. At the end of exercise, or on repeat CPET assessments, the differences between the exercise and control groups in terms of VO_2 peak and AT were not statistically significant. The median differences were 2.4 ml O_2/kg/min for VO_2 peak and 1.8 mlO_2/kg/min for AT. This is probably not a reflection of the true effect of exercise in this study due to the large difference in the number of patients (33 patient in the exercise, versus, 15 in the control groups) between the two groups, making a practical comparison more difficult. However, this could still be a clinically rather than a statistically significant difference.

In a large randomised controlled trial (*Study 1*), participants in the exercise group achieved a reduction in the incidence of postoperative cardiac, pulmonary, renal complications and the length of hospital stay when compared to a matched control group who did not exercise. This trial is unique as it implemented a specific exercise regimen and demonstrated that it can be an effective utilization of the preoperative the waiting or

investigation time period. To ensure safety, adequate exercise and compliance, the training was structured to include a mixture of tolerable aerobic and resistance exercises of appropriate intensity, weekly frequency and duration. The exercise environment was medically supervised throughout to ensure patient safety. In this trial, patients undergoing both open repair, and EVAR were included in the analysis. With randomisation, the number of subjects undergoing EVAR was equal in both groups ensuring comparability. However, the risk profile of both operations differs greatly, and the incidence of postoperative morbidity and mortality is reduced with EVAR. We opted to include subjects undergoing EVAR for two main reasons: The first being to investigate the effect of exercise on patients fit enough for an open repair and those in whom EVAR is the more suited approach; generally older, and perhaps less fit. The second is purely logistic: patients were approached and recruited early during the preoperative phase to ensure adequate participation in the exercise programme, many had no decision made on the type of repair at the time of baseline assessment and randomisation. In addition, including EVAR patients ensure that we had the largest possible pool of patients with AAA disease to facilitate the recruitment process.

Exercise attendance was an important determinant of favorable outcomes. In *Study 1* patients who attended more classes during their scheduled 6-week period had fewer complications. The group of patients who attended all their scheduled exercise sessions had a very low postoperative complication rate (9.4%). On the other hand, participants

who attended less than 75% of classes had a similar postoperative complication rate to the minority of patients who did not attend the class at all within the intervention group. After all, *Study 1* demonstrated that a good proportion of patients attended and complied with the exercise schedule described, showing that it is a feasible intervention in the preoperative setting. In *Study 2*, we noticed that those with the best attendance achieved the most significant improvements in the clinically relevant CPET parameters. This highlights the importance of patient commitment to attend the exercise classes in the potentially short-term preoperative window. Essentially, almost full attendance to the 6-week course is required in order to achieve a measurable improvement in cardiovascular health and functional capacity. It would be interesting to assess whether longer and more intense exercise sessions would add additional benefit.

It remains a complex task, however, to explain the mechanisms by which exercise improves cardiovascular function. A significant amount of research has shown that physical activity is associated with favorable cardiovascular outcomes, and this is especially true for patients with apparent or silent cardiac disease. Some of the advantages of exercise are related to the effects on glucose metabolism, insulin regulation, blood pressure control and body-fat distribution [214]. But for short-term training, the mechanisms are likely to be different.

Exercise has a well described effect on cardiac structure and functional ability, probably best seen by assessing its effects on left ventricular function [267]. This is generally applicable to short durations of exercise (weeks to months) as well as longer durations, and constitute a cornerstone of cardiac rehabilitation programmes following acute coronary events.

The following effects of exercise are the most important:

- An enhanced ability to withstand oxidative stress by an increased expression of antioxidative enzymes associated with exercise training.
- Overexpression of key heart shock proteins that protect cardiomyocytes against ischaemic changes.
- Protective effect against cardiomyocyte apoptosis by modulating pro-apoptotic and anti-apoptotic genes.
- Adaptation to the demands of exercise represented by mild ventricular hypertrophy and an increased myocardial cell length, with an associated enhancement in cardiac elasticity and reduction in cardiac fatigue.

Overall, these and other more complex changes result in prevention of functional decline and protection against ischaemic-reperfusion insults, commonly encountered in the acute postoperative phase in major surgery.

Equally important, are the effects of short-term exercise on vascular function. Researchers found that exercise training can improve endothelial function in the coronary [268] and the peripheral circulation [269]. Endothelial

dysfunction is regarded as an essential predictor of cardiovascular events [270]. A number of complex mechanisms account for that effect including: regulating the function and activity of nitric oxide, functional improvement and enhanced production of endothelial progenitor cells and a delay in the progress of atherosclerotic plaques. Additional documented beneficial effects of exercise on the circulatory system include improved regulation of the pulmonary and systemic venous circulation through a variety of endothelial and molecular mechanisms [267].

The effect of exercise on renal function is more difficult to assess and explain. The changes in the cardiovascular functions described above are likely to have a beneficial effect on renal haemodynamics [271]. In addition, exercise is known to alter renal plasma flow, glomerular filtration rate, and enhance tubular water and electrolyte reabsorption via an increased production of aldosterone and vasopressin [272]. This may result in an overall improvement in renal function [273], but it is difficult to ascertain whether perioperative exercise is specifically beneficial or protective due to the paucity of research in this area.

4.2.2 The benefits of perioperative exercise in surgical patients

The effect of exercise interventions on postoperative outcomes is an interesting area of surgical research. Despite the paucity of evidence to

support preoperative exercise as a beneficial intervention specifically in AAA patients, it has been investigated in other groups of surgical patients.

A recent systematic review identified 12 different controlled trials that assessed the role of preoperative exercise interventions on postoperative outcomes in different surgical specialties [213]. However, the studies included in this review differed widely with regards to the mode of exercise implemented and the outcome measures used. It pooled analyses on orthopaedic procedures separately from thoracic and abdominal surgeries. This review concluded that in cardiac, thoracic and abdominal surgery, exercise decreased the overall postoperative complication rates and the length of hospital stay, and strongly recommended that further research should specifically assess for these benefits in similar or other surgical arenas.

One of the main clinical trials assessing the clinical benefits of exercise in surgical populations was that reported by Arthur and colleagues [210]. This trial demonstrated that a perioperative exercise regime, in addition to educational and reinforcement measures, successfully improved postoperative recovery and shortened hospital stay following coronary artery bypass surgery. The authors suggested that such intervention can be a useful approach to utilize the preoperative ‘waiting’ period before major surgery, which is especially common in government-sponsored healthcare systems around the globe. To our knowledge, no similar research has been performed to establish such clinical value in major

vascular surgical interventions yet.

Other studies showed that specific inspiratory muscle training regimes prior to cardiothoracic and abdominal procedures significantly reduced postoperative lower respiratory infection rates [223-225], a very common complication that follows such procedures. Inspiratory muscle training techniques are relatively easy and safe for patients to perform independently, and therefore, easy to perform at home. In addition, it is also known that preoperative short term smoking cessation has favorable effects on postoperative outcomes. All these are important when counseling patients before surgery and before preoperative interventions that aim at improving patient health.

Study 1 illustrates that preoperative exercise reduced the length of hospital stay postoperatively; an important indicator of improved early recovery, mobility and independence. It is also likely to reflect the reduction in the major postoperative complications. Many studies demonstrated that postoperative complications that follow non-cardiac surgery result in an increased hospital stay with its associated higher costs [274-276], and these are relevant factors to consider when assessing any intervention that has a potential to improve clinical outcomes. In addition, the occurrence of postoperative complications is directly linked to inferior long-term survival [277,278]. Postoperative pulmonary complications are associated with a reduction on median survival of 87% [277]. Similarly, silent, or apparent cardiovascular complications also have unfavorable

effects on long-term survival, and this is especially true in vascular surgical patients [279].

4.2.3 Predicting morbidity following AAA repair

Studies that specifically investigate the postoperative morbidity rates following elective abdominal aortic aneurysm repair are surprisingly scarce in the literature. Numerous studies report mortality rates as the main outcome measure, and many others assess for technical complications, especially following EVAR only (e.g. endoleaks and re-intervention rates). We would suggest that it is equally as important to assess for the main organ-specific postoperative complications, as these are directly related to early recovery, length of hospital stay and the overall healthcare costs.

Study 1 clearly demonstrated a decrease in postoperative cardiac, pulmonary and renal complication rates with exercise following AAA repair. The incidence of postoperative complications including the main cardiac, pulmonary and renal morbidities reached above forty percent in the control group receiving standard perioperative care in this study. Specific incidences of cardiac complications reached 22 per cent in the control group, and that of pulmonary and renal complications also exceeded 20 per cent. These figures are higher than what is generally reported in the literature, probably as a result of the prospective nature of this study, which meant that the defined endpoints were actively sought by the investigators and not retrospectively recorded. More importantly, it

relates to the way we defined organ-specific complications in the study protocol, to include what clinicians may consider a mild or even a silent complication, or a sub-clinical deterioration in organ function. For example; the need for prolonged (>12 hour) perioperative inotropic support was one of the commonly recorded endpoints as it was the only recorded endpoint in 6 of the 19 patients who suffered a 'cardiac' complication, whether or not it led to a persistent haemodynamic abnormality. This phenomenon is not frequently considered a cardiovascular complication that is actively sought in prospective reports in the literature. Similarly, a fall in creatinine clearance that exceeded 20 per cent was considered a renal complication, and was the only renal dysfunction recorded in 10 out of 17 recorded renal complications in this trial, whether or not it led to persistent renal dysfunction or led to an actual acute kidney injury. Therefore, it is important to take in account that the primary endpoints in this study were defined to be inclusive of what some might not consider a relevant postoperative complication. However, we believe these to be important markers of organ dysfunction, especially in the early postoperative period that may have an unfavorable mid- or long-term clinical effect, and thus are clinically relevant when assessing for postoperative recovery in patients undergoing major vascular surgery.

In *Study 3*, we utilized the data collected for *Study 1* to assess the predictive value of some of the commonly used risk stratification tools prior to AAA repair, with a focus on the role of CPET parameters. In this study, AT was a clinically important predictor of postoperative complications with

good accuracy in identifying those at risk, whether undergoing EVAR or open repair. Interestingly, AT was more accurate in predicting complications following EVAR, where these are generally less common. A threshold "concern" value of 9.9 ml O_2/kg/min for EVAR is significantly lower than for open repair, and is another relevant factor to consider, especially that preoperative fitness can favor one type of repair over the other.

It was also interesting to note that AT independently predicted cardiac complications, as did V_E/VCO_2 for pulmonary complications, also with good accuracy. *Study 3* therefore, provides further evidence to demonstrate the ability of CPET to identify a sub-group of patients at high risk of postoperative cardiac and pulmonary complications following elective AAA repair. The V-POSSUM score was found to be a consistent predictor of cardiac, pulmonary and renal complications in *Study 3*. However, it must be highlighted that this score was the sum of the physiological and the operative components of V-POSSUM, which is not entirely applicable for preoperative assessment purposes.

In relation to major non-cardiac surgery, previous studies have shown that around 80% of postoperative mortalities occur in a group of patients that can be potentially identified in advance, further highlighting the importance of accurate preoperative risk assessment [280,281]. In addition to recording patient-specific risk factors (e.g. advanced age, co-morbid conditions and body mass index), the assessment of cardiopulmonary reserve has been

the focus of more recent interest. Snowden et al were amongst the first to investigate the value of CPET parameters in identifying patients at a high risk of postoperative complications in a group of subjects undergoing various major non-cardiac surgeries, including abdominal aortic and other retroperitoneal surgery [282]. They demonstrated the superiority of AT as a preoperative risk stratification tool, in comparison to the commonly used scoring systems and to patient reported levels of functional capacity. The same group later published a study specifically investigating the predictive value of CPET parameters in AAA patients, undergoing either open or endovascular repair [167]. AT independently predicted the occurrence of postoperative complications in the open repair subgroup, and identified patients who are more likely to spend longer times in hospital, or on critical care beds, in both groups of patients undergoing either type of repair. Our patient group had a higher proportion of patients undergoing open repair, and a higher incidence of postoperative morbidities due to our definitions. Both these factors are important to consider when examining the predictive value of a specific diagnostic test.

CPET primarily assesses the combined function of the cardiovascular and pulmonary systems within the controlled environment of exercise-induced stress. AT represents an important physiological phenomenon assessed by recording ventilatory expired gas, and is therefore more accurately termed the ventilatory threshold, or VT. Simply, it reflects a certain stage of work rate, when the supply of oxygen to the muscle does not meet the oxygen demand, and anaerobic glycolysis is required for the additional

energy production. This parameter is certainly of interest to clinicians, as it represents a submaximal measure of functional capacity, occurring at approximately 45% to 65% of the measured maximum oxygen consumption (VO_2 max) in untrained healthy individuals. This means that the estimation of AT does not necessarily require reaching the maximum effort during exercise, which would be, understandably, difficult to achieve in the elderly surgical population.

A growing body of literature now supports the use of AT (or VT) in the perioperative setting. Many prospective studies linked AT to postoperative morbidity. A value below 10.1 ml O_2/kg/min was more common in a diverse group of surgical patients who suffered an early postoperative cardiovascular complication (defined according to the postoperative morbidity survey [POMS]) as demonstrated by Snowden and colleagues [282]. Similarly, James et al also demonstrated that AT has a very good predictive accuracy in identifying surgical patients at risk of major adverse cardiac events [283]. To our knowledge, the specific value of AT as an independent predictor of postoperative cardiac complications has not been previously described for patients undergoing elective AAA repair, and therefore the ability of AT to identify patients at risk of postoperative cardiovascular morbidity certainly warrants further exploration. Parameters such as NT pro-BNP levels are considered good predictors of perioperative cardiac morbidity and mortality [284,285], however, in our analysis NT pro-BNP did not have a predictive role. Blood samples for the measurements of serum NT pro-BNP were sent at baseline (before

exercise) and not repeated after exercise, it might be useful in the future to investigate whether NT pro-BNP changes with exercise in subjects with AAA disease, and whether this correlates to a reduction in cardiovascular risk.

V_E/VCO_2 emerged in *Study 3* as an important parameter that was an independent predictor of pulmonary complications. This interesting parameter measured by CPET is the ratio of minute ventilation (V_E) to carbon dioxide production (VCO_2) and is generally considered a clinically useful index of ventilatory efficiency, particularly during exercise. It is also a reliable, repeatable and relatively accurate measure [286,287]. In the context of clinical assessment, patients with pulmonary hypertension, chronic heart failure and chronic obstructive airway disease are likely to show 'higher' values of V_E/VCO_2 when calculated during exercise testing [288-290], and therefore, an abnormal (i.e. high) V_E/VCO_2 result should alert the clinicians to the possibility of a ventilation-perfusion abnormality, and a significant physiological dead space should be considered a possibility. Studies have linked a high V_E/VCO_2 with inferior short- and mid-term outcomes following surgery [170,291]. Carlisle et al showed that in patients undergoing elective open AAA repair, abnormal V_E/VCO_2 was associated with an inferior postoperative survival [170]. A value of V_E/VCO_2 above 42 was useful in stratifying postoperative mortality risk.

We would suggest AT and V_E/VCO_2 have a real clinical value in preoperative risk stratification in patients undergoing elective AAA repair.

4.3 Validity and applicability

Study 1 in this thesis was a RCT carried out at a high-volume, tertiary vascular centre, where patients were referred for elective AAA repair from a wide geographical area populated by more than 1.2 million people.

Study Sample

The study sample represents closely the population of patients with AAA disease, with a predominance of male subjects (around 90 per cent) and an average age of 73 years. These are similar observations to those reported in large randomised trials such as the EVAR-1 and the DREAM trials [116,117].

A large proportion of our patients had a previous or current history of cigarette smoking, also a very important risk factor in the development and progression of AAA disease worldwide, the percentage of current smokers was slightly higher than commonly reported. Around 39 per cent of patients had a history of coronary artery disease and a similar percentage had a history of hyperlipidaemia, the distribution of these and other co-morbid conditions were also similar to that commonly reported amongst AAA patients. A significant proportion of our patients were not on best medical therapy (BMT) at baseline, namely statins. This is similar to recently presented (unpublished) data from the UK which showed that patients screen-detected aneurysms are still not being appropriately

started on BMT despite a high prevalence of cardiovascular risk factors. The reasons for this are still unknown, but probably relate to primary care education and the absence of a clear guideline to aid this process.

Of note, is the fact that all of our patients were from a White-Caucasian background, the ethnic group most commonly affected by AAA disease [292], however, this can also be considered a limitation with regards to the applicability of this study's outcomes amongst other ethnic backgrounds.

Eliminating Bias

Patient and investigator blinding was not possible in *Study 1*, due to the nature of the intervention, and the fact that the chief investigator was the responsible professional for both study recruitment and supervision throughout the different perioperative stages. The clinicians (supervising surgeon, radiologists and anaesthetist) were blinded to the group allocations in this study to eliminate any potential source of bias in that regard.

Exercise interventions are well known to attract motivated individuals who understand clearly the benefits of exercise in general and the nature of the proposed intervention. Randomisation, however, should be an effective way to eliminate this potential participation bias. However, over a third of patients approached, declined to participate and it is feasible that these

were the less motivated individuals. It is thus conceivable that the patients who had the most to gain excluded themselves. It is also possible that motivated individuals randomized to the control group may have increased the preoperative activity levels, simply stimulated by trial information and participation. We did try to negate the later effect by explaining the study process and the benefits of a randomised study design in order to truly assess for the value of the exercise intervention to participants. Those randomly allocated to the control group were given clear instructions to resume normal life activities and avoid doing any strenuous or unsupervised exercises, however, adherence to this advice was not specifically studied.

Applicability of intervention

The exercise intervention described in *Study 1* is practical, and can be effectively and safely delivered in hospital-based physiotherapy departments. There were no adverse events reported during assessments or exercise training, however, a presumption that this exercise regime can be undertaken at home in patients with large aneurysm cannot be made on the basis of the current research. The exercise regime we chose had many similarities to ongoing cardiac rehabilitation exercises and certainly similar to the exercise prescribed to patients with intermittent claudication at our centre [244].

4.4 Limitations of the study

The limitations of this research must be recognized. *Study 1* is a RCT, and both *Studies 2* and *3* utilized data that was primarily collected for the purpose of this RCT and therefore, would have similar limitations.

First, *Study 1* was a single centre trial, with patients recruited from a defined geographical area and undergoing assessments and interventions at a single unit. Understandably, single centre trials are considered to have inferior external validity. However, it simplified the logistics of organizing and conducting this project, and guaranteed the uniformity of the exercise intervention under investigation. One of the related limitations was that the work rate or energy expenditure for participants in the exercise group was not specifically measured. The exercise was not prescribed according to individual patient's AT or corresponding heart rates, and there was no monitoring during the sessions. This makes it difficult to draw conclusions on the relationship between the effort made by patients and the improvement in aerobic fitness or the recorded outcome measures.

As previously discussed, patient and investigator blinding was not possible due to the nature of the intervention. This would be a potential source of selection and participation bias. The exclusion of patients unable to exercise may also be viewed as a source of selection bias, i.e. patients

may be regarded as generally healthier if they can exercise. However, self-reported functional capacity has been a standard tool to estimate patient fitness prior to major surgery, and surgeons would generally consider those with limited exercise tolerance as high-risk individuals who are perhaps more likely to be turned down on the basis of an unbalanced risk-to-benefit operative profile. With regards to compliance with exercise, we noted that more fit patients were more likely to maintain their scheduled training session, and these later, achieved better outcomes. This, again, meant that despite encouraging participants to exercise we had a potential source of bias that we had no control over and an expected one in relation to research involving exercise interventions. It would be difficult to discuss whether this will affect the generalizability of the study findings, as exercise participation and motivation are always going to play a major role in compliance and adherence to exercise programmes and healthcare professionals can only explore measures to enhance these qualities.

Study 1 suffered with a prolonged recruitment period of over 4 years. This to some extent was due to the single centre nature of the study, which limited our recruitment pool. Additionally, due to the wide geographical area served by the single unit, this pool contained a significant number of patients residing a significant distance from the unit and the intervention. These patients were more likely to decline participation due to travel times and financial constraints. This unanticipated high “turn down” rate led to a recruitment period almost double that originally calculated. On the other

hand, it is worth mentioning that over the course of the 4 years, the mortality and morbidity rates remained constant, this was specifically reviewed and presented at departmental meetings at the study centre recently.

Finally, as this trial was primarily aimed at assessing for the defined outcome measures, no healthcare financial data was collected. This is a further weakness as in the current environment of practice, it is crucial to incorporate cost-effectiveness with clinical benefits when investigating new interventions and such data was not collected here.

4.5 Avenues for further research

In addition to investigating the feasibility and cost-effectiveness of exercise interventions, future research could also extend to investigate the value of exercise in the postoperative period as well, as part of a perioperative systematic rehabilitation programme. Although the vast majority of complications recorded were recorded within the duration of hospital stay in our study, the AAA patient population is at higher risks of cardiovascular complications and would be an appropriate population to target with prolonged rehabilitation and longer follow-up durations.

Now, that a mechanism by which preoperative exercise improves outcomes in patients undergoing elective AAA repair became apparent, it would be interesting to assess if modification of the intervention aimed at maximizing the mechanism would have additional clinical benefit. It would also be interesting to determine whether the benefits on aerobic fitness parameters associated with exercise interventions can be sustained for long durations or whether it goes back to its pre-exercise levels (or lower) after a certain period of time, postoperatively.

As the uptake was less than anticipated in recruiting to our research, further investigation regarding patient acceptability maybe worthwhile, e.g. community or home-based exercises with medical support rather than supervision. Investigating the values of exercises designed for individual

patients according to their response would be also interesting. The approaches can be different in terms of frequency and intensity for those demonstrating poor response. The role of additional interventions such as educational sessions and psychological support can further enhance the compliance with exercise and are worth investigating.

At present, there is much debate on to whether shorter durations of higher intensity exercise have similar or better value than regular exercises. It is certainly worth investigating more models and different exercise regimes that can be logistically easier and more effective. The beneficial effects of exercise are complex to describe and understand, some of its effects on cardiovascular health have been explored in the current research, but some of the mechanism on how exercise improves fitness on a cellular basis, and its effect on some of the serum biomarkers is a large area for future researchers to explore.

Whether similar exercise regimes can be equally beneficial in other groups of patients with peripheral vascular disease or other surgical patients is also an area where research is recommended. Some patients might have more pronounced responses to physical exercise than others and it would be interesting to identify what patient characteristics can be related to the extent of their response to exercise and whether such characteristics can be modified.

4.6 Conclusion

AAA repair remains one of the major surgical interventions that requires appropriate patient selection, risk stratification and rehabilitation to achieve satisfactory outcomes for a procedure that is considered the main prophylactic measure to prevent AAA rupture. With advancements in endovascular technologies more patients are being offered EVAR, however open repair remains a commonly performed procedure, and the first choice in the eyes of many for patients who can be classified as 'adequately fit', mainly due to the known durability and the lower rates of re-interventions when compared to EVAR.

The results of this research have been long awaited. Many researchers asked the question whether exercise can improve the postoperative clinical outcomes in AAA patients, and many pilot and feasibility studies failed to progress into a comprehensive assessment such as the one presented here. The RCT presented in this thesis is the first level I evidence to show benefits for preoperative exercise on postoperative outcomes in AAA patients.

The emphasis on postoperative outcomes in our current environment adds to the relevance of the research presented here. Many base their decision towards the method of repair (EVAR or open) on patient fitness, and with evidence that this can be improved, some may opt to revisit their choice

depending on the post-exercise fitness assessment in the future.

More research is published on a regular basis to shed the light on the benefits of exercise for almost all aspects of human health. The integration of exercise in perioperative care, we think, is only a matter of time, and we expect more researchers to invest resources in exploring the use of exercise in surgical practice over the next few years. Finally, we believe this research will contribute to a safer patient experience.

CHAPTER 5: REFERENCES

1. Lippi D. An aneurysm in the Papyrus of Ebers (108, 3-9). Med Secoli. 1990;2(1):1–4.

2. Fortner G, Johansen K. Abdominal aortic aneurysms. West J Med. 1984 Jan;140(1):50–9.

3. Livesay JJ, Messner GN, Vaughn WK. Milestones in the treatment of aortic aneurysm: Denton A. Cooley, MD, and the Texas Heart Institute. Texas Heart Institute journal / from the Texas Heart Institute of St. Luke“s Episcopal Hospital, Texas Children”s Hospital. 2005.

4. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg. 1991 Nov;5(6):491–9.

5. Bengtsson H, Sonesson B, Bergqvist D. Incidence and prevalence of abdominal aortic aneurysms, estimated by necropsy studies and population screening by ultrasound. Ann N Y Acad Sci. 1996 Nov 18;800:1–24.

6. Liddington MI, Heather BP. The relationship between aortic diameter and body habitus. Eur J Vasc Surg. 1992 Jan;6(1):89–92.

7. Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg. 1991. pp. 452–8.

8. McGregor JC, Pollock JG, Anton HC. The value of ultrasonography in the diagnosis of abdominal aortic aneurysm. Scott Med J. 1975 May;20(3):133–7.

9. Mortality statistics. Review of the Registrar General on deaths by cause, sex and age in England and Wales 2005. Series DH2 no.32.

10. Scott RA, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. Br J Surg. 1995 Aug;82(8):1066–70.

11. Anjum A, Allmen von R, Greenhalgh R, Powell JT. Explaining the decrease in mortality from abdominal aortic aneurysm rupture. Br J Surg. 2012 Apr 4;99(5):637–45.

12. Anjum A, Powell JT. Is the incidence of abdominal aortic aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and Scotland. Eur J Vasc Endovasc Surg. 2012 Feb;43(2):161–6.

13. Schwarze ML, Shen Y, Hemmerich J, Dale W. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001-2006. J Vasc Surg. 2009 Oct;50(4):722–2.

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

15. Lindholt JS, Norman PE. Meta-analysis of postoperative mortality after elective repair of abdominal aortic aneurysms detected by screening. Br J Surg. 2011 May;98(5):619–22.

16. Vascular Services Quality Improvement Programme. http://www.vsip.com/reports [accessed 1 June 2015].

17. Pleumeekers HJ, Hoes AW, van der Does E, van Urk H, Hofman A, de Jong PT, et al. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol. 1995 Dec 15;142(12):1291–9.

18. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study : The Tromsø Study. Am J Epidemiol. 2001 Aug 1;154(3):236–44.

19. Lederle FA, Johnson GR, Wilson SE, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med. 1997 Mar 15;126(6):441–9.

20. Wilmink TB, Quick CR, Day NE. The association between cigarette smoking and abdominal aortic aneurysms. J Vasc Surg. 1999 Dec;30(6):1099–105.

21. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. J Vasc Surg. 2003 Aug;38(2):329–34.

22. MacSweeney ST, O'Meara M, Alexander C, O'Malley MK, Powell JT, Greenhalgh RM. High prevalence of unsuspected abdominal aortic aneurysm in patients with confirmed symptomatic peripheral or cerebral arterial disease. Br J Surg. 1993 May;80(5):582–4.

23. Allardice JT, Allwright GJ, Wafula JM, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. Br J Surg. 1988 Mar;75(3):240–2.

24. Helgadottir A, Thorleifsson G, Magnusson KP, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet 2008 Feb;40(2):217–24.

25. Sofi F, Marcucci R, Giusti B, et al. High levels of homocysteine, lipoprotein (a) and plasminogen activator inhibitor-1 are present in patients with abdominal aortic aneurysm. Thromb Haemost 2005 Nov;94(5):1094–8.

26. Human Genetics ’99: The Cardiovascular System: The Molecular Basis of Vascular Disorders. 2007 Nov 9;:1–7.

27. Thompson AR, Cooper JA, Ashton HA, Hafez H. Growth rates of small abdominal aortic aneurysms correlate with clinical events. Br J Surg. 2010 Jan;97(1):37–44.

28. Brady AR. Abdominal Aortic Aneurysm Expansion: Risk Factors and Time Intervals for Surveillance. Circulation. 2004 Jun 21;110(1):16–21.

29. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Annals of Surgery. 1999 Sep;230(3):289–96–discussion296–7.

30. Schouten O, van Laanen JHH, Boersma E, et al. Statins are Associated with a Reduced Infrarenal Abdominal Aortic Aneurysm Growth. Eur J Vasc Endovasc Surg. 2006 Jul;32(1):21–6.

31. Sukhija R, Aronow WS, Sandhu R, Kakar P, Babu S. Mortality and size of abdominal aortic aneurysm at long-term follow-up of patients not treated surgically and treated with and without statins. Am J Cardiol. 2006 Jan 15;97(2):279–80.

32. Schlösser FJV, Tangelder MJD, Verhagen HJM, et al. Growth predictors and prognosis of small abdominal aortic aneurysms. J Vasc Surg. 2008 Jun;47(6):1127–33.

33. Ferguson CD, Clancy P, Bourke B, et al. Association of statin prescription with small abdominal aortic aneurysm progression. Am Heart J. 2010 Feb;159(2):307–13.

34. Propanolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72–9.

35. Lindholt JS, Heegaard NH, Vammen S, Fasting H, Henneberg EW, Heickendorff L. Smoking, but not lipids, lipoprotein(a) and antibodies against oxidised LDL, is correlated to the expansion of abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2001 Jan;21(1):51–6.

36. Chang JB, Stein TA, Liu JP, Dunn ME. Risk factors associated with rapid growth of small abdominal aortic aneurysms. Surgery. 1997 Feb;121(2):117–22.

37. De Rango P, Cao P, Cieri E, et al. Effects of diabetes on small aortic aneurysms under surveillance according to a subgroup analysis from a randomized trial. J Vasc Surg. 2012 Dec;56(6):1555–63.

38. Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. J Vasc Surg. 2003 Feb;37(2):280–4.

39. Reed WW, Hallett Jr JW, Damiano MA, Ballard DJ. Learning from the last ultrasound. A population-based study of patients with abdominal aortic aneurysm. Arch Intern Med 1997;157:2064-8.

40. Norman PE, Powell JT. Abdominal aortic aneurysm: the prognosis in women is worse than in men. Circulation. 2007 Jun 5;115(22):2865–9.

41. Dalman RL, Tedesco MM, Myers J, Taylor CA. AAA disease: mechanism, stratification, and treatment. Ann N Y Acad Sci. 2006 Nov;1085:92–109.

42. Cronenwett JL, Murphy TF, Zelenock GB, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery. 1985 Sep;98(3):472–83.

43. Hatakeyama T, Shigematsu H, Muto T. Risk factors for rupture of abdominal aortic aneurysm based on three-dimensional study. J Vasc Surg. 2001 Mar;33(3):453–61.

44. Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2006 May;26(5):987–94.

45. Wanhainen A, Bergqvist D, Boman K, Nilsson TK, Rutegård J, Björck M. Risk factors associated with abdominal aortic aneurysm: a population-based study with historical and current data. J Vasc Surg. 2005 Mar;41(3):390–6.

46. Hobbs SD, Claridge MWC, Quick CRG, Day NE, Bradbury AW, Wilmink ABM. LDL cholesterol is associated with small abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2003 Dec;26(6):618–22.

47. Blanchard JF, Armenian HK, Peeling R, Friesen PP, Shen C, Brunham RC. The relation between Chlamydia pneumoniae infection and abdominal aortic aneurysm: case-control study. Clin Infect Dis. 2000 Jun;30(6):946–7.

48. Zweers MC, Peeters ACTM, Graafsma S, et al. Abdominal aortic aneurysm is associated with high serum levels of tenascin-X and decreased aneurysmal tissue tenascin-X. Circulation. 2006 Apr 4;113(13):1702–7.

49. Golledge J, Tsao PS, Dalman RL, Norman PE. Circulating markers of abdominal aortic aneurysm presence and progression. Circulation. 2008 Dec 2;118(23):2382–92.

50. Dobrin PB, Mrkvicka R. Failure of elastin or collagen as possible critical connective tissue alterations underlying aneurysmal dilatation. Cardiovasc Surg. 1994 Aug;2(4):484–8.

51. Thompson RW, Parks WC. Role of matrix metalloproteinases in abdominal aortic aneurysms. Ann N Y Acad Sci. 1996 Nov 18;800:157–74.

52. Tamarina NA, McMillan WD, Shively VP, Pearce WH. Expression of matrix metalloproteinases and their inhibitors in aneurysms and normal aorta. Surgery. 1997 Aug;122(2):264–71–discussion271–2.

53. Shah PK. Inflammation, metalloproteinases, and increased proteolysis: an emerging pathophysiological paradigm in aortic aneurysm. Circulation. 1997 Oct 7;96(7):2115–7.

54. Davis V, Persidskaia R, Baca-Regen L, et al. Matrix metalloproteinase-2 production and its binding to the matrix are increased in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 1998 Oct;18(10):1625–33.

55. Keeling WB, Armstrong PA, Stone PA, Bandyk DF, Shames ML. An overview of matrix metalloproteinases in the pathogenesis and treatment of abdominal aortic aneurysms. Vasc Endovascular Surg. 2005 Nov;39(6):457–64.

56. Wassef M, Baxter BT, Chisholm RL, et al. Pathogenesis of abdominal aortic aneurysms: A multidisciplinary research program supported by the National Heart, Lung, and Blood Institute. J Vasc Surg. 2001 Oct;34(4):730–8.

57. Mao D, Lee JK, VanVickle SJ, Thompson RW. Expression of collagenase-3 (MMP-13) in human abdominal aortic aneurysms and vascular smooth muscle cells in culture. Biochem Biophys Res Commun. 1999 Aug 11;261(3):904–10.

58. Huffman MD, Curci JA, Moore G, Kerns DB, Starcher BC, Thompson RW. Functional importance of connective tissue repair during the development of experimental abdominal aortic aneurysms. Surgery. 2000 Sep;128(3):429–38.

59. Liao S, Curci JA, Kelley BJ, Sicard GA, Thompson RW. Accelerated replicative senescence of medial smooth muscle cells derived from abdominal aortic aneurysms compared to the adjacent inferior mesenteric artery. J Surg Res. 2000 Jul;92(1):85–95.

60. Gregory AK, Yin NX, Capella J, Xia S, Newman KM, Tilson MD. Features of autoimmunity in the abdominal aortic aneurysm. Arch Surg. 1996 Jan;131(1):85–8.

61. Koch AE, Haines GK, Rizzo RJ, et al. Human abdominal aortic aneurysms. Immunophenotypic analysis suggesting an immune-mediated response. Am J Pathol. 1990 Nov;137(5):1199–213.

62. Ocana E, Bohórquez J-C, Pérez-Requena J, Brieva JA, Rodríguez C. Characterisation of T and B lymphocytes infiltrating abdominal aortic aneurysms. Atherosclerosis. 2003 Sep;170(1):39–48.

63. Hirose H, Tilson MD. Abdominal aortic aneurysm as an autoimmune disease. Ann N Y Acad Sci. 2001 Dec;947:416–8.

64. Petersen E, Boman J, Persson K, et al. Chlamydia pneumoniae in human abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 1998 Feb;15(2):138–42.

65. Ailawadi G, Knipp BS, Lu G, et al. A nonintrinsic regional basis for increased infrarenal aortic MMP-9 expression and activity. J Vasc Surg. 2003 May;37(5):1059–66.

66. Wolinsky H. Comparison of medial growth of human thoracic and abdominal aortas. Circ Res. 1970 Oct;27(4):531–8.

67. Zatina MA, Zarins CK, Gewertz BL, Glagov S. Role of medial lamellar architecture in the pathogenesis of aortic aneurysms. J Vasc Surg. 1984 May;1(3):442–8.

68. Moore JE, Ku DN, Zarins CK, Glagov S. Pulsatile flow visualization in the abdominal aorta under differing physiologic conditions: implications for increased susceptibility to atherosclerosis. J Biomech Eng. 1992 Aug;114(3):391–7.

69. Pedersen EM, Sung HW, Yoganathan AP. Influence of abdominal aortic curvature and resting versus exercise conditions on velocity fields in the normal abdominal aortic bifurcation. J Biomech Eng. 1994 Aug;116(3):347–54.

70. Yamazumi K, Ojiro M, Okumura H, Aikou T. An activated state of blood coagulation and fibrinolysis in patients with abdominal aortic aneurysm. Am J Surg. 1998 Apr;175(4):297–301.

71. Lindholt JS, Jørgensen B, Fasting H, Henneberg EW. Plasma levels of plasmin-antiplasmin-complexes are predictive for small abdominal aortic aneurysms expanding to operation-recommendable sizes. J Vasc Surg. 2001 Oct;34(4):611–5.

72. Vorp DA, Lee PC, Wang DH, Makaroun MS, Nemoto EM, Ogawa S, et al. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. J Vasc Surg. 2001 Aug;34(2):291–9.

73. Sakalihasan N, Delvenne P, Nusgens BV, Limet R, Lapière CM. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. J Vasc Surg. 1996 Jul;24(1):127–33.

74. Fontaine V, Jacob M-P, Houard X, et al. Involvement of the mural thrombus as a site of protease release and activation in human aortic aneurysms. Am J Pathol. 2002 Nov;161(5):1701–10.

75. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. Lancet. 2005 May;365(9470):1577–89.

76. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med. 1988 Aug;148(8):1753–6.

77. Quill DS, Colgan MP, Sumner DS. Ultrasonic screening for the detection of abdominal aortic aneurysms. Surg Clin North Am. 1989 Aug;69(4):713–20.

78. Sparks AR, Johnson PL, Meyer MC. Imaging of abdominal aortic aneurysms. Am Fam Physician. 2002 Apr 15;65(8):1565–70.

79. Lamah M, Darke S. Value of routine computed tomography in the preoperative assessment of abdominal aneurysm replacement. World J Surg. 1999 Oct;23(10):1076–80–discussion1080–1.

80. Vowden P, Wilkinson D, Ausobsky JR, Kester RC. A comparison of three imaging techniques in the assessment of an abdominal aortic aneurysm. J Cardiovasc Surg (Torino). 1989 Nov;30(6):891–6.

81. Jaakkola P, Hippeläinen M, Farin P, Rytkönen H, Kainulainen S, Partanen K. Interobserver variability in measuring the dimensions of the abdominal aorta: comparison of ultrasound and computed tomography. Eur J Vasc Endovasc Surg. 1996 Aug;12(2):230–7.

82. Balm R, Eikelboom BC, van Leeuwen MS, Noordzij J. Spiral CT-angiography of the aorta. Eur J Vasc Surg. 1994 Sep;8(5):544–51.

83. Armon MP, Yusuf SW, Latief K, et al. Anatomical suitability of abdominal aortic aneurysms for endovascular repair. Br J Surg. 1997 Feb;84(2):178–80.

84. Beebe HG, Kritpracha B, Serres S, Pigott JP, Price CI, Williams DM. Endograft planning without preoperative arteriography: a clinical feasibility study. J Endovasc Ther. 2000 Feb;7(1):8–15.

85. van Keulen JW, van Prehn J, Prokop M, Moll FL, van Herwaarden JA. Dynamics of the aorta before and after endovascular aneurysm repair: a systematic review. Eur J Vasc Endovasc Surg. 2009 Nov;38(5):586–96.

86. Boules TN, Compton CN, Stanziale SF, et al. Can computed tomography scan findings predict "impending‘’ aneurysm rupture? Vasc Endovascular Surg. 2006 Jan;40(1):41–7.

87. Heng MS, Fagan MJ, Collier JW, Desai G, McCollum PT, Chetter IC. Peak wall stress measurement in elective and acute abdominal aortic aneurysms. J Vasc Surg. 2008 Jan;47(1):17–22.

88. Vande Geest JP, Di Martino ES, Bohra A, Makaroun MS, Vorp DA. A biomechanics-based rupture potential index for abdominal aortic aneurysm risk assessment: demonstrative application. Ann N Y Acad Sci. 2006 Nov;1085:11–21.

89. Tennant WG, Hartnell GG, Baird RN, Horrocks M. Radiologic investigation of abdominal aortic aneurysm disease: comparison of three modalities in staging and the detection of inflammatory change. YMVA. 1993 Apr;17(4):703–9.

90. Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002 Nov 16;360(9345):1531–9.

91. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. BMJ. 2005 Apr 2;330(7494):750.

92. Norman PE, Jamrozik K, Lawrence-Brown MM, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. BMJ. 2004 Nov 27;329(7477):1259.

93. Ellis M, Powell JT, Greenhalgh RM. Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. Br J Surg. 1991 May;78(5):614–6.

94. Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet. 2002 Jan 12;359(9301):114–7.

95. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. Ann Surg. 2008 Nov;248(5):739–45.

96. Thomsen T, Tønnesen H, Møller AM. Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg. 2009 May;96(5):451–61.

97. Moll FL, Powell JT, Fraedrich G, et al. Management of Abdominal Aortic Aneurysms Clinical Practice Guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg. 2011 Jan 1;41(S1):S1–S58.

98. Albert MA, Danielson E, Rifai N, Ridker PM, PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA. 2001 Jul 4;286(1):64–70.

99. Durazzo AES, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg. 2004 May;39(5):967–75–discussion975–6.

100. Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med. 2009 Sep 3;361(10):980–9.

101. Feringa HHH, Schouten O, Karagiannis SE, et al. Intensity of statin therapy in relation to myocardial ischemia, troponin T release, and clinical cardiac outcome in patients undergoing major vascular surgery. J Am Col Cardiol. 2007 Oct 23;50(17):1649–56.

102. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA. 2004 May 5;291(17):2092–9.

103. Kertai MD, Boersma E, Westerhout CM, et al. A Combination of Statins and Beta-blockers is Independently Associated with a Reduction in the Incidence of Perioperative Mortality and Nonfatal Myocardial infarction in Patients Undergoing Abdominal Aortic Aneurysm Surgery. Eur J Vasc Endovasc Surg. 2004 Oct;28(4):343–52.

104. Le Manach Y, Ibanez Esteves C, Bertrand M, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing vascular surgery. Anesthesiology. 2011 Jan;114(1):98–104.

105. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation. 1993 Feb;87(2):659–75.

106. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849–60.

107. 813715. Investigation into possible violation of scientific integritySummary. 2011 Dec 8;:1–10.

108. 198661. Report on the 2012 follow-up investigation of possible breaches of academic integrity. 2012 Oct 10;:1–27.

109. Auerbach AD, Goldman L. beta-Blockers and reduction of cardiac events in noncardiac surgery: clinical applications. JAMA. 2002 Mar 20;287(11):1445–7.

110. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of -blockade to prevent perioperative death in non-cardiac surgery. Heart. 2013 Jul 31.

111. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014 Sep 14;35(35):2383–431.

112. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008 May 31;371(9627):1839–47.

113. Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms (Review). Cochrane Database Syst Rev. 2013 Aug 25;:1–51.

114. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. Lancet. 2006 Aug 19;368(9536):659–65.

115. Economopoulos KP, Martinou E, Hakimian S, et al. An overview of laparoscopic techniques in abdominal aortic aneurysm repair. J Vasc Surg. Society for Vascular Surgery; 2013 Aug 1;58(2):512–20.

116. Greenhalgh RM, Brown LC, Kwong GPS, Powell JT, Thompson SG, EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet. 2004 Sep;364(9437):843–8.

117. Prinssen M, Verhoeven ELG, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004 Oct 14;351(16):1607–18.

118. Chong T, Nguyen L, Owens CD, Conte MS, Belkin M. Suprarenal aortic cross-clamp position: a reappraisal of its effects on outcomes for open abdominal aortic aneurysm repair. J Vasc Surg. 2009 Apr;49(4):873–80.

119. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG. Open infrarenal abdominal aortic aneurysm repair: the Cleveland Clinic experience from 1989 to 1998. J Vasc Surg. 2002 Jun;35(6):1145–54.

120. Johnston KW, Scobie TK. Multicenter prospective study of nonruptured abdominal aortic aneurysms. I. Population and operative management. J Vasc Surg. 1988 Jan;7(1):69–81.

121. Huber TS, Wang JG, Derrow AE, et al. Experience in the United States with intact abdominal aortic aneurysm repair. J Vasc Surg. 2001 Feb;33(2):304–10–discussion310–1.

122. Killeen SD, Andrews EJ, Redmond HP, Fulton GJ. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures. J Vasc Surg. 2007 Mar;45(3):615–26.

123. Eckstein H-H, Bruckner T, Heider P, Wolf O, Hanke M, Niedermeier H-P, et al. The relationship between volume and outcome following elective open repair of abdominal aortic aneurysms (AAA) in 131 German hospitals. Eur J Vasc Endovasc Surg. 2007 Sep;34(3):260–6.

124. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med. 2009 Oct 1;361(14):1368–75.

125. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet. 2005 Jul;365(9478):2187–92.

126. Verhoeven ELG, Cinà CS, Tielliu IFJ, et al. Local anesthesia for endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2005 Sep;42(3):402–9.

127. Auerbach A. Assessing and Reducing the Cardiac Risk of Noncardiac Surgery. Circulation. 2006 Mar 14;113(10):1361–76.

128. Crawford ES, Saleh SA, Babb JW, Glaeser DH, Vaccaro PS, Silvers A. Infrarenal abdominal aortic aneurysm: factors influencing survival after operation performed over a 25-year period. Ann Surg. 1981 Jun;193(6):699–709.

129. L'Italien GJ, Cambria RP, Cutler BS, Leppo JA, Paul SD, Brewster DC, et al. Comparative early and late cardiac morbidity among patients requiring different vascular surgery procedures. J Vasc Surg. 1995 Jun;21(6):935–44.

130. Older P, Smith R. Experience with the preoperative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery. Anaesth Intensive Care. 1988 Nov;16(4):389–95.

131. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology. 1995 Apr;82(4):1026–60.

132. Feringa HHH, Karagiannis S, Vidakovic R, et al. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. Am J Cardiol. 2007 Nov 1;100(9):1479–84.

133. Thompson JP, Boyle JR, Thompson MM, Strupish J, Bell PR, Smith G. Cardiovascular and catecholamine responses during endovascular and conventional abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 1999 Apr;17(4):326–33.

134. Patterson BO, Holt PJE, Hinchliffe R, Loftus IM, Thompson MM. Predicting Risk in Elective Abdominal Aortic Aneurysm Repair: A Systematic Review of Current Evidence. Eur J Vasc Endovasc Surg. ; 2008 Dec 1;36(6):637–45.

135. Giles KA, Schermerhorn ML, O'Malley AJ, et al. Risk prediction for perioperative mortality of endovascular vs open repair of abdominal aortic aneurysms using the Medicare population. J Vasc Surg. The Society for Vascular Surgery; 2009 Aug 1;50(2):256–62.

136. Heller JA, Weinberg A, Arons R, et al. Two decades of abdominal aortic aneurysm repair: have we made any progress? J Vasc Surg. 2000 Dec;32(6):1091–100.

137. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, van Bockel JH, Eijkemans MJ, Habbema JD. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. Arch Intern Med. 1995 Oct 9;155(18):1998–2004.

138. Katz DJ, Stanley JC, Zelenock GB. Operative mortality rates for intact and ruptured abdominal aortic aneurysms in Michigan: an eleven-year statewide experience. J Vasc Surg. 1994 May;19(5):804–15–discussion816–7.

139. Brady AR, Fowkes FG, Greenhalgh RM, Powell JT, Ruckley CV, Thompson SG. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial. On behalf of the UK Small Aneurysm Trial participants. Br J Surg. 2000 Jun;87(6):742–9.

140. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg. 1989 Mar;9(3):437–47.

141. Nathan DP, Brinster CJ, Jackson BM, Wang GJ, Carpenter JP, Fairman RM, et al. Predictors of decreased short- and long-termsurvival following open abdominal aorticaneurysm repair. J Vasc Surg.; 2011 Nov 1;54(5):1237–43.

142. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation. 2002 Dec 3;106(23):2913–8.

143. Omland T, Aakvaag A, Vik-Mo H. Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. Heart. 1996 Sep;76(3):232–7.

144. Yeh HM, Lau HP, Lin JM, Sun WZ, Wang MJ, Lai LP. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. Br J Surg. 2005;92(8):1041–5.

145. Feringa HHH, Bax JJ, Elhendy A, et al. Association of Plasma N-Terminal Pro-B-Type Natriuretic Peptide With Postoperative Cardiac Events in Patients Undergoing Surgery for Abdominal Aortic Aneurysm or Leg Bypass. Am J Cardiol. 2006 Jul;98(1):111–5.

146. Rajagopalan S, Croal BL, Bachoo P, Hillis GS, Cuthbertson BH, Brittenden J. N-terminal pro B-type natriuretic peptide is an independent predictor of postoperative myocardial injury in patients undergoing major vascular surgery. J Vasc Surg. 2008 Oct;48(4):912–7.

147. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation. 2002 Oct 29;106(18):2366–71.

148. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol. 2003 Nov 5;42(9):1547–54.

149. Barbagallo M, Casati A, Spadini E, et al. Early increases in cardiac troponin levels after major vascular surgery is associated with an increased frequency of delayed cardiac complications. J Clin Anesth. 2006 Jun;18(4):280–5.

150. Goei D, van Kuijk JP, Flu WJ, et al. Usefulness of Repeated N-Terminal Pro-B-Type Natriuretic Peptide Measurements as Incremental Predictor for Long-Term Cardiovascular Outcome After Vascular Surgery. Am J Cardiol.; 2011 Feb 15;107(4):609–14.

151. Ryding ADS, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. Anesthesiology. 2009 Aug;111(2):311–9.

152. Arve S, Savikko N, Lavonius S, Lehtonen A, Isoaho H. Physical functioning, health and survival: a ten-year follow-up study. Aging Clin Exp Res. 2006 Oct;18(5):367–73.

153. Girish M. Symptom-Limited Stair Climbing as a Predictor of Postoperative Cardiopulmonary Complications After High-Risk Surgery. Chest. 2001 Oct 1;120(4):1147–51.

154. Gaensler EA, Cugell DW, Lindgren I, et al. The role of pulmonary insufficiency in mortality and invalidism following surgery for pulmonary tuberculosis. J Thorac Surg. 1955 Feb;29(2):163–87.

155. Brunelli A, Monteverde M, Refai Al M, Fianchini A. Stair climbing test as a predictor of cardiopulmonary complications after pulmonary lobectomy in the elderly. Ann Thorac Surg. 2004 Jan;77(1):266–70.

156. Girish M, Trayner E, Dammann O, Pinto-Plata V, Celli B. Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery. CHEST. 2001 Oct;120(4):1147–51.

157. Pollock M, Roa J, Benditt J, Celli B. Estimation of ventilatory reserve by stair climbing. A study in patients with chronic airflow obstruction. Chest. 1993 Nov;104(5):1378–83.

158. Mendes M. Contribution of CPET to prognostic assessment of patients with left ventricular systolic dysfunction. Rev Port Cardiol. 2010 Sep;29(9):1323–9.

159. Arena R, Myers J, Guazzi M. Cardiopulmonary Exercise Testing Is a Core Assessment for Patients With Heart Failure. Congestive Heart Failure. 2011 Apr 13;17(3):115–9.

160. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. Int J Sports Med. 2005 Feb;26 Suppl 1:S49–55.

161. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol. 2008 Aug;9(8):757–65.

162. Hennis PJ, Meale PM, Grocott MPW. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. Postgraduate Medical Journal. 2011 Jul 25;87(1030):550–7.

163. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. Anaesthesia. 2009 Aug;64(8):883–93.

164. Whipp BJ. Carotid bodies and breathing in humans. Thorax. 1994 Nov;49(11):1081–4.

165. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003 Jan 15;167(2):211–77.

166. Hartley RA, Pichel AC, Grant SW, et al. Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair. Br J Surg. 2012 Sep 21;99(11):1539–46.

167. Prentis JM, Trenell MI, Jones DJ, Lees T, Clarke M, Snowden CP. Submaximal exercise testing predicts perioperative hospitalization after aortic aneurysm repair. J Vasc Surg.; 2012 Aug 1;:1–7.

168. Young EL, Karthikesalingam A, Huddart S, Pearse RM, Hinchliffe RJ, Loftus IM, et al. European Journal of Vascular and Endovascular Surgery. Eur J Vasc Endovasc Surg; 2012 Jul 1;44(1):64–71.

169. Nugent AM, Riley M, Megarry J, O'Reilly MJ, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the pre-operative assessment of patients for repair of abdominal aortic aneurysm. Ir J Med Sci. 1998 Oct;167(4):238–41.

170. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. Br J Surg. 2007;94(8):966–9.

171. Thompson AR, Peters N, Lovegrove RE, Ledwidge S, Kitching A, Magee TR, et al. Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients. Ann R Coll Surg Engl. 2011 Sep 1;93(6):474–81.

172. Samy AK, Murray G, MacBain G. Glasgow aneurysm score. Cardiovasc Surg. 1994 Feb;2(1):41–4.

173. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. Br J Surg. 1991 Mar;78(3):355–60.

174. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818–29.

175. Hadjianastassiou VG, Tekkis PP, Goldhill DR, Hands LJ. Quantification of mortality risk after abdominal aortic aneurysm repair. Br J Surg. 2005;92(9):1092–8.

176. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med. 1986 Jul;1(4):211–9.

177. Samy AK, Murray G, MacBain G. Prospective evaluation of the Glasgow Aneurysm Score. J R Coll Surg Edinb. 1996 Apr;41(2):105–7.

178. Biancari F, Leo E, Ylönen K, Vaarala MH, Rainio P, Juvonen T. Value of the Glasgow Aneurysm Score in predicting the immediate and long-term outcome after elective open repair of infrarenal abdominal aortic aneurysm. Br J Surg. 2003 Jul;90(7):838–44.

179. Biancari F, HEIKKINEN M, Lepantalo M, Salenius J-P. Glasgow Aneurysm Score in patients undergoing elective open repair of abdominal aortic aneurysm: a Finnvasc study. Eur J Vasc Endovasc Surg. 2003 Dec;26(6):612–7.

180. Hirzalla O, Emous M, Ubbink DT, Legemate D. External validation of the Glasgow Aneurysm Score to predict outcome in elective open abdominal aortic aneurysm repair. J Vasc Surg. 2006 Oct;44(4):712–6–discussion717.

181. Baas AF, Janssen KJM, Prinssen M, Buskens E, Blankensteijn JD. The Glasgow Aneurysm Score as a tool to predict 30-day and 2-year mortality in the patients from the Dutch Randomized Endovascular Aneurysm Management trial. J Vasc Surg. 2008 Feb;47(2):277–81.

182. Biancari F, Hobo R, Juvonen T. Glasgow Aneurysm Score predicts survival after endovascular stenting of abdominal aortic aneurysm in patients from the EUROSTAR registry. Br J Surg. 2006 Feb;93(2):191–4.

183. Whiteley MS, Prytherch DR, Higgins B, Weaver PC, Prout WG. An evaluation of the POSSUM surgical scoring system. Br J Surg. 1996 Jun;83(6):812–5.

184. Midwinter MJ, Tytherleigh M, Ashley S. Estimation of mortality and morbidity risk in vascular surgery using POSSUM and the Portsmouth predictor equation. Br J Surg. 1999 Apr;86(4):471–4.

185. Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Br J Surg. 1998 Sep;85(9):1217–20.

186. Prytherch DR, Ridler BM, Beard JD, Earnshaw JJ, Audit and Research Committee, The Vascular Surgical Society of Great Britian and Ireland. A model for national outcome audit in vascular surgery. Eur J Vasc Endovasc Surg. 2001 Jun;21(6):477–83.

187. Prytherch DR, Sutton GL, Boyle JR. Portsmouth POSSUM models for abdominal aortic aneurysm surgery. Br J Surg. 2001 Jul;88(7):958–63.

188. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991 Dec;100(6):1619–36.

189. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med. 1981 Aug;9(8):591–7.

190. Maziak DE, Lindsay TF, Marshall JC, Walker PM. The impact of multiple organ dysfunction on mortality following ruptured abdominal aortic aneurysm repair. Ann Vasc Surg. 1998 Mar;12(2):93–100.

191. Kabbani LS, Escobar GA, Knipp B, et al. APACHE III Score on ICU Admission Predicts Hospital Mortality After Open Thoracoabdominal and Open Abdominal Aortic Aneurysm Repair. Ann Vasc Surg; 2010 Nov 1;24(8):1060–7.

192. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999 Sep 7;100(10):1043–9.

193. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann Intern Med. 2010 Jan 5;152(1):26–35.

194. Schouten O, Sillesen H, Poldermans D, European Society of Cardiology. New guidelines from the European Society of Cardiology for perioperative cardiac care: a summary of implications for elective vascular surgery patients. Eur J Vasc Endovasc Surg. 2010 Jan;39(1):1–4.

195. Sicari R, Ripoli A, Picano E, et al. Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: A large-scale multicenter study in 509 patients. EPIC (Echo Persantine International Cooperative) Study Group. Circulation. 1999 Nov 9;100(19 Suppl):II269–74.

196. Lalka SG, Sawada SG, Dalsing MC, et al. Dobutamine stress echocardiography as a predictor of cardiac events associated with aortic surgery. J Vasc Surg. 1992 May;15(5):831–40–discussion841–2.

197. Poldermans D, Fioretti PM, Forster T, et al. Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation. 1993 May 1;87(5):1506–12.

198. Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Role of pre-operative multiple gated acquisition scanning in predicting long-term outcome in patients undergoing elective abdominal aortic aneurysm repair. World J Surg. 2013 May;37(5):1169–73.

199. Kazmers A, Cerqueira MD, Zierler RE. The role of preoperative radionuclide ejection fraction in direct abdominal aortic aneurysm repair. J Vasc Surg. 1988 Aug;8(2):128–36.

200. Karkos CD, Thomson GJL, Hughes R, et al. Prediction of Cardiac Risk prior to Elective Abdominal Aortic Surgery: Role of Multiple Gated Acquisition Scan. World J Surg. 2003 Oct 1;27(10):1085–92.

201. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004 Dec 30;351(27):2795–804.

202. Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J Am Coll Cardiol. 2007 May 1;49(17):1763–9.

203. Landesberg G, Mosseri M, Zahger D, et al. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. J Am Coll Cardiol. 2001 Jun 1;37(7):1839–45.

204. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol. 1996 May 15;77(12):1126–8.

205. Smoking, lung function and the prognosis of abdominal aortic aneurysm. The UK Small Aneurysm Trial Participants. Eur J Vasc Endovasc Surg. 2000 Jun;19(6):636–42.

206. Azizzadeh A, Sanchez LA, Miller CC III, et al. Glomerular filtration rate is a predictor of mortality after endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2006 Jan;43(1):14–8.

207. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation. 2007 Mar 13;115(10):1211–7.

208. Bartels MN, Kim H, Whiteson JH, Alba AS. Pulmonary rehabilitation in patients undergoing lung-volume reduction surgery. Arch Phys Med Rehabil. 2006 Mar;87(3 Suppl 1):S84–8–quizS89–90.

209. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. Am Heart J. 2009 Dec;158(6):1031–7.

210. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med. 2000 Aug 15;133(4):253–62.

211. Beaupre LA, Lier D, Davies DM, Johnston DBC. The effect of a preoperative exercise and education program on functional recovery, health related quality of life, and health service utilization following primary total knee arthroplasty. J Rheumatol. 2004 Jun;31(6):1166–73.

212. Rooks DS, Huang J, Bierbaum BE, et al. Effect of preoperative exercise on measures of functional status in men and women undergoing total hip and knee arthroplasty. Arthritis Rheum. 2006 Oct 15;55(5):700–8.

213. Valkenet K, van de Port IG, Dronkers JJ, de Vries WR, Lindeman E, Backx FJ. The effects of preoperative exercise therapy on postoperative outcome: a systematic review. Clinical Rehabilitation. 2011 Jan 21;25(2):99–111.

214. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. Circulation. 1999 Feb 23;99(7):963–72.

215. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. JAMA. 1988 Aug 19;260(7):945–50.

216. Cardiac rehabilitation programs. A statement for healthcare professionals from the American Heart Association. Circulation. 1994 Sep;90(3):1602–10.

217. Gould KL, Ornish D, Kirkeeide R, et al. Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification. Am J Cardiol. 1992 Apr 1;69(9):845–53.

218. Belardinelli R, Georgiou D, Ginzton L, Cianci G, Purcaro A. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation. 1998 Feb 17;97(6):553–61.

219. Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation. 1994 Mar;89(3):975–90.

220. Donnelly JE, Jacobsen DJ, Heelan KS, Seip R, Smith S. The effects of 18 months of intermittent vs. continuous exercise on aerobic capacity, body weight and composition, and metabolic fitness in previously sedentary, moderately obese females. Int J Obes Relat Metab Disord. 2000 May;24(5):566–72.

221. Swain DP. Moderate or vigorous intensity exercise: which is better for improving aerobic fitness? Prev Cardiol. 2005;8(1):55–8.

222. Kothmann E, Batterham AM, Owen SJ, et al. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. Br J Anaesth. 2009 Sep 11;103(4):505–10.

223. Dronkers J, Veldman A, Hoberg E, van der Waal C, van Meeteren N. Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. Clinical Rehabilitation. 2008 Feb;22(2):134–42.

224. Hulzebos EHJ, Helders PJM, Favié NJ, et al. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006 Oct 18;296(15):1851–7.

225. Fagevik Olsén M, Hahn I, Nordgren S, Lönroth H, Lundholm K. Randomized controlled trial of prophylactic chest physiotherapy in major abdominal surgery. Br J Surg. 1997 Nov;84(11):1535–8.

226. Nieman DC, Nehlsen-Cannarella SL, Markoff PA, et al. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int J Sports Med. 1990 Dec;11(6):467–73.

227. Taaffe DR, Duret C, Wheeler S, Marcus R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. J Am Geriatr Soc. 1999 Oct;47(10):1208–14.

228. Howe TE, Rochester L, Neil F, Skelton DA, Ballinger C. Exercise for improving balance in older people. Cochrane Database Syst Rev. 2011;(11):CD004963.

229. Angevaren M, Aufdemkampe G, Verhaar HJJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2008;(3):CD005381.

230. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev. 2005;(3):CD000335.

231. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011;(7):CD000333.

232. Gill DL, Williams K, Williams L, Butki BD, Kim BJ. Physical activity and psychological well-being in older women. Womens Health Issues. 1997 Jan;7(1):3–9.

233. Newsom JT, Schulz R. Social support as a mediator in the relation between functional status and quality of life in older adults. Psychol Aging. 1996 Mar;11(1):34–44.

234. Ruuskanen JM, Ruoppila I. Physical activity and psychological well-being among people aged 65 to 84 years. Age Ageing. 1995 Jul;24(4):292–6.

235. Gillison FB, Skevington SM, Sato A, Standage M, Evangelidou S. The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. Soc Sci Med. 2009 May;68(9):1700–10.

236. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. Circulation. 1989 Feb;79(2):324–9.

237. Gaskill SE, Walker AJ, Serfass RA, Bouchard C, Gagnon J, Rao DC, et al. Changes in ventilatory threshold with exercise training in a sedentary population: the HERITAGE Family Study. Int J Sports Med. 2001 Nov;22(8):586–92.

238. Londeree BR. Effect of training on lactate/ventilatory thresholds: a meta-analysis. Med Sci Sports Exerc. 1997 Jun;29(6):837–43.

239. Tew GA, Moss J, Crank H, Mitchell PA, Nawaz S. Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Arch Phys Med Rehabil. 2012 Dec;93(12):2148–53.

240. Myers J, McElrath M, Jaffe A, et al. A randomized trial of exercise training in abdominal aortic aneurysm disease. Med Sci Sports Exerc. 2014 Jan;46(1):2–9.

241. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2004 Jun;11(3):216–22.

242. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. Am J Cardiol. 2006 Jan 1;97(1):141–7.

243. Berney S, Haines K, Skinner EH, Denehy L. Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness. Phys Ther. 2012 Dec;92(12):1524–35.

244. Mazari FAK, Khan JA, Carradice D, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg. 2013 Aug;100(9):1172–9.

245. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. Angiology. 1997 Apr;48(4):291–300.

246. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. Eur J Vasc Endovasc Surg. 2013 Dec;46(6):690–706.

247. Ernst CB. Abdominal aortic aneurysm. N Engl J Med. 1993 Apr 22;328(16):1167–72.

248. Henebiens M, van den Broek TAA, Vahl AC, Koelemay MJW. Relation between hospital volume and outcome of elective surgery for abdominal aortic aneurysm: a systematic review. Eur J Vasc Endovasc Surg. 2007 Mar;33(3):285–92.

249. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA. 2009 Oct 14;302(14):1535–42.

250. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. J Vasc Surg. 2004 Mar;39(3):497–505.

251. Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med. 2008 Jan 31;358(5):464–74.

252. Diehl JT, Cali RF, Hertzer NR, Beven EG. Complications of abdominal aortic reconstruction. An analysis of perioperative risk factors in 557 patients. Ann Surg. 1983 Jan;197(1):49–56.

253. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med. 1990 Dec 27;323(26):1781–8.

254. Silverstein PR, Caldera DL, Cullen DJ, Davison JK, Darling RC, Emerson CW. Avoiding the hemodynamic consequences of aortic cross-clamping and unclamping. Anesthesiology. 1979 May;50(5):462–6.

255. Attia RR, Murphy JD, Snider M, Lappas DG, Darling RC, Lowenstein E. Myocardial ischemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. Circulation. 1976 Jun;53(6):961–5.

256. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology. 2005 May;102(5):885–91.

257. Adams JE, Sicard GA, Allen BT, Bridwell KH, Lenke LG, Dávila-Román VG, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med. 1994 Mar 10;330(10):670–4.

258. Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal surgery. Chest. 1997 Mar;111(3):564–71.

259. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000 Aug;232(2):242–53.

260. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006 Mar;43(3):460–466–discussion466.

261. Myers JN, White JJ, Narasimhan B, Dalman RL. Effects of exercise training in patients with abdominal aortic aneurysm: preliminary results from a randomized trial. J Cardiopulm Rehabil Prev. 2010 Nov;30(6):374–83.

262. Akkersdijk GJ, van der Graaf Y, Moll FL, et al. Complications of standard elective abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 1998 Jun;15(6):505–10.

263. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986 Jun;60(6):2020–7.

264. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Journal of the American College of Cardiology. 2002. pp. 1531–40.

265. Abdominal Aortic Aneurysm Quality Improvement Programme. http://www.aaaqip.com [accessed 11 May 2014].

266. Takeshima N, Tanaka K, Kobayashi F, Watanabe T, Kato T. Effects of aerobic exercise conditioning at intensities corresponding to lactate threshold in the elderly. Eur J Appl Physiol Occup Physiol. 1993;67(2):138–43.

267. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. Circulation. 2010 Sep 21;122(12):1221–38.

268. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000 Feb 17;342(7):454–60.

269. Gokce N, Vita JA, Bader DS, Sherman DL, Hunter LM, Holbrook M, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am J Cardiol. 2002 Jul 15;90(2):124–7.

270. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000 Apr 25;101(16):1899–906.

271. Middlekauff HR, Nitzsche EU, Nguyen AH, Hoh CK, Gibbs GG. Modulation of renal cortical blood flow during static exercise in humans. Circ Res. 1997 Jan;80(1):62–8.

272. Poortmans JR, Vanderstraeten J. Kidney function during exercise in healthy and diseased humans. An update. Sports Med. 1994 Dec;18(6):419–37.

273. Toyama K, Sugiyama S, Oka H, Sumida H, Ogawa H. Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. J Cardiol. 2010 Sep;56(2):142–6.

274. McAleese P, Odling-Smee W. The effect of complications on length of stay. Ann Surg. 1994 Dec;220(6):740–4.

275. Khan NA, Quan H, Bugar JM, Lemaire JB, Brant R, Ghali WA. Association of postoperative complications with hospital costs and length of stay in a tertiary care center. J Gen Intern Med. 2006 Feb;21(2):177–80.

276. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg. 2004 Oct;199(4):531–7.

277. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005 Sep;242(3):326–41–discussion341–3.

278. Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. Anesth Analg. 2003 Feb;96(2):583–9.

279. Simons JP, Goodney PP, Baril DT, et al. The effect of postoperative stroke and myocardial infarction on long-term survival after carotid revascularization. J Vasc Surg. 2013 Jun;57(6):1581–8.

280. Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care. 2006;10(3):R81.

281. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM. Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. Anaesthesia. 2008 Jul;63(7):695–700.

282. Snowden CP, Prentis JM, Anderson HL, et al. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. Ann Surg. 2010 Mar;251(3):535–41.

283. James S, Jhanji S, Smith A, O'Brien G, Fitzgibbon M, Pearse RM. Comparison of the prognostic accuracy of scoring systems, cardiopulmonary exercise testing, and plasma biomarkers: a single-centre observational pilot study. Br J Anaesth. 2014 Mar;112(3):491–7.

284. Choi J-H, Cho DK, Song Y-B, et al. Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery. Heart. 2010 Jan;96(1):56–62.

285. Schouten O, Hoeks SE, Goei D, Bax JJ, Verhagen HJM, Poldermans D. Plasma N-terminal pro-B-type natriuretic peptide as a predictor of perioperative and long-term outcome after vascular surgery. J Vasc Surg. 2009 Feb;49(2):435–41–discussion441–2.

286. Bensimhon DR, Leifer ES, Ellis SJ, , et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). Am J Cardiol. 2008 Sep 15;102(6):712–7.

287. Lehmann G, Kölling K. Reproducibility of cardiopulmonary exercise parameters in patients with valvular heart disease. Chest. 1996 Sep;110(3):685–92.

288. Yasunobu Y, Oudiz RJ, Sun X-G, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest. 2005 May;127(5):1637–46.

289. Holverda S, Bogaard HJ, Groepenhoff H, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Cardiopulmonary exercise test characteristics in patients with chronic obstructive pulmonary disease and associated pulmonary hypertension. Respiration. 2008;76(2):160–7.

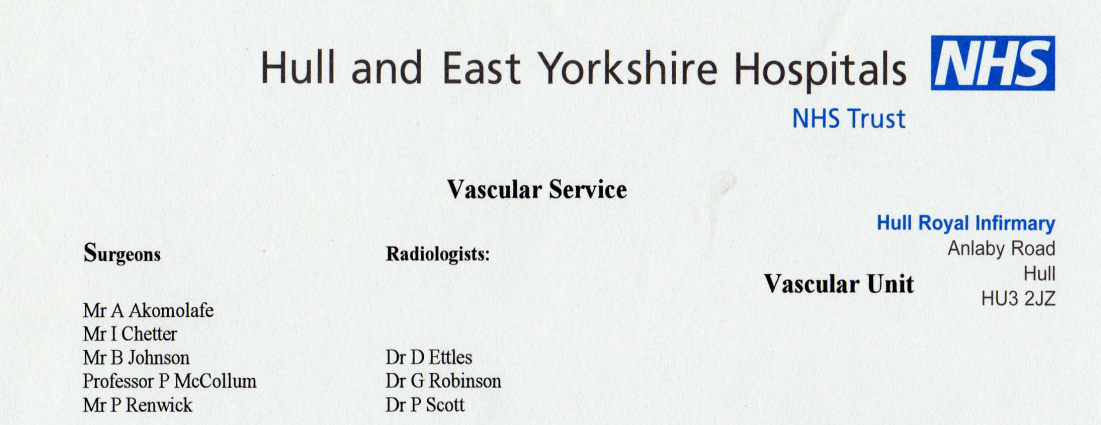
290. Ponikowski P, Chua TP, Piepoli M, et al. Ventilatory response to exercise correlates with impaired heart rate variability in patients with chronic congestive heart failure. Am J Cardiol. 1998 Aug 1;82(3):338–44.

291. West MA, Lythgoe D, Barben CP, et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2013 Dec 8.

292. Hobbs SD, Wilmink ABM, Bradbury AW. Ethnicity and peripheral arterial disease. Eur J Vasc Endovasc Surg. 2003 Jun;25(6):505–12.

Appendix 1

1. Participant Information Leaflet:



PARTICIPANT INFORMATION LEAFLET:

(Thank you for reading this.)

Effect of a pre-operative supervised exercise programme on outcome following intervention for abdominal aortic aneurysms.

You are invited to take part in this research study. It is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

The main artery that runs through your abdomen (tummy) is bigger than it should be (known as an aneurysm) and is now at the size where the consultant in charge of your care feels that something needs to be done to repair this artery. Although these types of operations are commonly performed at Hull Royal Infirmary, they are associated with some risks to your heart, kidneys and chest. These risks would have been explained to you by your consultant.

Gentle exercise prior to undergoing a major operation may well reduce the risk of developing complications following surgery. Exercise has been shown to be beneficial in patients undergoing heart bypass surgery but as yet we are not sure if it has a beneficial effect prior to an operation on the main artery in your tummy. We are therefore writing to you to invite you to take part in a research study that is trying to determine whether a

period of supervised exercise prior to your surgery will have benefits upon you recovering after your surgery.

Why have I been invited?

You have been invited to participate in this study because you have an aneurysm in your tummy and your consultant has decided that you would benefit from treatment for this.

Do I have to take part?

Participation in this study is entirely voluntary.

You may refuse to participate or withdraw from the study at any time. You do not need to tell the researchers why you do not want to take part. If you choose to withdraw or not to participate, your decision will in **No way** affect your future treatment. It may be that the investigator or sponsor of the study feels that you would not benefit from participation and may withdraw you from the study but this withdrawal will not harm your continuing care.

What will happen if I decide to take part?

If you decide to take part in this study, you will be invited to the Vascular Laboratory at Hull Royal Infirmary. When you arrive at the Vascular Laboratory the following will happen:

The study will be explained to you in detail and you will be free to ask any questions or concerns. We will also assess if you are suitable to take part in the study.
You will be asked to sign the consent form and complete two questionnaires to assess how your health is before operation.
Patients will be divided into two groups by randomisation (lottery) into an exercise group and a non exercise group. There are equal chances that you might not get exercise element of the study.

As part of the study you will need the following assessments:

You will be asked to walk on a treadmill for a maximum of 5-8 minutes at slow speed. While doing this you will be asked to also wear a mask on your face similar to those used to give oxygen to patients on the hospital programmes on television. This mask allows us to measure how much oxygen you are breathing in and out while you are walking on the treadmill.

We will also ask you to climb up a set of stairs within the hospital as far possible, at your own pace using the railing only for balance. A post stair climbing heart tracing will also be performed. This is one of the tests to predict complications after surgery.

If you have been allocated to the exercise class, this will be performed three times a week with average duration of 40 minutes for 4-6 weeks. The class is held in the physiotherapy department at Hull Royal Infirmary. This will mean extra attendances at the exercise class for the duration of exercise period. The exercise class is composed of a set of gentle exercises. Each station is of 2 minutes duration with 2 minutes walking in between each station.
Various stations include;

Step ups which means stepping on and off a 20 cm high step, alternating their lead leg after 10 step ups.

Knee extensions in which participants sit on a high stool with a 1-2kg bean bag hung over ankle and fully extend knee. Weight transferred to other leg after 10 extensions.

Heel raises in which participants whilst standing with support from a wall bar, raise heels off the floor to stand on tip toes, hold for 5 seconds then lower back to floor.

Knee bends in which participants whilst standing on one leg with support from a wall bar, flex and extend the weight bearing knee for 10 times - then change legs.

Two minutes on exercise bike.

Arms exercise in which participants while holding 2kg dumbbells flex and extend their elbows.

As part of the routine care you will need the following assessments:

As part of routine care you will also be asked to attend the pre assessment clinic in which a chest x-ray will be performed.
You will also get an appointment to attend the Nuclear Medicine department for a scan to evaluate the function of the heart. This is routinely performed in all our Aortic Aneurysm patients who are planned for surgery. In this test a radioactive dye is given to show the heart up on a special camera.
A blood sample will be taken at the initial visit also during your operation and recovery period after surgery. This is standard practice.
You will be followed up 3 months after your operation as routine standard care.

Are there any risks involved?
Appropriate safety measures will be taken at all times. You will be assessed on the potential risk of you climbing a set of stairs using a standard form. The exercise class is being run by medically qualified personnel.

Are there any costs involved?

No cost is involved but the patients who will be attending the exercise class will have to make their own transport arrangements.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your withdrawal will not harm your continuing care. If you decide to continue in the study you will be asked to sign an updated consent form. This will have no effect on your surgery.

Also on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

What if something goes wrong?

If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. If you consent to participate in the trial we will inform your GP unless this is against your wishes.

What will happen to the results of the research study?

The overall results will be published in leading scientific and medical journals in approximately 4 years. Your confidentiality will be preserved in all published articles. We would be happy to supply you with a copy of the results on request.

Who is organising the study?

This study is organised by the Department of Vascular Surgery, Hull Royal Infirmary.

Who has reviewed this study?

The ethics behind this study have been reviewed and supported by the South Humber Local Research Ethics Committee.

Thank you for taking the time to read this information sheet. If you have any further queries or questions please don't hesitate to contact;

Mr Hashem Barakat (Clinical Research Fellow in Vascular Surgery)

Contact No: 01482674643

2. Consent Form

Patient ID number;

Title of project:

Effect of a pre-operative supervised exercise programme on outcome following intervention for abdominal aortic aneurysms.

Names of researchers;

[redacted]. Professor of Vascular Surgery. Hull and East Yorkshire NHS Trust

[redacted]. Senior Lecturer in Vascular Surgery. Hull and East Yorkshire NHS Trust

Mr Hashem Barakat MRCS. Clinical Research Fellow, Vascular Surgery, Hull and East Yorkshire NHS Trust.

Contact Address:

Vascular Laboratory,

First Floor, Hull Royal Infirmary,

Anlaby Road, Hull HU3 2JZ

Telephone No: 01482 674643

Fax No: 01482 674765

Please initial box

1. I confirm that I have read and understand the information sheet dated 08/10/09 (Version 3) for the above study and have had the opportunity to ask questions.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I agree to take part in the above study.	
4. I agree to my GP being informed of my participation in the study.	

_____ _____

Name of Subject (BLOCK CAPITALS) Date Signature

_____ _____

Name of Person taking consent Date Signature

_____ _____

Researcher/witness Date Signature

1 for patient, 1 for researcher, 1 to be kept with hospital notes

Appendix 2

1. Glasgow Aneurysm Score calculator:

Please refer to Figure 13 on page 74.

2. V-POSSUM score calculator:

This was calculated by adding the physiological score and the operative score: please refer to Figures 14 and 15 on page 77.

3. RCRI score:

Each risk factor is assigned one point.

1. High-risk surgical procedures

• Intraperitoneal

• Intrathoracic

• Suprainguinal vascular

2. History of ischemic heart disease

• History of myocardial infarction

• History of positive exercise test

• Current complain of chest pain considered secondary to myocardial ischemia

• Use of nitrate therapy

• ECG with pathological Q waves

3. History of congestive heart failure

• History of congestive heart failure

• Pulmonary edema

• Paroxysmal nocturnal dyspnea

• Bilateral rales or S3 gallop

• Chest radiograph showing pulmonary vascular redistribution

4. History of cerebrovascular disease

• History of transient ischemic attack or stroke

5. Preoperative treatment with insulin

6. Preoperative serum creatinine > 176.8 umol/L

4. DETSKY score calculator:

The calculator used the following information for each participant within the study:

1. Myocardial infarction

No history (0 points)

Within 6 months (10 points)

Beyond 6 months (5 points)

2. Canadian Cardiovascular Society Angina

Class I - II (0 points)

Class III (10 points)

Class IV (20 points)

Unstable angina within 3 months (10 points)

3. Pulmonary Edema

Never (0 points)

Within 1 week (10 points)

Ever (5 points)

- Valvular Disease

Possible aortic stenosis of a critical nature (20 points)

4. Arrhythmias

Abnormal heart rhythm (other than sinus with premature atrial beats) (5 points)

5 or more PVC's / min (5 points)

General Medical Conditions

$PO_2 < 60$; $PCO_2 > 50$; $K < 3$; $HCO_3 < 20$; BUN > 50; Creat > 3; elevated SGOT; chronic liver disease; bedridden (5 points)

4. Operation

Emergency (10 points)

5. Age

Age > 70 (5 points)

5. APACHE II calculator:

Please refer to Figure16 on page 79.

Appendix 3

1. SF 8™ health survey:

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

For each of the following questions, please mark an [x] in the one box that best describes your answer.

Overall, how would you rate your health during the **past 4 weeks**?

Excellent	Very good	Good	Fair	Poor	Very poor
○	○	○	○	○	○

During the **past 4 weeks**, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
○	○	○	○	○

During the **past 4 weeks**, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

None at all	A little bit	Some	Quite a lot	Could not do daily work
○	○	○	○	○

How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very Severe
○	○	○	○	○	○

During the **past 4 weeks**, how much energy did you have?

Very much	Quite a lot	Some	A little	None
○	○	○	○	○

During the **past 4 weeks**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
○	○	○	○	○

During the **past 4 weeks**, how much have you been bothered by **emotional problems** (such as feeling anxious, depressed or irritable)?

Not at all	Slightly	Moderately	Quite a lot	Extremely
○	○	○	○	○

During the **past 4 weeks**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
○	○	○	○	○

ank you for completing these questions!

2. Euroqol (E5-QD):

By placing a tick in one box in each group below, please indicate which statements best describe your own health today.

Mobility

I have no problems in walking about □
I have some problems in walking about □
I am confined to bed □

Self-care

I have no problems with self care □
I have some problems washing or dressing myself □
I am unable to wash or dress myself □

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities □
I have some problems with performing my usual activities □
I am unable to perform my usual activities □

Pain/ Discomfort

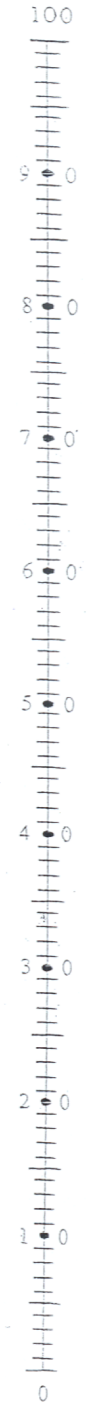
I have no pain or discomfort □
I have some pain or discomfort □
I have extreme pain or discomfort □

Anxiety/ Depression

I am not anxious or depressed □
I am moderately anxious or depressed □
I am extremely anxious or depressed □

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Glossary of abbreviations

95% CI	95 per cent confidence interval (see page 147)
X^2	Chi square test
AAA	Abdominal aortic aneurysms (see page 19)
AAAQIP	Abdominal aortic aneurysm quality improvement programme (see page 100)
ABPI	Ankle-brachial pressure index (see page 109)
ACEI	Angiotensin converting enzyme inhibitors (see page 48)
ACS	Acute coronary syndrome (see page 61)
AD	Anno Domini (see page 21)
AP	Antero-posterior (see page 44)
APACHE	Acute Physiology and Chronic Health Evaluation (see pages 73, 78)
ARB	Angiotensin receptor blockers (see page 48)
ATP	Adenosine triphosphate (see page 68)
ARDS	Adult respiratory distress syndrome (see page 97)
ARR	Absolute risk reduction (see page 131)
ASA	American Society of Anesthesia (see page 124)
AUC	Area under the curve (see pages 75 &147)
BC	Before Christ (see page 20)
BMI	Body mass index (see page 109)
CABG	Coronary artery bypass grafting (see page 84)
CER	Control event rate (see page 131)
CHF	Congestive heart failure (page 60)
CIN	Contrast induced nephropathy (see page 83)
COPD	Chronic obstructive pulmonary disease (see page 60)
CPET	Cardiopulmonary exercise testing (see pages 64, 66)
CRP	C-reactive protein (see page 109)
CTA	Computed tomography angiography (see pages 38)
DSA	Digital subtraction angiography (see page 39)
E5-QD	Euroqol (5 domains) questionnaire (see page 118)

ECG	Electrocardiography (see page 63)
EER	Experimental event rate (see page 131)
EVAR	Endovascular aneurysm repair (see pages 49, 52)
FEV1	Forced expiratory volume (see page 61)
FET	Fisher exact test (see page 131)
FRC	Functional residual capacity (see page 87)
FVC	Forced vital capacity (see page 88)
GAS	Glasgow aneurysm score (see pages 74)
HDU	High dependency unit (see page 126)
IQR	Interquartile range (see page 122)
ITU	Intensive therapy unit (see page 127)
LAT	Lactate anaerobic threshold (see page 68)
LBBB	Left bundle branch block (see page 125)
LDL	Low-density lipoprotein (see page 46)
LVEF	Left ventricular ejection fraction (see page 80)
MAP	Mean arterial pressure (see page 95)
MCP-1	Monocyte chemptactic protein 1 (see page 33)
MI	Myocardial infarction (see page 96)
MMP	Matrix metalloproteinases (see page 32)
MRA	Magnetic resonance angiography (see page 42)
MUGA	Multi-gated acquisition (see page 110)
NIHR	National Institute for Health Research (see page 49)
NNT	Number needed to treat (see page 131)
NT-pro BNP	N-terminal of the prohormone brain natriuretic peptide (see page 61)
OAR	Open aneurysm repair
PAI-1	Plasminogen activator inhibitor 1 (see page 31)
PAWP	Pulmonary artery wedge pressure (see page 57)
PEFR	Peak expiratory flow rate (see page 88)
POMS	Postoperative morbidity survey (see page 203)
POSSUM	Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (see page 76)
RCRI	Revised cardiac risk index (see page 73)
RPE	Rate of perceived exertion (see page 114)

ROC curve	Receiver operator characteristic curve (see page 147)
RRR	Relative risk reduction (see page 131)
SD	Standard deviation (see page 129)
SF8	Short form 8 for quality of life assessment (see page 118)
SIRS	Systemic inflammatory response syndrome (page 126)
SPSS	Statistical package for the social sciences (see page 129)
SVR	Systemic vascular resistance (see page 94)
TIMP	Tissue inhibitors of matrix metalloproteinases (see page 32)
VSMC	Vascular smooth muscle cells (see page 31)
VAT	Ventilatory anaerobic threshold (see page 69)
V_E	Expired minute volume (see page 68)
VCO_2	Carbon dioxide production (see page 68)
VO_2	Oxygen consumption (see page 68)