A Comparison Of Different Treatments For The Repair Of Juxtarenal And Complex-Neck Abdominal Aortic Aneurysms

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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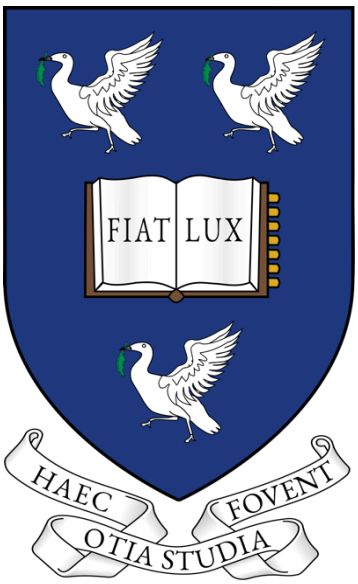

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Dedication

I dedicate this work primarily to my wonderfully supportive wife **Daxina** and our two daughters, **Anaiya and Siyena**, who were both born during this academic journey. You are the shining lights that kept me going.

To **my parents**, I will always be indebted to you. Your everlasting support, sacrifices and encouragement to pursue education have guided me to where I am now.

To **my Ba**, thank you for providing me with your love, humour and the sanctuary of your attic where I wrote most of this thesis.

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Declaration

This thesis contains work that was carried out as part of the **UK Comp**lex **A**neury**s**m **S**tudy (UK-COMPASS). UK-COMPASS is a study commissioned and funded by the National Institute for Health Research Health Technology Assessment (NIHR-HTA) Programme, the primary aim being to answer the following research question: "What is the clinical and cost-effectiveness of strategies for the management of juxtarenal AAA, including fenestrated endovascular repair?".

Not all of the work presented in this thesis is carried out within the umbrella of UK-COMPASS, and conversely not all of the output for UK-COMPASS is included in this thesis. The Chief Investigator of the UK-COMPASS trial is Prof SR Vallabhaneni, who is also my primary supervisor for this PhD. I sit on the Trial Management Group for UK-COMPASS as a Clinical Expert and am also the Research Fellow for the trial.

Certain statistical analyses were performed independently by me (network meta-analysis) whereas others were performed primarily by professional statisticians (propensity-based comparative statistics). On the whole, only work for which I have performed a leading role is included in this thesis.

All patient data was collected and analysed with prior approval from a Research Ethics Committee (REC), the Confidentiality Advisory Group (CAG) and the Health Research Authority (HRA) of the United Kingdom.

Abstract

A comparison of different treatments for the repair of juxtarenal and complex-neck abdominal aortic aneurysms – Shaneel Rajendra Patel

Background: Many abdominal aortic aneurysms (AAAs) are not suitable for standard endovascular aneurysm repair (EVAR) due to a suboptimal aneurysm "neck", the aortic segment between renal arteries and aneurysm. It may be too short ("juxtarenal") or exhibiting other adverse features ("complex-neck"), requiring alternative techniques: Open Surgical Repair (OSR), fenestrated EVAR (FEVAR) or EVAR with adjuncts (chimney stents/endoluminal screws). Standard EVAR may also be used against manufacturers' advice (off-label). This work aimed to provide comparative outcomes between treatments for repair of juxtarenal and complex-neck AAAs.

Methods: First, the existing evidence base was appraised with systematic review and network meta-analysis (NMA). Second, a cohort study captured all cases of AAA repair in England over 2 years. After successful validation, AAA anatomy was assessed in a study Corelab using a measurement protocol. This identified juxtarenal/complex-neck AAAs meeting pre-defined anatomical inclusion criteria. Follow-up data for comparative analyses was extracted from routinely-collected sources. Confounding and selection bias were addressed with propensity score analysis as well as subgrouping by "neck" length (0-4mm, 5-9mm, ≥10mm) and physiological fitness (British Aneurysm Repair score).

Results: Twenty-four observational studies (7854 patients) met systematic search inclusion criteria. NMA demonstrated that off-label EVAR and FEVAR had lower perioperative myocardial infarction and mortality rates compared to OSR, but mortality differences were lost at mid-term follow-up. Statistical confidence in the network findings was generally "Low". For the cohort study, a computerised tomography (CT) scan measurement protocol was successfully shown to produce consistent results across three raters. Nearly 9000 CT scans were subsequently analysed in the Corelab, identifying 2757 juxtarenal/complex-neck AAAs repaired in England (November 2017-October 2019). Propensity score-based comparisons included 1916 patients undergoing OSR, FEVAR or EVAR+/-adjuncts. Perioperative death rate was 2.9%, lower for EVAR (1.2%) and FEVAR (2.2%) than OSR (4.5%). In standard-risk patients, mortality for juxtarenal cases (0-4mm neck) was 7.4% following OSR and 2.3% following FEVAR. Differences were smaller for patients with neck length ≥5mm: 2.1% OSR versus 1.0% FEVAR. Widespread off-label use of standard EVAR devices was noted. Mortality rate at 3.5years was 20.7%, notably higher following FEVAR (27.6%) and EVAR (25.2%) than after OSR (14.2%), though not in the 0-4mm neck subgroup. Aneurysm-related mortality was equivalent between treatments at 3.5years, but mid-term re-intervention was more common after EVAR and FEVAR than OSR.

Conclusion: The existing comparative evidence base for juxtarenal/complex-neck AAA repair is of poor quality. This new cohort study reveals significant insights into the comparative effectiveness of OSR, FEVAR and EVAR for these cases. Notably, for juxtarenal aneurysms (0-4mm neck length), FEVAR proves safer than OSR in the perioperative period with comparable mid-term survival up to 3.5 years. For patients with short neck (5-9mm) and complex-neck AAAs (≥10mm), FEVAR and EVAR demonstrate inferior long-term survival compared to OSR. This warrants re-appraisal of the current clinical application of endovascular strategies in such patients.

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List of Abbreviations and Acronyms

AAA	Abdominal Aortic Aneurysm
AKI	Acute Kidney Injury
APC	Admitted Patient Care (Hospital Episodes Statistics Dataset)
ASA	American Society of Anaesthesiologists (Score)
BAR	British Aneurysm Repair (Score)
BMI	Body Mass Index
ChEVAR	Chimney Endovascular Aneurysm Repair
CI	Confidence Interval
CKD	Chronic Kidney Disease
CT	Computerised Tomography
CTA	Computerised Tomographic Angiography
DICOM	Digital Imaging and Communications in Medicine
DID	Diagnostic Imaging Dataset (Hospital Episodes Statistics Dataset)
ECG	Electrocardiogram
EVAR	Endovascular Aneurysm Repair
FEVAR	Fenestrated Endovascular Aneurysm Repair
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDU	High Dependency Unit
HES	Hospital Episodes Statistics
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
ICC	Intra-class Correlation
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IEP	Internet Exchange Portal
IFU	Instructions For Use
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
MI	Myocardial Infarction
MPR	Multiplanar Reconstruction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NVR	National Vascular Registry
ONS	Office for National Statistics
OPCS	Office of Population Conseuses and Surveys
OSR	Open Surgical Repair
PACS	Picture Archival and Communication System
QOL	Quality of Life
RCT	Randomised Controlled Trial
SD	Standard Deviation

SMA	Superior Mesenteric Artery
SUCRA	Surface Under the Cumulative Ranking (Curve)
TAAA	Thoracoabdominal Aortic Aneurysm

1. An Introduction To Abdominal Aortic Aneurysms (AAA), Morphological Complexity Of The Infrarenal Neck And Options For Repair

1.1 Defining Abdominal Aortic Aneurysms

An aneurysm is the localised dilatation of a blood vessel. Aneurysms are defined by a vessel diameter increase in excess of 50% (or 2 standard deviations above the mean) compared to the normal expected diameter of the vessel in question. This comparison can also be made to the diameter of an adjacent segment of normal vessel (1).

An abdominal aortic aneurysm (AAA) is a localised dilatation of the aorta as it passes through the abdomen between the diaphragm and its point of bifurcation into the common iliac arteries. This is the most common site for aneurysm development in the peripheral arterial system. 30% of all aneurysms in the body, and 80% of all aortic aneurysms develop in the infrarenal abdominal segment as shown in Figure 1-1, with the remaining 20% affecting the thoracic aorta (2).

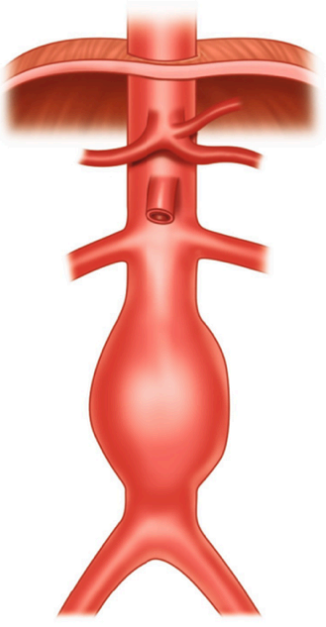


Figure 1-1 An infrarenal abdominal aortic aneurysm (3)

As normal abdominal aortic diameter is 20mm (4), an absolute diameter of 30mm can be used for defining a AAA, although it is accepted that women have smaller aortic diameters than men (5) and therefore may demonstrate aneurysmal change at diameters smaller than 30mm.

1.2 Epidemiology, Pathophysiology and Natural History of Abdominal Aortic Aneurysms

AAAs occur almost exclusively in individuals over the age of 55, the incidence increases with age, and they are considerably more common in males compared to females. The most significant modifiable risk factor for developing AAA (and for subsequently experiencing aneurysm-related complications) is smoking, both the intensity and duration of the practice (6). Prevalence and incidence of AAA have decreased since 1990 in both developing and developed countries, associated with a reduction in smoking over the same period. In 1990, global prevalence of AAA in individuals aged between 75 and 79 was 2423/100,000 population compared to 2275/100,000 population in 2010 (7).

Screening programmes provide contemporary data for national populations, albeit limited by gender and age. In men aged 65 and over, the screening pick-up rate for AAA is 1.5% in the Swedish Screening Programme (8), over 1.3% in the UK National Screening Programme (9) and 3.3% in Denmark (10). A programme in the USA that further restricts the same screening population to only those that smoke, reports a detection rate of 5.1% (11).

Atherosclerotic (or degenerative) aneurysms are by far the most common subtype of aortic aneurysm. Inflammatory, traumatic, infectious, and congenital aneurysms are much rarer. In atherosclerotic aneurysms, degeneration of the media and adventitial layers of the AAA wall involves an inflammatory response, thrombosis, necrosis of vascular smooth muscle cells as well as remodelling and degradation of extracellular matrix by abnormally high levels of matrix metalloproteinases (12). However, the exact biochemical and mechanical pathways through which this occurs are complex (Figure 1-2).

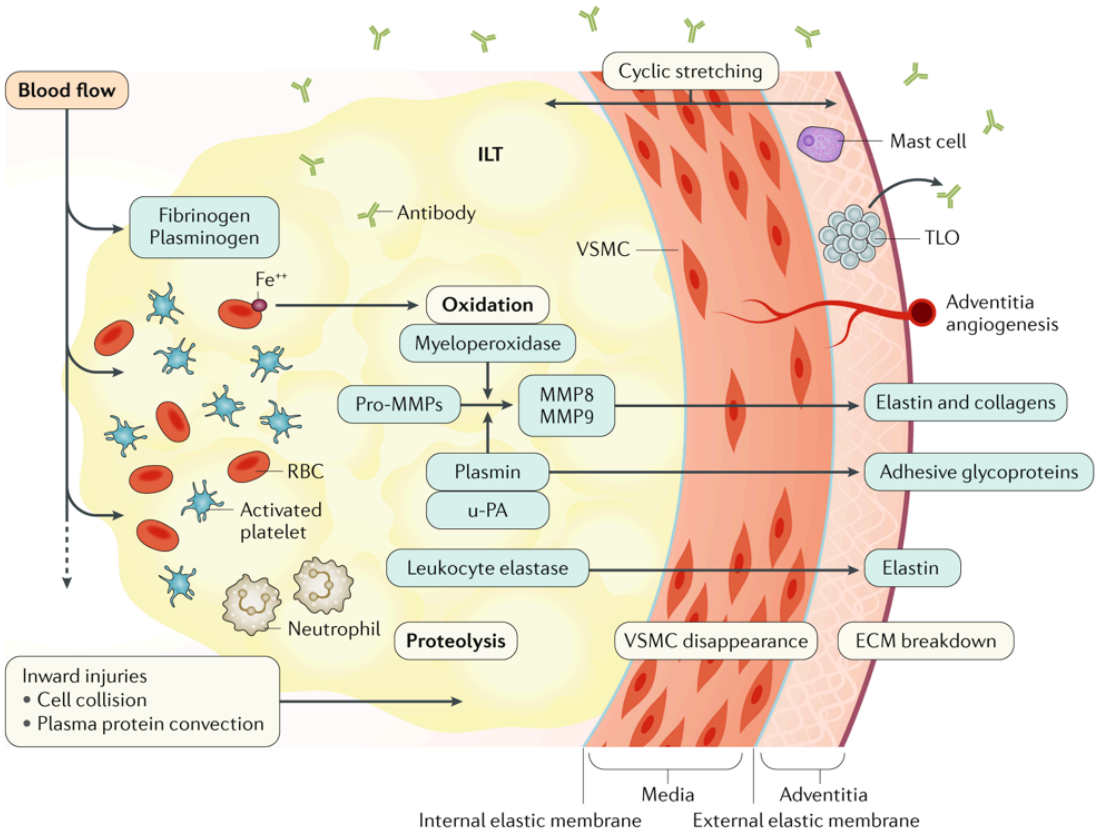


Figure 1-2 A model for AAA development and progression (13)

The natural history of a AAA is "growth", referring to a continuous enlargement over time. A meta-analysis of 15,475 patients under follow-up for a small aneurysm (39-49mm in diameter) demonstrated a mean growth rate of 2.21mm per year. This increased by 0.35mm per year in smokers and decreased by 0.51mm per year in diabetics (14). The most notable complication of an enlarging aneurysm is rupture, which is defined by a full thickness breach in the wall of the aneurysm leading to internal haemorrhage. Aneurysm rupture carries a mortality rate of >80%, with 50% of ruptured aneurysms resulting in pre-hospital death (15). Rupture of AAA leading to massive internal haemorrhage is a fatal complication in approximately 3000 individuals each year in the United Kingdom (16).

The most important risk factor for rupture of AAA is increasing aneurysm diameter. Rupture is exceedingly rare in small (30-44mm) and medium (45-54mm) sized aneurysms, with annual risk of rupture being 0.03% and 0.28% respectively (17). As aneurysms grow beyond these sizes, growth rates accelerate, with annualised rupture risk for aneurysms sized 55-60mm, 61-70mm and >70mm being 3.5%, 4.1% and 6.3% respectively (18).

1.3 The Rationale For Elective Repair of AAAs

AAAs are usually identified through incidental discovery on abdominal imaging or through a screening programme. In England, the National Health Service AAA Screening Programme (NAAASP) invites all 65 year old males for an abdominal ultrasound scan to screen for AAA, approximately 300,000 men/year (17). Due to growth being the primary risk factor for rupture, the diameter of small (30-44mm) and medium (45-54mm) sized aneurysms is surveyed using colour duplex ultrasound on an annual or 3-monthly basis respectively, until a decision is made to repair the aneurysm after an accepted threshold of 55mm maximum diameter.

Prevention of rupture, and subsequent death, is the primary indication for elective repair of AAAs. Current accepted practice is to intervene on aneurysms once they have reached 55mm in diameter. This threshold has been suggested in international guidelines due to accelerated growth rates of aneurysms greater than 55mm in diameter, as well as randomised controlled trial evidence (UKSAT and ADAM trials) suggesting equivalent outcomes between continued surveillance and operative repair of medium sized (40-55mm) aneurysms just below this size threshold (19, 20). There is no trial evidence demonstrating a survival benefit for repair of a 55mm aneurysm as compared to continued surveillance. There have been calls for conducting such a trial (21), although it has also been suggested that personalised decision making taking into account a variety of factors may be more appropriate in the future, as compared to the development of population-based treatment indications using a single parameter such as aneurysm diameter (22).

The decision to electively repair a AAA on an individual basis assumes that the accepted risk of operative intervention does not exceed the estimated risk of death without surgery. This is a complex estimation that should take into account the risk of aneurysm rupture (based on diameter) at the time of surgery, the life expectancy of the patient taking into account their comorbidities, as well as likelihood of the patient surviving the physiological stress of either open or endovascular surgery (5). This is estimated using clinical judgement by an experienced treating team.

Currently, there are no predictive risk models in routine clinical use. The British Aneurysm Repair (BAR) Score developed using prospectively collected data from the National Vascular Database in the U.K (23) can predict overall mortality for a group of patients. It has been externally validated on a regional cohort from the North West of England and has demonstrated

encouraging discriminatory ability overall and between repair methods as compared to other proposed predictive models (24). It takes into account 11 preoperative clinical risk factors for perioperative mortality and was developed with the primary intention of aiding risk adjustment for in-hospital mortality outcome analyses (23). Its use has thus far been restricted to the research setting.

1.4 Treatment Options and Outcomes for the Repair of Standard Infrarenal AAAs

This section will detail treatment options and comparative outcomes for the management of infrarenal abdominal aortic aneurysms. These aneurysms are characterised by the presence of an infrarenal neck (Figure 1-3), of sufficient length and quality to undergo conventional aneurysm repair with either open or minimally invasive/endovascular techniques, as described below. The infrarenal neck refers to the segment of aorta between the renal arteries and the proximal extent of the AAA.

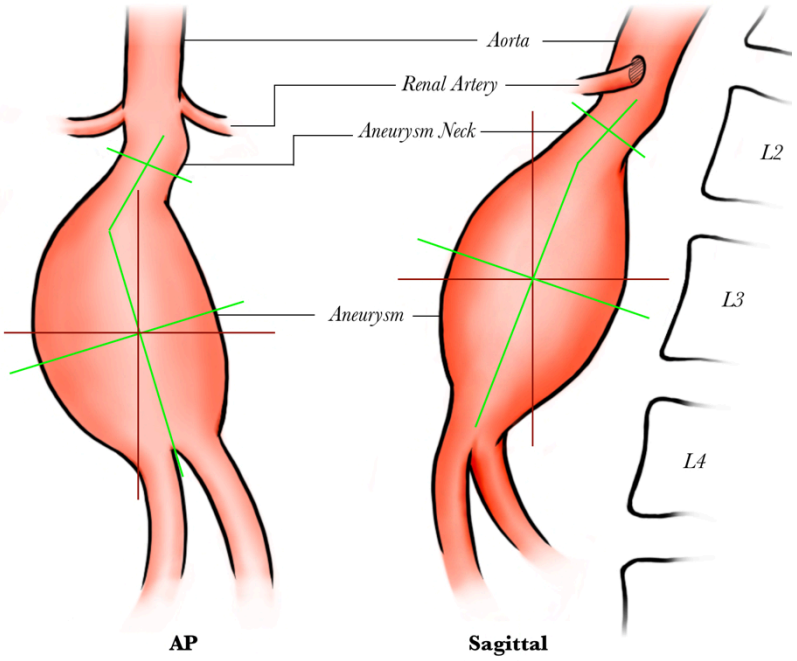


Figure 1-3 Morphology of a standard infrarenal AAA. The "neck" describes the aortic segment between the renal arteries and the aneurysm. Illustration by Dr Kitty Wong (Bristol, U.K.)

1.4.1 Open Repair of Infrarenal AAAs

Open surgery for the repair of standard abdominal aortic aneurysms, first described in 1952 (25), requires a laparotomy under general anaesthesia, which is a major operation involving incision

and access into the abdominal cavity. The aorta is accessed in the retroperitoneal compartment of the abdomen and blood flow through the aneurysmal segment of the aorta is temporarily controlled by clamp occlusion of the aorta and iliac arteries either side of the aneurysm. Standard infrarenal AAAs have an infrarenal neck that permits the placement of a proximal aortic clamp below the level of the renal arteries. This avoids visceral ischaemia during the operation. The aneurysmal segment of the aorta is then replaced with a polyester tube graft which is manually secured to native artery with a polypropylene suture (Figure 1-4).

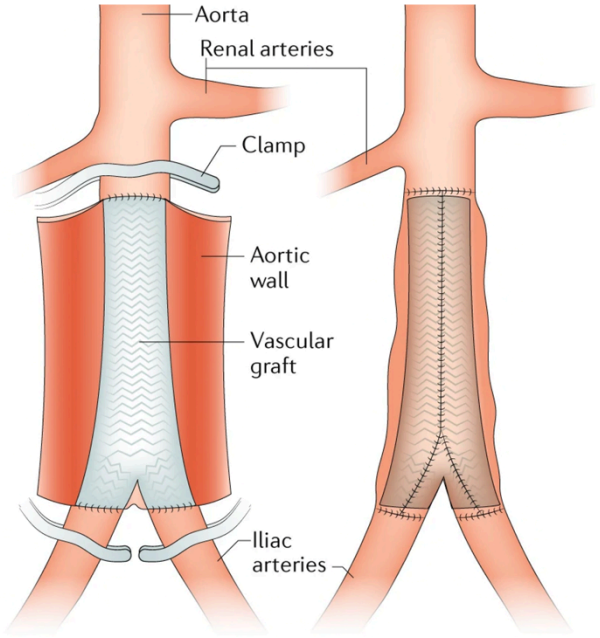


Figure 1-4 Open repair of a standard infrarenal abdominal aortic aneurysm (13)

The recovery from an open AAA repair requires organ support in an intensive care unit followed by a prolonged period of rehabilitation on the ward and in the community. In 2019, 1355 open repairs of infrarenal AAAs were logged on the National Vascular Registry (England, U.K.) (26), with a perioperative mortality rate of 2.3%, an average hospital stay of 7 days and a 30-day re-admission rate of 4.7%. The perioperative period for open repair also carries significant risk for the development of major complications. In the fittest tertile of patients from the Vascular Study Group of New England (VSGNE) database between 2003 and 2014, 126/476 (26.5%) patients developed postoperative complications including those of cardiac, renal, pulmonary and visceral ischaemic aetiology (27). There has been significant improvement in the mortality outcomes of open AAA repair in the U.K. over the last two decades: in a 2008 European audit (VASCUNET), the perioperative mortality rate after elective open AAA surgery was 7.9% (28). This improvement down to 2.3% in 2019 is likely a result of centralisation of services, as well as

more judicious case selection driven by an increase in popularity for alternative endovascular techniques.

For those individuals who survive the perioperative period, open repair of infrarenal AAA is an extremely durable operation. In the 15-year follow-up of patients undergoing open repair as part of the EVAR-1 randomised controlled trial, aneurysm-related mortality was only 0.9 per 100 person-years (29). All-cause mortality over the same period was 8.9 per 100 person-years, reflective of a co-morbid population who eventually succumb to death from cardiovascular disease and cancer, as opposed to their previously treated aneurysm. The re-intervention rate to the repaired aneurysm (reflective of aneurysm-related complications) was very low at 1.7 per 100 person-years over the 15-year follow up period, suggesting excellent durability. As a result of this, in the U.K., most patients can be discharged from follow-up with the treating team after a single post-operative clinic visit.

1.4.2 Endovascular Repair of Infrarenal AAAs (EVAR)

EVAR involves the placement of a stent-graft within the lumen of the aorta, with the intention of excluding the AAA from arterial blood flow. A stent-graft is a device made of a metallic nitinol stent component that serves to anchor the device in the artery, as well as provide structural support for the graft component. The graft component is usually woven polyester and serves to act as a conduit for blood flow (Figure 1-5).

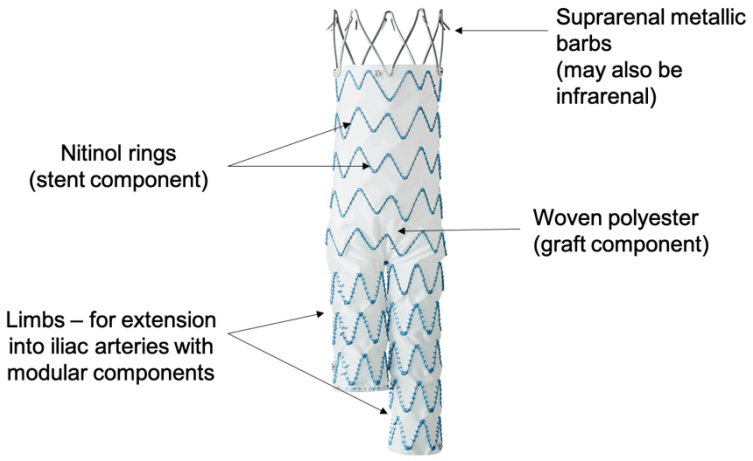


Figure 1-5 Main body of an EVAR stent graft (Medtronic Endurant II)

The stent-graft can be introduced percutaneously through access sites at the common femoral artery in both groins, is of a modular configuration and is deployed under fluoroscopic guidance.

Radial force exerted onto the aortic wall by the stent-graft, proximally in the infrarenal neck and distally in the iliac arteries, achieves a "seal" and this is dependent on careful sizing of the graft relative to the native artery (Figure 1-6).

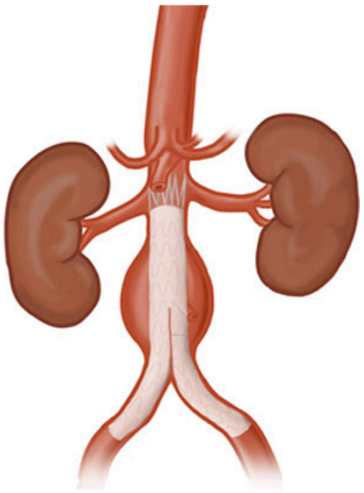


Figure 1-6 Position of EVAR stent graft in abdominal aorta

A successful seal allows blood to flow in continuity from the visceral aorta into the graft, out of the graft into the lower limb arterial tree and prevents transmission of blood pressure onto aneurysmal aortic wall, thereby preventing rupture. Often, metal barbs at the top of the fabric engage the aortic wall providing fixation. Fixation refers to stable positioning of the stent graft within the abdominal aorta, resisting "migration", and depending on the specific graft, fixation may be augmented in the suprarenal aorta by metallic barbs extending up from the graft, across the renal artery ostia (Figure 1-6).

Standard EVAR can be performed under local or general anaesthesia, does not require intensive care support for post-operative recovery in the vast majority of cases and is associated with short hospital stays. In 2019, 2090 standard EVAR procedures were logged on the National Vascular Registry (England, U.K.) (26), with a perioperative mortality rate of 0.4%, an average hospital stay of 2 days and a 30-day re-admission rate of 5.7%.

It is accepted that EVAR carries an appreciable risk of treatment failure in the medium to long term with a significant secondary intervention rate seen in multiple clinical trials. In the EVAR-1 (at 15 years), DREAM (at 6 years) and OVER (at 9 years) randomised controlled trials comparing open surgery with EVAR for standard infrarenal AAAs, re-intervention rates in the EVAR arms were 26% (29), 30% (30) and 20% (31) respectively.

The most common indication for re-intervention after EVAR is the presence of endoleak. This refers to continued flow within, and pressurisation of, the AAA despite the implantation of a stent graft. Type Ia (inadequate sealing at a proximal seal zone), type Ib (inadequate sealing at a distal seal zone), type IIIa (a disconnect and leak between two modular components) and type IIIb (a hole or defect in the stent graft material) are referred to as graft-related endoleaks and the subsequent high-pressure effect within the aneurysm can lead to rupture after EVAR. Type II endoleaks refer to back filling of the aneurysm through branches of the infrarenal aorta (most commonly the inferior mesenteric artery or lumbar arteries); these are largely considered benign due to low level pressurisation and subsequent negligible risk of rupture. Type IV endoleak refers to blood flow into the aneurysm through porous graft material and is largely a relic of older and now decommissioned stent grafts. Type V endoleak, also known as endotension refers to aneurysm expansion with no demonstrable leak on imaging, although it is accepted that the endoleak is either intermittent or simply not visualised on imaging.

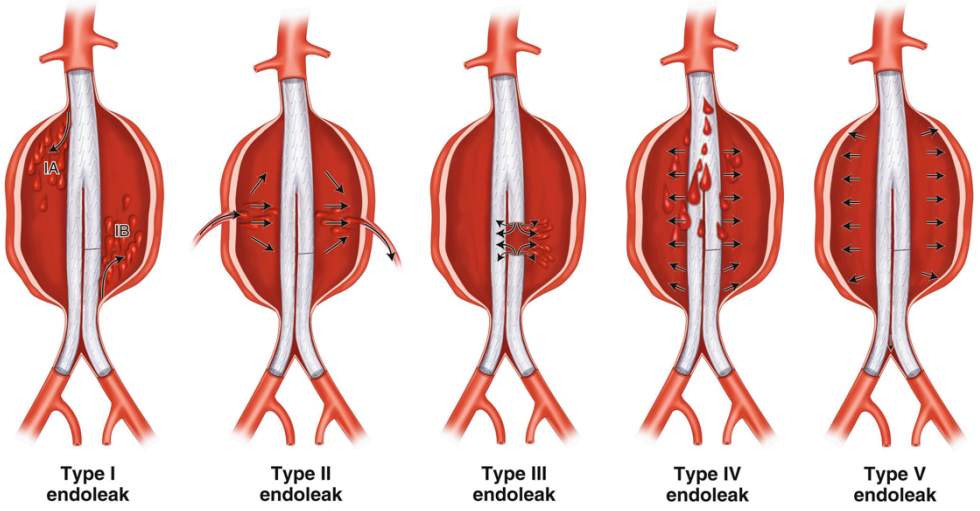


Figure 1-7 Classification of endoleaks after EVAR (3)

Other significant complications after EVAR include stent graft migration and effacement. Migration refers to positional displacement of the stent graft in relation to the proximal and/or distal sealing zones (distal displacement at the proximal sealing zone or proximal displacement at the distal sealing zone) by at least 5mm. Effacement refers to diameter increase of the native artery at a seal zone and thus a loss of sealing length without stent graft migration. Both migration and effacement can lead to type I endoleak and a subsequent increased risk of aneurysm rupture.

Patients who have undergone EVAR are therefore enrolled on a surveillance programme for life, with the aim of early detection of EVAR related complications, the need for reintervention, and ultimately to prevent secondary aneurysm rupture. This is now considered standard practice having been incorporated into international guidelines (5) and is commonly in the form of annual duplex ultrasound and/or computerised tomography (CT) scanning.

1.4.3 EVAR versus Open Surgery for Infrarenal AAAs

There have been 4 major randomised controlled trials (RCTs) comparing EVAR with open surgery for the repair of infrarenal AAAs: EVAR-1 (United Kingdom) (32), DREAM (The Netherlands/Belgium) (33), ACE (France) (34) and OVER (USA) (35). Across all 4 RCTs, 2800 patients were studied with recruitment undertaken between 1999 and 2008.

All 4 trials initially reported an intention to treat analysis for perioperative mortality rate. The trials demonstrated a statistically and clinically significant perioperative survival benefit with EVAR compared to open repair. Meta-analysis of these results has estimated a 40% (95% CI 0.22-0.74) reduction in odds of perioperative death with EVAR (36) (Figure 1-8).

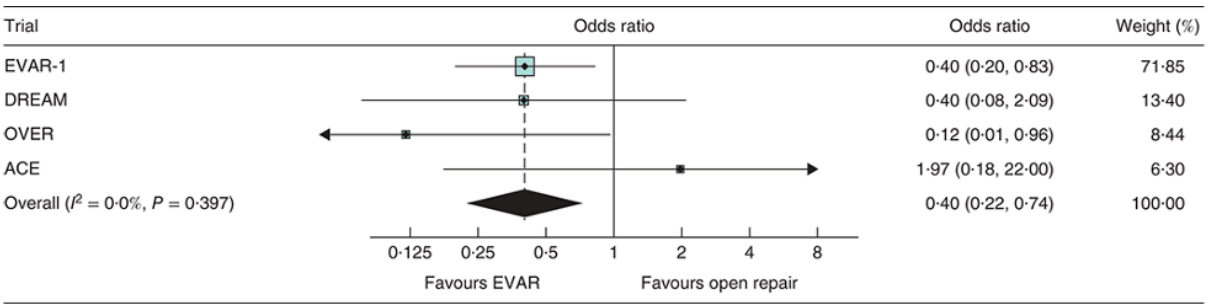


Figure 1-8 Forest plot of pooled odds ratio of perioperative mortality after EVAR or open repair of infrarenal AAA across four RCTs (36)

Rates of perioperative complications other than death were reported heterogeneously across the trials. Meta-analysis of RCT data combined with registry data has demonstrated equivalent rates of renal failure and stroke between EVAR and open surgery, but a higher rate of myocardial infarction after open surgery compared to EVAR (37). It has therefore been postulated that perioperative cardiac complications are a major driver for the observed perioperative mortality difference between open and EVAR (37).

It is this perioperative survival benefit that has propelled EVAR into being the most utilised treatment for the repair of infrarenal AAA. There is a tendency to reserve open surgery for the fittest patients only, whereas EVAR is utilised across a whole spectrum of patient fitness and is usually the only treatment option offered to the least fit patients. This is because endovascular techniques eliminate the need for laparotomy as well as aortic cross clamping which are considered to be the two main drivers of perioperative mortality and morbidity with open surgery.

Medium term follow-up was reported at different time points across the 4 RCTs: EVAR-1 at 4 and 8 years (38, 39), DREAM at 2 and 6 years (30, 40), ACE at 3 years (34) and OVER at 9 years (31). Meta-analysis of these medium-term data has demonstrated a loss of the perioperative survival benefit conferred by EVAR, within 3 years of randomisation. Categorisation of survival data into 6months-4years and >4year time periods showed equivalent all-cause mortality between EVAR and Open Surgery (Figure 1-9). 5-year mortality rate after either EVAR or Open Surgery is approximately 25% (36).

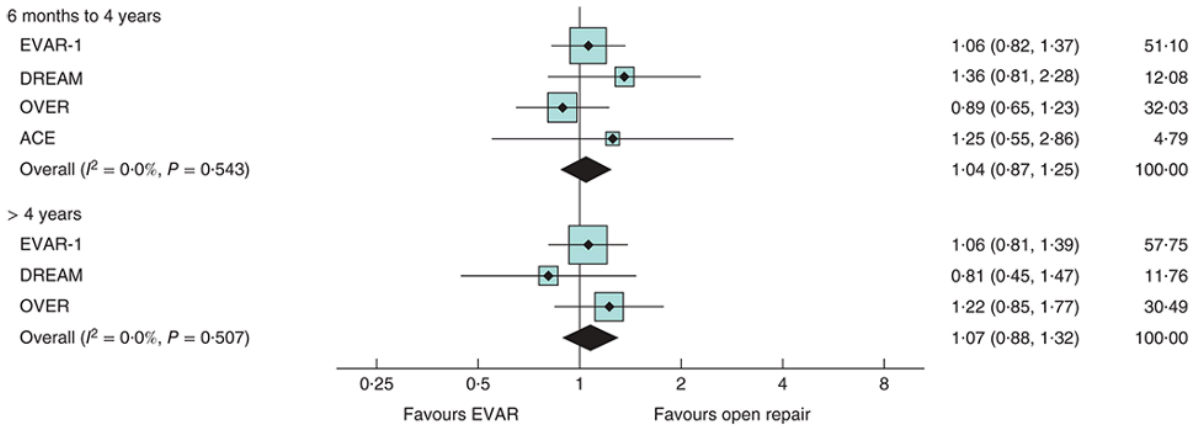


Figure 1-9 Forest plot of unadjusted hazard ratios for all-cause mortality at 6 months to 4 years and >4 years since randomisation in four randomised trials (36)

Aneurysm related mortality is a composite outcome measure of death within 30 days of a primary aneurysm repair, death within 30 days of a reintervention to a previously repaired aneurysm and death from any aneurysm related complication. The same meta-analysis of mid-term RCT data demonstrated a 44% reduction in aneurysm related mortality with EVAR compared to open surgery in the first 6 months after randomisation with a catch up by 3 years. After 3 years, there is a significant advantage to open surgery: 3 aneurysm related deaths/1054 patients as compared to 19/1096 for EVAR (HR 5.16, p=0.01) (36).

Reintervention rate has been shown to be higher after EVAR compared to open repair in the medium term. In a meta-analysis of combined RCT and registry data, there were 7005 reinterventions after 24219 EVARs compared to 6185 out of 24216 Open repairs (OR 2.08, p=0.003) (37), although complications and reinterventions were reported heterogeneously across trials. Of particular note, the OVER trial reported equivalent reintervention rates between the two arms (31), suggesting possible under-reporting in the other RCTs; in the EVAR-1 trial, incisional hernia repairs after open surgery were not included in the reintervention analysis. It is relevant to also note that reinterventions after EVAR in the earlier stages of the trial involved intervening on type II endoleaks which are now known to be largely benign and mostly managed conservatively. Furthermore, the trials utilised first generation stent grafts for EVAR, some of which have now been discontinued based on concerns surrounding durability.

Long-term comparative data are provided by 3 RCTs: EVAR-1 up to 15 years (29), DREAM up to 15 years (41) and OVER up to 14 years (42). Overall, all 3 trials demonstrated equivalent all-cause mortality between EVAR and Open surgery, up to the final follow-up study time points (Figure 1-10).

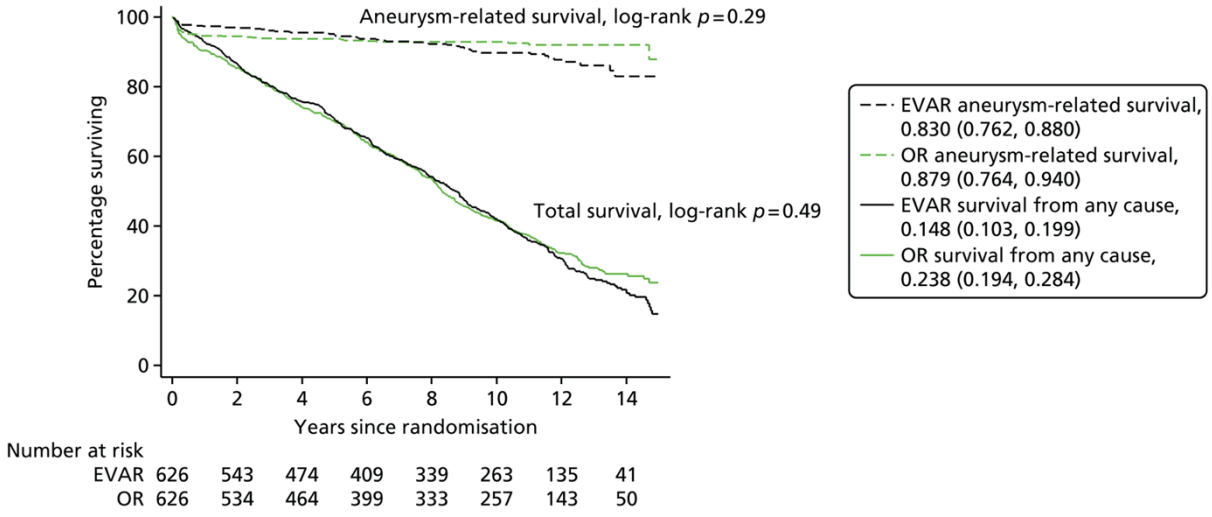


Figure 1-10 Kaplan-Meier estimates for total and aneurysm-related survival over a maximum of 15 years' follow-up in the EVAR-1 RCT (29)

In the EVAR-1 trial alone, late mortality after EVAR was higher than after open surgery in the subset of patients who were alive at 8 years. This was also the case for aneurysm-related mortality and was attributed to a higher rate of secondary aneurysm rupture in the EVAR group (29). This pattern was not seen in the DREAM or OVER trials, but in the UK led to calls to consider open

surgery as the primary treatment option for the elective repair of AAAs, especially in young patients (43).

Given the decrease in perioperative mortality associated with both techniques in recent years, the use of this outcome measure may be less discriminatory as a measure of patient outcome. In addition to this, given equivalent mid-term and longer-term survival rates between the two techniques, Quality of Life (QOL) difference may become an especially important factor in clinical decision making around the repair of AAA. The EVAR-1, DREAM and OVER randomised controlled trials assessed health-related quality of life (HRQL) differences between open surgery and EVAR as a secondary outcome measure. All 3 trials utilised the same generic scoring instruments of HRQL, namely the Medical Outcomes Study 36-Item Short Form Survey (SF-36) (44) and the EuroQol 5-Domain 3-Level score (EQ-5D-3L) (45). The EVAR-1 trial (38) demonstrated baseline pre-operative EQ-5D scores that were similar between open surgery and EVAR, and similar to age and sex-matched population controls. The post-operative HRQL results demonstrated lower EQ-5D weighted index scores for open surgery compared to EVAR in the first 3 months after randomisation, but equivalent scores at the 3-12 months and 12-24 months timepoints. The same pattern was seen for the physical component summary scores of the SF-36 system. There were no differences in the SF-36 mental component summary scores between the two treatments at any time point studied up to 2 years.

A systematic review on QoL differences between Open Surgery and EVAR concluded that there was a lack of good-quality data in the literature (46); there were no aneurysm repair-specific instruments used to measure QoL and multiple non-randomised studies contribute to heterogeneity in results. Also, studies tended to report HRQL as secondary outcome measures and use wide time intervals in which to report results (e.g. 3-12 months or 12-24 months). However, the review does accept that two randomised controlled trials, described as higher-quality studies, demonstrated worse QoL after Open Surgery than after EVAR in the first few weeks after intervention. In the longer term, most studies demonstrate no difference between the two techniques.

1.5 Anatomical Variation of AAAs and Complexity of the Aortic Neck

1.5.1 Defining Juxtarenal and Complex-Neck AAAs

The extensive comparative evidence described above, between Open Surgery and EVAR, relates to a specific group of patients: those with a "standard" anatomical profile to the AAA. The

anatomical complexity of a AAA largely relates to the infrarenal neck, the segment of aorta between the renal arteries and the proximal extent of the aneurysm (Figure 1-3). The neck is crucial for permitting repair by conventional methods, either through placement of an infrarenal clamp during Open Surgery or as a site for proximal sealing of a standard endograft in EVAR. To provide the optimal conditions for these standard interventions, the neck needs to be of adequate length and free from other adverse features, including angulation, conicality, thrombus load and calcification. An anatomical profile including any one of these adverse features to the infrarenal aortic segment would be described as a "complex-neck" AAA.

Traditional terminology regarding complex necks is largely descriptive, focuses on the proximal extent of the aneurysm alone and provides limited practical use: "infrarenal" describes an aneurysm with a "standard" neck, "juxtarenal" describes an aneurysm where the proximal extent is close to or up to the renal arteries (i.e. there is a short or absent neck), and "suprarenal" describes an aneurysm where there is no neck and the proximal extent is above the renal arteries and often involves the visceral branches of the abdominal aorta including the superior mesenteric artery (SMA) and coeliac artery (CA) (Figure 1-11). These descriptive terms are based on subjective interpretation of imaging appearances and stem from the pre-endovascular era, in which a surgeon would use such terminology to justify the need for an infrarenal, suprarenal or supravisceral aortic clamp level during open repair.

It should be noted that aneurysmal disease can also affect other segments of the aorta, namely in the chest (thoracic aortic aneurysms) or even concomitantly spanning the chest and abdominal cavities (thoracoabdominal aortic aneurysms). There is precedence for all aneurysms other than standard infrarenal aneurysms to be termed "complex aneurysms", i.e., pooling complex-neck aneurysms, juxtarenal aneurysms, thoracoabdominal aneurysms and thoracic aneurysms, such as in national reporting with the National Vascular Registry of England and Wales (26).

The focus of this body of work will however limit anatomical heterogeneity by focussing on juxtarenal and complex-neck AAAs alone, i.e. it will not include cases where the proximal extent of the AAA involves the superior mesenteric branch of the aorta in the abdomen.

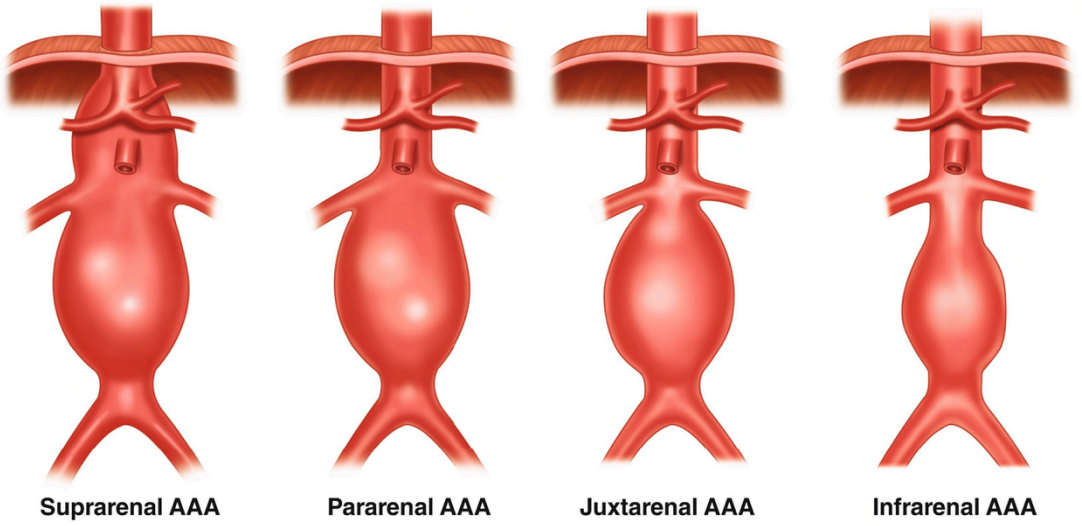


Figure 1-11 Descriptive definitions of complex AAAs with varied length or absence of an infrarenal neck (3)

There is no objective neck length criterion differentiating between the need for infrarenal vs suprarenal/supravisceral aortic clamping during open repair, although guidelines set by the European Society for Vascular Surgery have defined a short neck as being <10mm in length (5). This decision for level of clamp will be influenced by surgeon experience and by surrounding anatomy (for example, the willingness to retract/divide the left renal vein which often crosses the neck). Record-keeping is complicated by the fact that the clamp level can initially be placed proximally to allow neck dissection and then moved distally for formation of the proximal anastomosis.

In contrast to open repair, there are objective criteria regarding neck length guiding the suitability for EVAR. Stent graft manufacturers publish an "Instructions-for-use" (IFU) document for their EVAR devices detailing basic operational information, indications/contraindications, warnings/hazards, as well as detailing the precise conditions for which the device has been designed and under which it has been tested. The document provides both clinical and medico-legal contextualisation to the use of endovascular stent grafts. Infrarenal neck morphology is a core, but not sole, component of a stent graft's IFU, and neck length specifically is often the most important anatomical criterion cited in the document. IFU criteria for EVAR provide a pragmatic objective definition for neck complexity, such that neck morphology outside the IFU's anatomical parameters can be considered complex (Table 1-1) and repair of such complex-neck AAAs with standard EVAR is considered “off-label”.

Table 1-1 Anatomical parameters of the infrarenal neck as specified on the "instructions for use" (IFU) document of commonly used endografts.

Manufacturer	**Device Name**	**Neck length** *(definition of acceptability)*	**Neck diameter** (definition of acceptability)	**Alpha angle** *(definition of acceptability)*	**Beta angle** *(definition of acceptability)*	**Conicality** *(definition of unacceptability)*	**Thrombus load** *(definition of unacceptability)*	**Calcification** *(definition of unacceptability)*
Cook	Zenith Flex	≥15mm	18-32mm	<45°	<60°	>10% diameter increase over 15mm	circumferential	circumferential or irregular
Cook	Zenith Alpha	≥15mm	18-32mm	<45°	<60°	>10% diameter increase over 15mm	circumferential	circumferential or irregular
Medtronic	Endurant II	≥10mm (if beta angle ≤60° and if alpha angle ≤45°) OR ≥15mm (if beta angle ≤75° and if alpha angle ≤60°)	19-32mm	≤45° or ≤60° (see neck length)	≤60° or ≤75° (see neck length)	>4mm diameter increase over 10mm	>25% circumference	significant
Gore	Excluder	≥15mm	19-32mm	n/a	≤60°	n/a	≥2mm thickness and/or ≥25% of circumference	irregular
Endologix	Ovation iX	n/a	16-30mm at a point 13mm below lowest renal artery	n/a	≤60° if neck length ≥10mm OR	n/a	significant	significant or irregular

					≤45° if neck length <10mm			
Endologix	AFX	≥15mm	18-32mm	n/a	≤60°	n/a	significant	significant or irregular
Endologix	Nellix (2016)	≥10mm	18-28mm	n/a	≤60°	n/a	significant	significant or irregular
Terumo Aortic	Anaconda	≥15mm	17.5-31mm	n/a	≤90°	n/a	significant	significant
Terumo Aortic	Treo	≥15mm	17-32mm	≤45°	≤60°	>10% diameter increase over 15mm OR >7% over 10mm	significant or circumferential	significant or circumferential
Lombard	Altura	≥15mm	18-28mm	n/a	≤60°	n/a	irregular or circumferential	irregular or circumferential
Lombard	Aorfix	≥15mm	19-29mm	n/a	≤90°	≥5mm diameter increase over 15mm	irregular	irregular
Cardinal Health (Cordis)	Incraft	≥10mm	17-31mm	≤60°	≤60°	>10% diameter increase over 10mm	>25% circumference	irregular

1.5.2 Adverse Morphological Characteristics of the Infrarenal Neck

Neck length is defined as the distance between the lower most major renal artery and the proximal extent of the abdominal aortic aneurysm (Figure 1-12). There is no consensus on what constitutes the most proximal extent of a AAA; however, it may refer to the abrupt point of change in diameter along the aorta, or where the aorta becomes >30mm in diameter. The IFUs of the most widely utilised standard stent grafts generally specify an acceptable neck length of 10 or 15mm (Table 1-1).

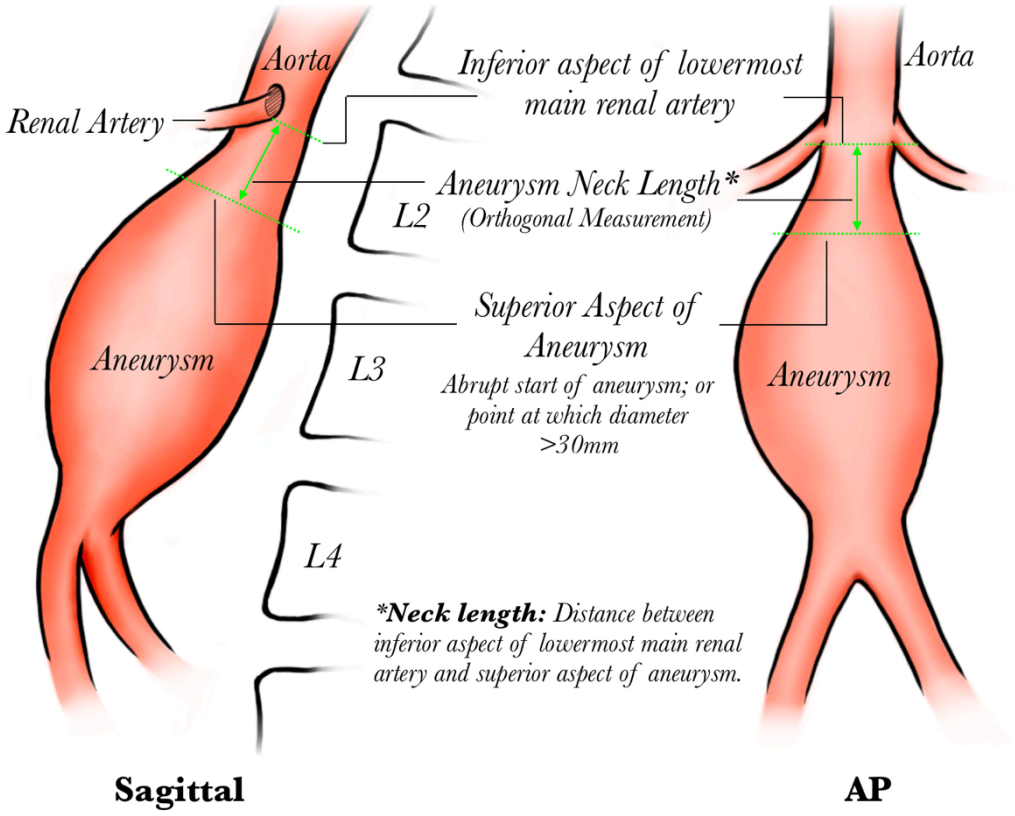


Figure 1-12 Diagrammatic representation of infrarenal neck length (the distance between the lowermost main renal artery and the superior aspect of the aneurysm). Illustration by Dr Kitty Wong (Bristol, U.K.).

Beta (β) angulation refers to the angle between the infrarenal neck and the long axis of the aneurysm (Figure 1-13). A necessary beta angle of less than 60 degrees is commonly stipulated in EVAR IFUs, although certain grafts allow for beta angulation up to 90 degrees (Table 1-1).

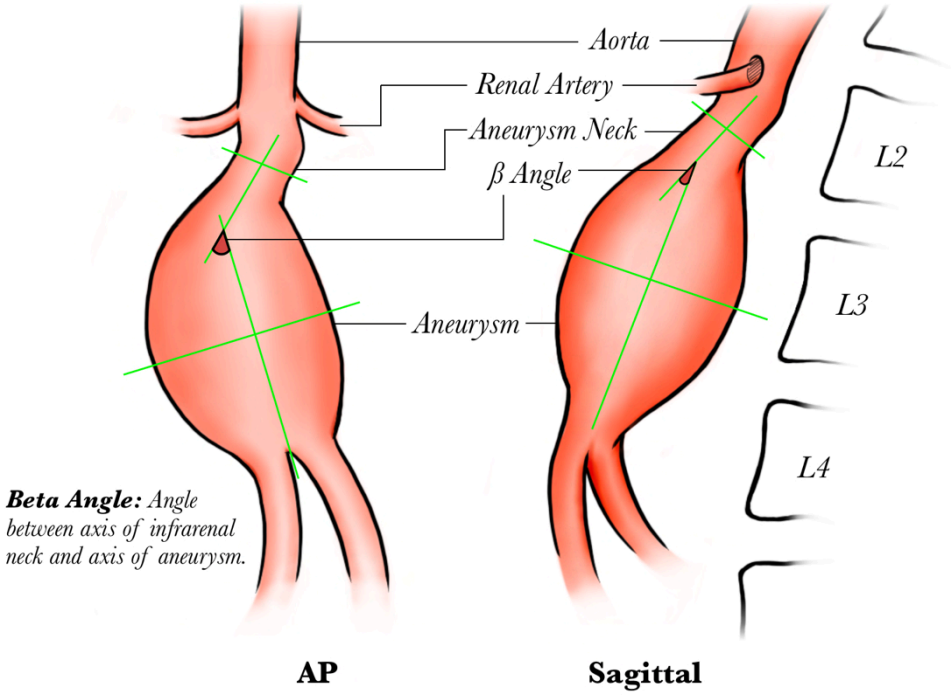


Figure 1-13 Diagrammatic representation of beta (β) angulation (the angle in degrees between the axis of the infrarenal neck and the axis of the aneurysm). Illustration by Dr Kitty Wong (Bristol, U.K.).

Alpha (α) angulation refers to the angle between the suprarenal aorta and the infrarenal neck (Figure 1-14). A necessary alpha angle of less than 45 degrees is a standard prerequisite for grafts with suprarenal fixation (Table 1-1) but is less clinically relevant for stent grafts which do not have components in the suprarenal aorta.

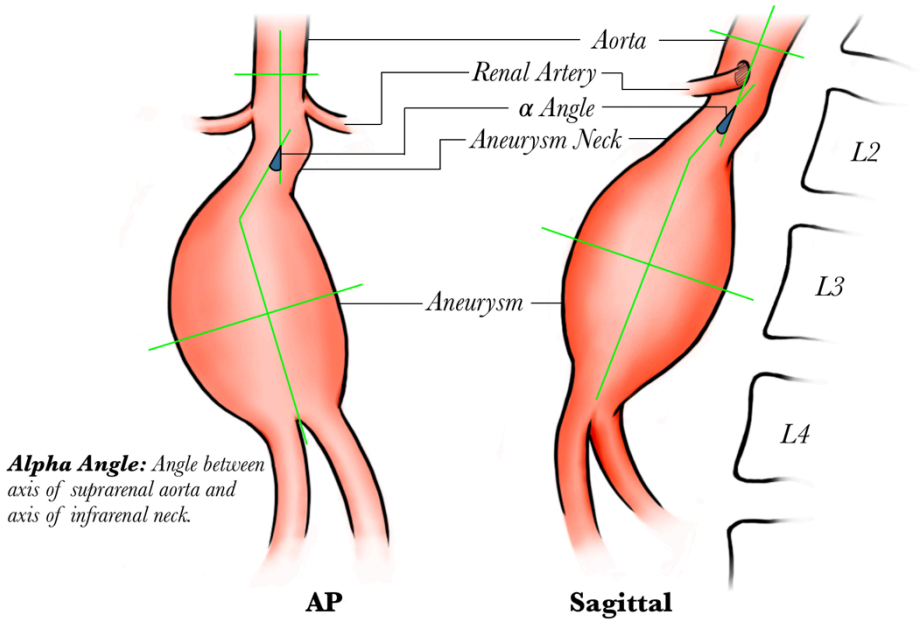


Figure 1-14 Diagrammatic representation of alpha (α) angulation (the angle in degrees between the axis of the suprarenal aorta and the axis of the infrarenal neck). Illustration by Dr Kitty Wong (Bristol, U.K.).

Acceptable maximum neck diameter is a contentious issue. It is widely accepted that the upper limit of normal for the diameter of the abdominal aorta is 30mm (5). It would therefore be logical to designate infrarenal neck diameters larger than this as an adverse neck feature. Yet, the majority of standard endovascular stent grafts "permit" on-label repair with EVAR for diameters up to 32mm (Table 1-1). Therefore, for a small subset of aneurysms with neck diameters between 30 and 32mm, where is no consensus on whether the anatomy is adverse or not. Additionally, there is a requirement for the neck diameter to be uniform down its length, i.e., the neck to be parallel-sided. A neck with increasing diameter down its length is described as conical or trapezoidal (Figure 1-15). The majority of IFU documents would define a conical neck as one in which the diameter increases by more than 10% along the first 15mm of neck (Table 1-1).

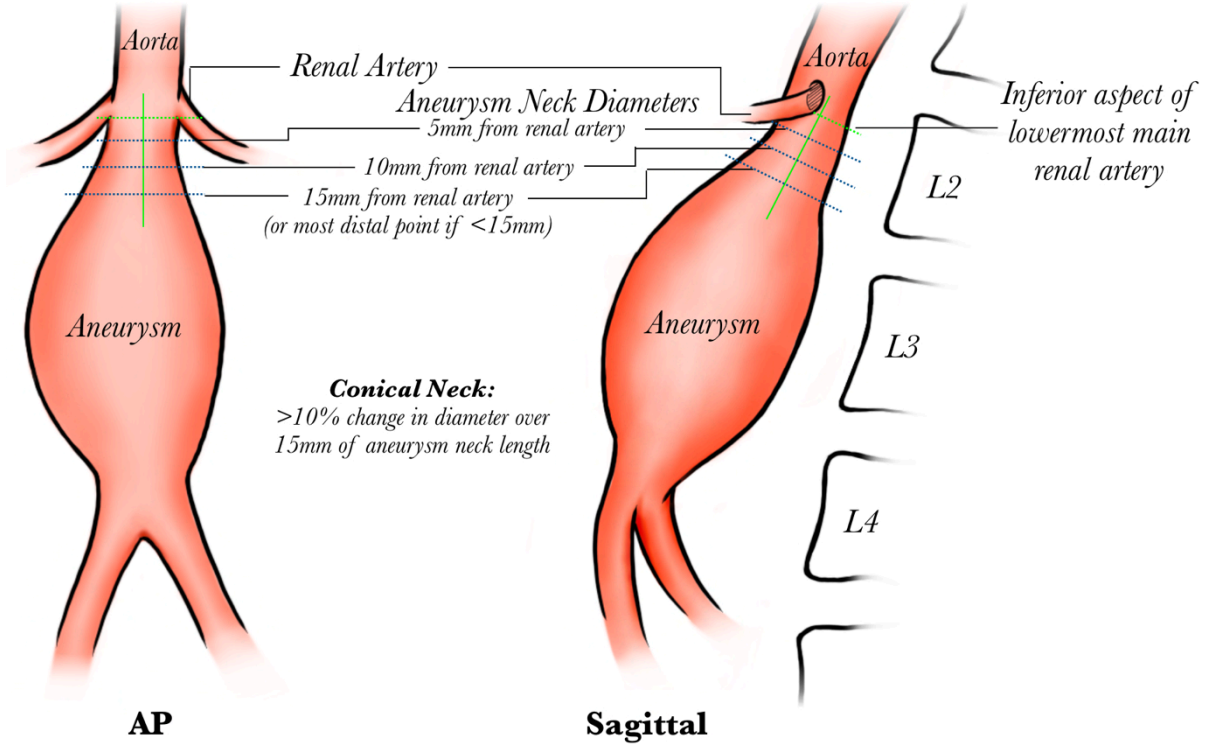


Figure 1-15 Diagrammatic representation of conicality: a significant increase, commonly cited as 10%, in the diameter of the infrarenal neck along its length. Illustration by Dr Kitty Wong (Bristol, U.K.).

Thrombus and calcification within the infrarenal neck must be within acceptable limits according to the IFUs of stent grafts. The definition of acceptability is rarely quantitative and often refers to a "significant" burden or "irregular" morphology (Table 1-1). Thrombus and calcification morphologically affect the infrarenal neck in similar ways: either by lining and affecting a variable proportion of the circumference and/or by protruding into the lumen and reducing luminal cross-sectional area (Figure 1-16).

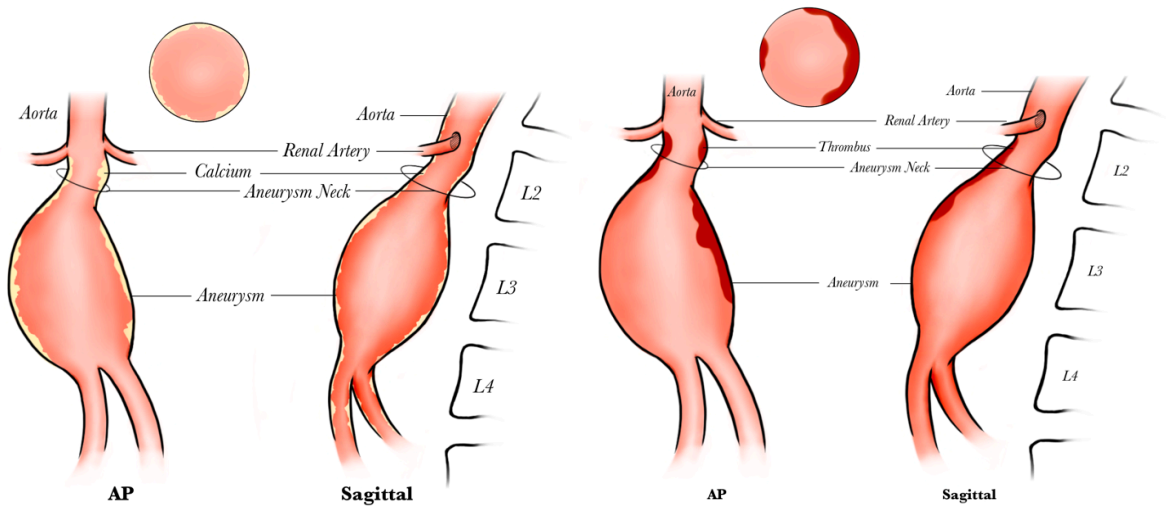


Figure 1-16 Diagrammatic representation of thrombus and calcification within the infrarenal neck. Illustration by Dr Kitty Wong (Bristol, U.K.).

In the literature, cases of AAA with adverse infrarenal neck anatomy have often been referred to as having a "hostile neck". It has been demonstrated that between 40% and 60% of all AAAs have hostile neck morphology that precludes on-label use of standard EVAR (47-49).

Relying on graft manufacturers to define complex anatomical profiles (through the IFU document) requires caution. The IFU parameters are not decided upon through the analysis of long-term in-vivo data but rather in-vitro testing of the device, and therefore on a theoretical basis for clinical efficacy. Furthermore, what constitutes complex neck anatomy varies between graft manufacturers, even when the stent grafts themselves are extremely similar in construct and material. This poses an issue in that certain anatomical profiles may be complex if used with a certain device, but not with others. It would therefore be safer to consider a complex-neck AAA to be one that is off-label for all modern stent-grafts. Lastly, IFU requirements have become less stringent over time as technology advances. Now, there are devices on the market which "permit" implantation in necks as short as 10mm (as opposed to 15mm for earlier generation stent grafts) and in necks with up to 90 degrees of beta angulation (as opposed to 60 degrees for earlier generation stent grafts). These criteria are further relaxed if the proximal seal zone is reinforced with adjuncts as will be described in a later section. There is the potential that a complex-neck AAA by modern day standards could be considered "standard" anatomy in the future.

There is one report in the literature of a group in Italy attempting to generate an expert consensus on what constitutes a complex-neck profile, through Delphi methodology (48). They concluded that a neck length threshold of 10mm was the most important (red category) anatomical parameter to consider when performing infrarenal EVAR. A neck diameter threshold of 28mm and beta angulation of 60 degrees were considered the next most important factors (orange category). Interestingly, calcification affecting >50% of the neck circumference and conical neck were not considered factors precluding safe conduct of standard EVAR if present alone, but if present together, then the authors concluded that infrarenal EVAR should not be undertaken. Ultimately, there is no international consensus on what constitutes a complex-neck and so the IFUs of stent grafts provide the only pragmatic definitions.

1.6 Treatment Options for the Repair of Juxtarenal and Other Complex-Neck AAAs

The principles for repairing juxtarenal and complex-neck AAAs are the same as for standard infrarenal AAAs. The aneurysm requires exclusion from arterial flow and pressure, and this can be achieved either by open surgery or endovascular techniques. However, the fact that the infrarenal aorta may be absent or suffering from adverse morphology means that technical aspects to standard repair strategies require modification.

1.6.1 Open Repair of Juxtarenal and Complex-Neck AAAs

Open repair is modified to potentially involve placement of a clamp above the level of the renal arteries. The clamp may be above the level of the renal arteries (suprarenal), above the level of the SMA (supramesenteric) or above the level of the CA (supracoeliac). The surgical approach may be similar to that of a standard AAA repair, in that the operation may involve a midline laparotomy and transperitoneal approach (through the main abdominal cavity from front to back). Alternatively, a complex AAA repair may involve a modified approach through the retroperitoneum (avoiding the main abdominal cavity contents with approach from the flank), with resection of ribs as required. It should be noted that clinically, infrarenal clamp position is influenced more by neck length than other adverse features. For example, a conical or angulated neck would likely still be repaired with infrarenal clamping given adequate neck length. However, insufficient neck length to accommodate an infrarenal clamp, regardless of the presence or absence of other adverse features, would require a more proximal clamp position.

Ultimately, the morbidity and mortality following open surgery for juxtarenal and complex-neck AAAs exceeds that of standard infrarenal AAAs and is presumably due to the more proximal clamp positions utilised. It has been demonstrated from registry data that the more proximal the clamp position, the worse the outcomes in terms of perioperative complication rates including acute kidney injury (supracoeliac clamp 12% vs suprarenal clamp 6%) as well as mortality (supracoeliac clamp 8% vs suprarenal clamp 2.8%) (50).

1.6.2 Endovascular Repair of Juxtarenal and Complex-Neck AAAs

Standard EVAR is unsuitable in cases with adverse infrarenal neck morphology, as stipulated by the manufacturer's IFU document. However, this off-label use of EVAR is still performed frequently around the world. Drivers for this practice include no alternative endovascular technology or expertise being available to certain vascular centres and, in the case of patients being unfit for the physiological stress of open repair, a hesitancy on the part of practitioners and patients to treat large aneurysms conservatively. Utilising an off-the-shelf EVAR stent-graft off-label is also cheaper than alternative endovascular options. It is known that implantation of standard EVAR stent grafts into complex necks (i.e., cases that are off-label with regards to neck anatomy) is associated with poor early and long-term outcomes, including higher rates of type I endoleak and mortality, as compared to EVAR used within the constraints of IFU (51-56). The mechanisms for this are likely to be a loss of adequate seal in the infrarenal neck and/or distal migration of the stent graft. Therefore, several distinct treatment options exist for the repair of complex cases, that compensate for the lack of an adequate infrarenal aortic neck.

Fenestrated EVAR (FEVAR) is a stent graft-based technology, first described in 1999 nearly a decade after the first standard infrarenal EVAR. It involves placement of a stent-graft up into the suprarenal aorta, as opposed to below the renal arteries in the case of standard EVAR. This allows adequate sealing and fixation in a segment of aorta that is healthier than the infrarenal neck. Fenestrations in the main body of the stent graft permit adjunctive stenting into the visceral vessels (renal arteries, SMA and CA) enabling continued perfusion of the abdominal organs while maintaining exclusion of the AAA from the arterial circulation (Figure 1-17). Due to the variable positioning of visceral aortic branches in native anatomy, the fenestrated stent graft is customised to the patient's pre-operative CT scan.

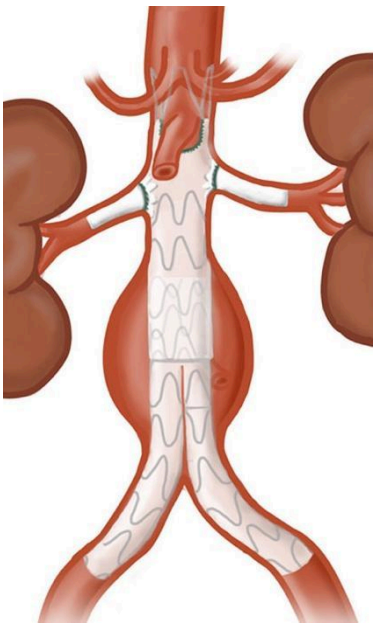


Figure 1-17 - Configuration of a fenestrated endovascular stent-graft (57).

Over time, as experience with FEVAR has increased, the complexity of FEVAR configurations being utilised has also increased. Initial experiences were almost universally limited to fenestrations at the renal artery level only. However, with time the superior mesenteric artery and coeliac artery are increasingly being stented as standard. The justification for moving more proximally in the aorta is to seal the stent graft in a length of aorta that is a) longer and b) healthier than peri-aneurysmal aorta (Figure 1-18).

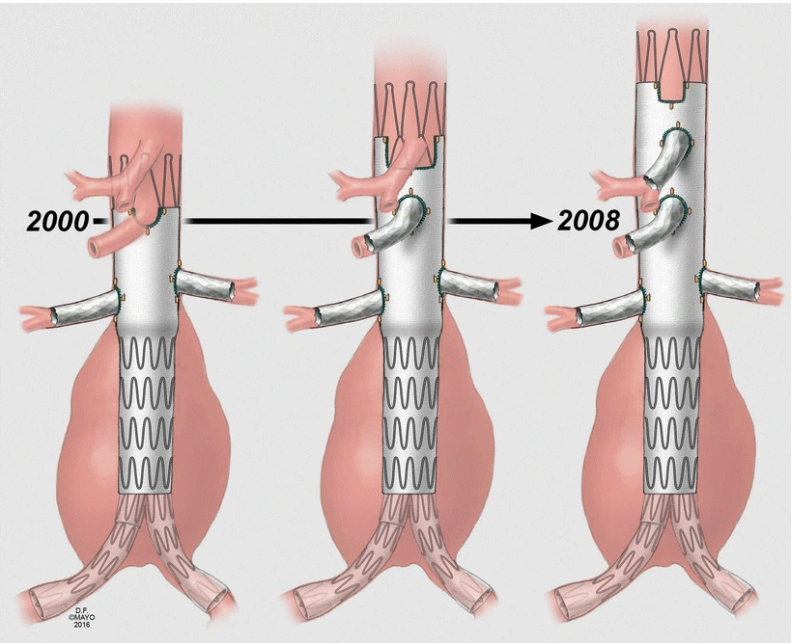


Figure 1-18 The evolution of FEVAR over time, from early 2-fenestrated devices to more contemporary 4-fenestrated devices (58).

The more complicated configurations of FEVAR are performed with the intention to maximise durability with a more secure proximal seal zone. However, these more complicated operations entail longer procedural times, more radiation exposure to the patient and operator, and evidence fails to consistently demonstrate short or long term benefit with regards to durability, compared to less complicated configurations (59-61). It should be noted that 4-vessel FEVAR is not a comparable alternative to 2-vessel FEVAR for most patients, in that the proximal extent of a FEVAR stent-graft will be dictated by anatomical considerations such as the degree of inter-vessel separation (the distance between renal arteries, SMA and CA), as opposed to operator preference.

Possible complications after FEVAR are similar to those described for standard EVAR. However, there is increased risk for visceral organ ischaemia if bridging stents lose patency. Additionally, there is the potential for endoleaks to occur at sites specific to FEVAR: these can arise from disconnection of the bridging stents from the fenestration of the main body (type IIIa), or from loss of seal between the bridging stent and the native aortic branch (type Ic).

Early experience of FEVAR in the U.K. (practice between 2007 and 2010) was described in the GLOBALSTAR Registry report (59); In 318 patients across 14 centres, perioperative mortality was 4.1%, perioperative reintervention rate was 7%, late reintervention rate at 3 years was 30% and bridging stent loss of patency at 3 years was 15%. Interestingly, more contemporaneous reports demonstrate similar perioperative outcomes. In a Vascular Quality Initiative (VQI) database study from the USA, 4424 patients under the age of 80 who underwent FEVAR between 2010 and 2019 suffered a perioperative mortality rate of 5% (62).

Durability of endovascular techniques in the long term is increasingly being recognised as a more important marker of success, as opposed to any perioperative outcome measure. With respect to this, reintervention rates and loss of target vessel patency are of paramount importance when evaluating the success of FEVAR. In 2018, a meta-analysis exploring this theme, across 7 studies and 772 patients, demonstrated a reintervention rate of 24% at 4 years and a target vessel loss of patency rate of 12% at the same time point (63). It is therefore likely that FEVAR for the repair of complex AAA generates the same concerns regarding long-term durability as standard EVAR after the repair of infrarenal AAA.

Standard EVAR can be adapted with the use of adjuncts to generate a more robust proximal seal and fixation. Firstly, endoluminal screws reinforce the fixation and seal in the infrarenal neck by increasing the apposition between the stent-graft and the native aortic wall. They are introduced via a catheter passed up through the lumen of the stent graft and a motorised mechanism places small screws through the fabric of the stent graft and into the aortic wall. They are placed in a radial distribution around the aortic neck (Figure 1-19).

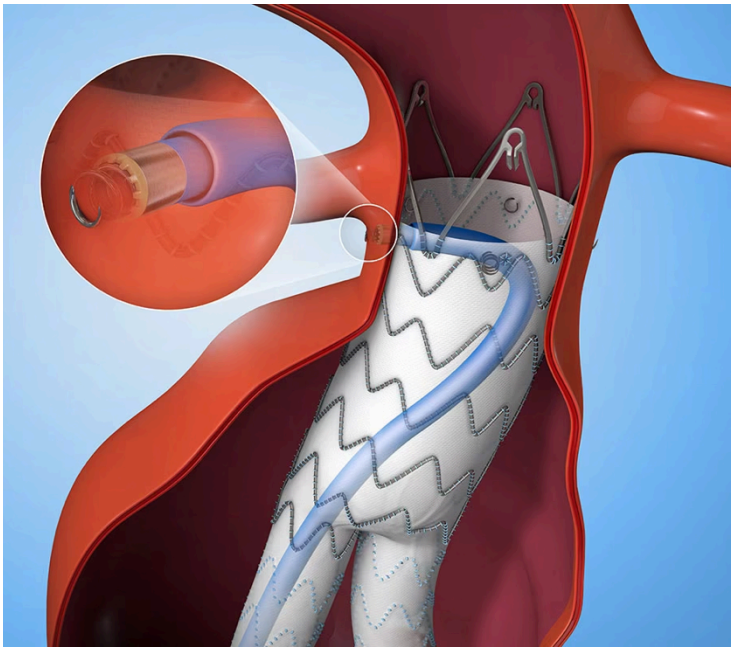


Figure 1-19 Graphic demonstrating the placement of endoluminal screws into a stent-graft at the proximal seal zone [accessed at www.europe.medtronic.com on 08/04/2023].

Although initially used to treat type 1a endoleaks and cases of stent graft migration, there has been increasing popularity for using the technology prophylactically in cases of adverse infrarenal neck anatomy. In this context, the ANCHOR registry reported on 73 patients in the USA and Europe up to 1 year of follow-up. The authors demonstrated a freedom from type 1a endoleak of 95% and reported no cases of significant post-EVAR aneurysm expansion (64). In a propensity-based study comparing EVAR cases with and without endoluminal screws, there was no difference in the rates of type 1a endoleak, effacement or sac expansion at 2 years. However, the endoluminal screws group had a significantly greater incidence of sac regression (81% vs 48%) which is a marker of successful aneurysm exclusion (65).

Given that this is the newest of endovascular options for the repair of complex-neck aneurysms, there is limited medium- or long-term follow-up data around its use. Only one study has provided outcomes for endoluminal screws up to 5 years, in a propensity-based comparison

between EVAR with (n=96) and without (n=96) screws for complex neck AAAs. The authors concluded that more patients achieved sac regression with the use of screws compared to without (59% vs 32%). There were no differences in overall or aneurysm related mortality during follow-up. Further data in the long-term is awaited for what is a novel technology.

Chimney EVAR (ChEVAR), also known as snorkel or parallel graft EVAR, is a further example of EVAR employing the use of adjuncts to maximise proximal sealing length. The snorkel or chimney refers to an off-the-shelf stent deployed into visceral branches of the aorta, from a parallel course adjacent to the main aortic stent-graft which seals in the visceral segment of the abdominal aorta (Figure 1-20).

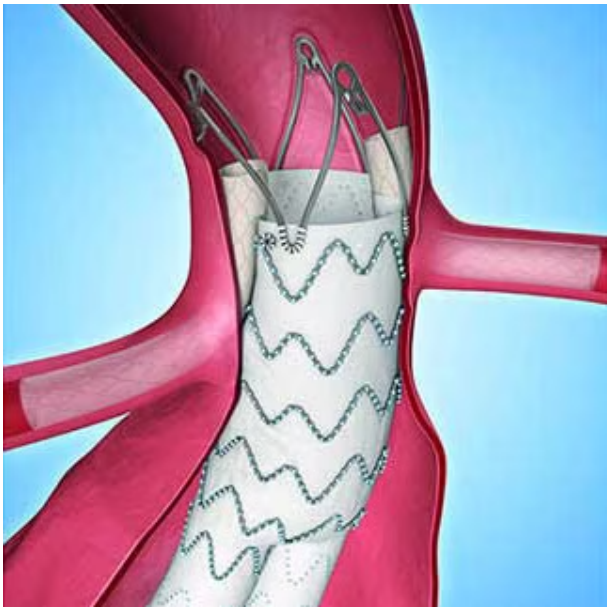


Figure 1-20 Graphic demonstrating Chimney EVAR (ChEVAR) with 2 parallel chimneys alongside the main stent-graft in the visceral aorta [accessed at www.medtronic.com on 08/04/2023].

Although initially an endovascular technique developed to tackle inadvertent coverage of visceral vessel ostia during standard EVAR or for emergencies in general, its use has now expanded to include primary repair of juxtarenal aneurysms. The largest case series reporting on outcomes for ChEVAR is the "PERformance of the chimney technique for the treatment of Complex aortic pathoLogiES" (PERICLES) Registry. Although the majority of cases in the registry were primary aneurysm repairs (78%), there was inclusion of treatment for type 1a endoleak, para-anastamotic aneurysms following open surgery as well as thoracoabdominal aortic aneurysms. Reporting on 517 patients across USA and Europe, 30-day mortality for elective ChEVAR was 3.7% and late mortality at 17 months was 15.5%. Chimney patency at this time point was 94% and

reintervention rate was 6.6% (66). 5 year estimated survival was 66% and in those surviving beyond 30 months, primary chimney patency was 90% at 5 years. It was found that absence of infrarenal neck and large neck diameter were adverse features significantly associated with long-term device-related complications (67).

It is clear from the published outcomes of these different treatments that the perioperative risks are significantly greater for juxtarenal/complex-neck AAAs than for cases of standard infrarenal AAA, across all treatment modalities. Furthermore, long-term durability has not been established for these techniques. There are no RCTs comparing these treatment options in the short nor long-term and there is a pressing need for further research in this area.

1.7 Hypotheses and Aims

The topic of this thesis will be comparing clinical outcomes between the different treatment options for the repair of juxtarenal and other complex-neck aneurysms. This will be through existing evidence in the literature as well as an original research study conducted on a national scale. The hypotheses and aims are as follows:

Hypothesis 1:
The existing evidence underpinning the practice of repairing juxtarenal and complex-neck AAAs is of poor quality.
Aim 1:
To critically appraise and summarise the published comparative evidence between different treatment options for the repair of juxtarenal and complex-neck AAAs.

Hypothesis 2:
According to existing evidence, endovascular techniques are safer in the perioperative period compared to open surgery for the repair of juxtarenal and complex-neck AAAs.
Aim 2: To compare perioperative safety between different treatment options for the repair of juxtarenal and complex-neck AAAs, as reported in published literature.

Hypothesis 3:
According to existing evidence, endovascular techniques confer equivalent mid-term efficacy to open surgery for the repair of juxtarenal and complex-neck AAAs but are associated with greater re-interventions and cost.

Aim 3: To compare medium term comparative outcomes between different treatment options for the repair of juxtarenal and complex-neck AAAs, as reported in published literature.

Hypothesis 4:

According to existing evidence, fenestrated EVAR provides greater long-term efficacy compared to other endovascular techniques for the repair of juxtarenal and complex-neck AAAs.

Aim 4: To compare long-term comparative outcomes between different endovascular treatment options for the repair of juxtarenal and complex-neck AAAs, as reported in published literature.

Hypothesis 5:

When identifying complex aortic neck morphology on a pre-operative computerised tomographic (CT) scan, utilising a pre-designed measurement protocol can produce acceptable inter-rater consistency and accuracy.

Aim 5: To design and validate the use of a measurement protocol for the assessment of complex-neck morphology on pre-operative CT scan in a "Corelab" setting.

Hypothesis 6:

Capturing all cases of complex neck morphology from a wider population of AAA repairs in England over a 2-year period is feasible using a validated measurement protocol in a "Corelab" setting. Additionally, that there are as many AAAs repaired in England with complex-neck morphology as there as standard cases.

Aim 6: To objectively assess and characterise neck morphology for all cases of juxtarenal and complex-neck AAA that were repaired in England over a 2-year period.

Hypothesis 7:

When adjusting for A) anatomical variation between different subtypes of neck complexity, and B) confounding from variation in physiological risk between groups undergoing different methods of repair, endovascular techniques confer a perioperative safety benefit over open surgery for the repair of juxtarenal and complex-neck AAAs.

Aim 7:

To compare the perioperative safety profile of different treatment options for the repair of juxtarenal and complex-neck AAAs across England, with statistical correction for baseline indication biases.

Hypothesis 8:

When adjusting for A) anatomical variation between different subtypes of neck complexity, and B) confounding from variation in physiological risk between groups undergoing different methods of repair, FEVAR is associated with equivalent mid-term efficacy to open surgery for the repair of juxtarenal and complex-neck AAAs.

Aim 8:

To compare the mid-term effectiveness of different treatment options for the repair of juxtarenal and complex-neck AAAs across England, with statistical correction for baseline indication biases.

2 A Systematic Review and Network Meta-Analysis of Comparative Outcomes Between Different Treatments For Juxtarenal And Complex-Neck Abdominal Aortic Aneurysms

2.1 Introduction

Repair of complex abdominal aortic aneurysms (AAA) carries a greater risk of perioperative death, complications (26, 68) and higher costs (68) compared to that of infrarenal AAA. Aneurysm complexity is predominantly determined by the length and quality of the infrarenal neck, although what exactly constitutes neck complexity is contentious. Endovascular aneurysm repair (EVAR) has provided to a pragmatic definition of neck complexity utilising objective criteria of a stent-graft's "Instructions-for-use" (IFU) document. This is the clinically relevant definition used by United Kingdom's National Institute for Health and Care Excellence (NICE)(43).

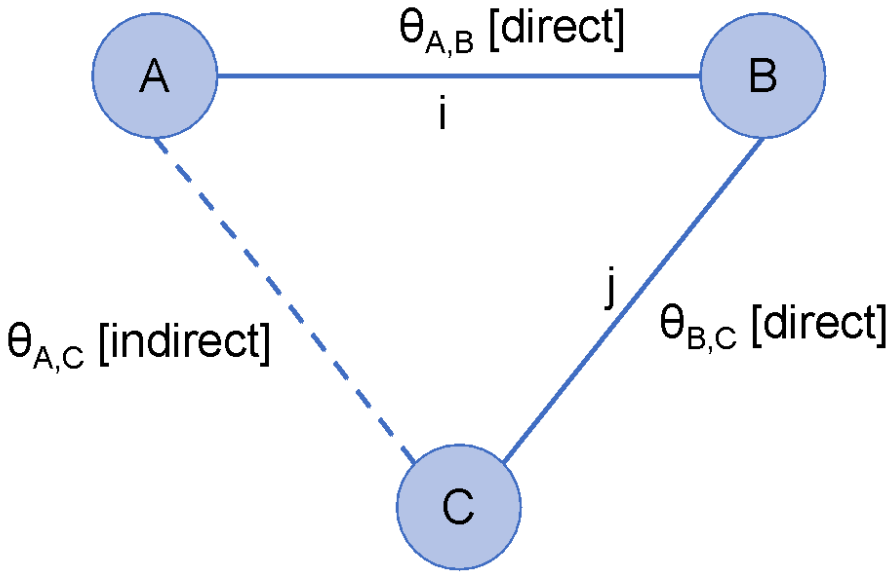
Using real-world IFU criteria, up to 60% percent of all AAAs are complex (69). This is predominantly based on neck length of <10-15mm (juxtarenal/pararenal aneurysms) but also takes into consideration other adverse morphological features including angulation, conicality, large diameter and excessive calcification or thrombus.

Techniques for repairing complex AAAs currently include Open Surgical Repair (OSR) and various endovascular options. OSR involves application of an aortic occlusion clamp at various levels. On-label endovascular techniques include fenestrated endovascular aneurysm repair (FEVAR) and EVAR with adjunctive measures such as chimney stent-grafts (ChEVAR) or endoluminal screws. Off-label EVAR (EVAR used outside the constraints of IFU) is also used widely to treat complex AAAs and should be evaluated as a distinct modality.

Existing reviews and meta-analyses on this topic typically use pooled case series of single techniques, comparisons are largely limited to OSR and FEVAR, or group all endovascular treatments for comparison with OSR (70-73). Additionally, studies often combine juxtarenal aneurysms, those with adverse neck features, thoracoabdominal aortic aneurysms (TAAAs) and aneurysms of the visceral aorta, resulting in significant anatomical heterogeneity.

In a Network Meta-analysis (NMA), data from multiple separate comparisons are pooled to derive multiple inter-connected comparisons of more than two treatments. NMA also allows

ranking of multiple interventions. Analyses combine aggregate-level pairwise comparisons and infer treatment effects for pairwise comparisons that have not been directly compared. This is demonstrated in Figure 2-1.



$$\theta_{A,C}\,[\text{indirect}] = \theta_{A,B}\,[\text{direct}] - \theta_{B,C}\,[\text{direct}]$$

Figure 2-1 A diagrammatic representation for an example network of 3 treatments (A, B & C).

In this example, A vs B and B vs C have been directly studied in the literature (in studies i and j respectively), with effect sizes $\theta_{A,B}$ and $\theta_{B,C}$ respectively. However, A and C have never been directly compared. An indirect inference on the effect size for A vs C (θAC) can be made using the equation shown in the figure. All direct and indirect effect sizes in the network can then be statistically combined to provide an estimate on A vs B vs C.

Advantages to this increasingly popular technique over traditional meta-analysis, include the ability to compare more than two treatments, as well as those that have not previously been directly compared in the literature. However, various assumptions regarding the treatment cohorts require rigorous testing to ensure validity, more so than with a standard meta-analysis.
The aim of this chapter was to conduct a systematic review of treatment options for complex AAAs and quantitatively compare each modality against every other with a network meta-analysis.

2.2 Methods

This systematic review and network meta-analysis was conducted and reported according to PRISMA guidelines (74), as per a pre-registered protocol (PROSPERO-CRD42020177482).

2.2.1 Literature Search

An electronic search was performed using EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL). These databases were interrogated using the PubMed interface and the Healthcare Databases Advanced Search (HDAS) interface developed by NICE. The date of search completion was 24 April 2020. The reference lists of articles meeting the search criteria were also searched to identify further relevant citations. Full search strings can be found in Appendix 1.

2.2.2 Inclusion and Exclusion Criteria

Studies providing direct comparison of outcomes between two or more modalities for treating complex AAAs were included (aneurysms with at least one of the following neck features: absence, short length, conicality, excessive angulation, excessive calcification, large diameter, excessive thrombus). Studies reporting on the outcomes for standard infrarenal AAAs, ruptured AAAs and TAAAs (including aneurysms involving the visceral segment at the level of the coeliac artery) were excluded. Studies published earlier than the year 2000 or written in a language other than English were excluded. Studies published as a single technique case series or as an abstract for an oral conference presentation were excluded.

2.2.3 Study Selection and Data Extraction

Two researchers independently assessed titles and abstracts of articles identified from the search. Full texts of relevant reports were retrieved and discrepancies in decisions for inclusion/exclusion were resolved with further review and discussion. Two researchers independently extracted data into an electronic spreadsheet and disagreements were resolved by further review and discussion.

2.2.4 Outcome Measures

Outcome measures were decided a priori. The primary outcome measure was perioperative mortality, as a binary variable. Secondary outcome measures were perioperative renal failure, perioperative myocardial infarction, early reintervention, mid-term follow-up results of all-cause mortality rates, reintervention, aneurysm-related mortality, and cost/cost-effectiveness.

2.2.5 Statistical Analysis

A random effects NMA was performed using the BUGSnet package, operated through RStudio (R Foundation for Statistical Computing, Vienna, Austria)(75). Comparative outputs from the BUGSnet model were relative risks for dichotomous event data (perioperative outcomes) and hazard ratios for survival data (mid-term outcomes), both with 95% confidence intervals. Sum under the cumulative ranking (SUCRA) scores were used to rank interventions; this is a measure expressed as a percentage showing the relative probability of an intervention being among the best options. A sensitivity analysis was performed on the primary outcome measure, omitting data from sources with a high risk of bias.

2.2.6 Rating the Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was completed for the primary outcome measure. Grade assessment aims to assign a degree of certainty to the findings of the NMA between each pairwise combination of the network and for each outcome. The process has been detailed by the GRADE Working Group in several publications(76, 77). Ratings are High, Moderate, Low and Very Low and they are then adjusted up and down that scale based on degrees of concern from various assumption analyses. As all studies were non-randomised, the starting point for the process was Low.

The following flow chart demonstrates the process that would be carried out for each pairwise comparison in the network:

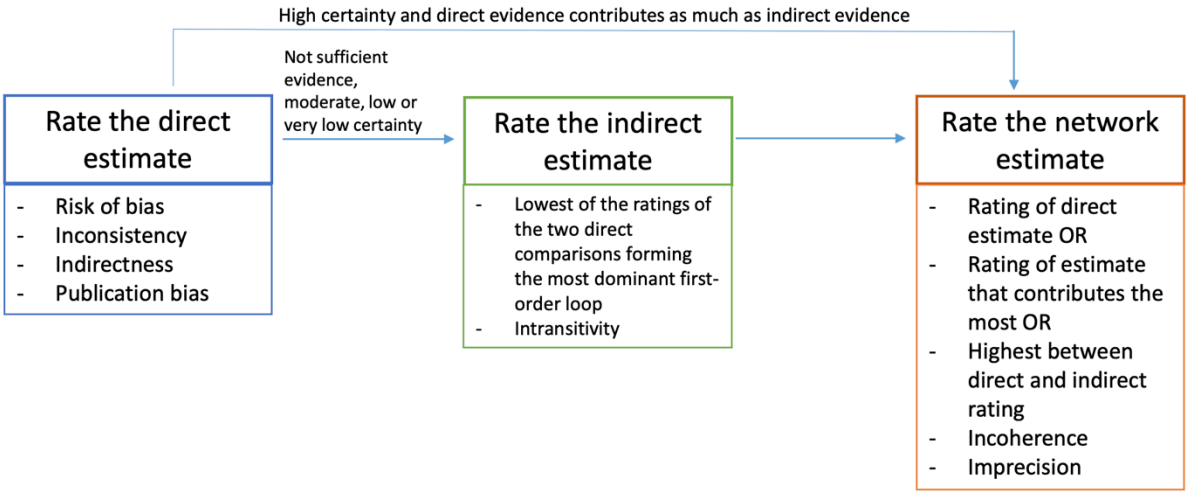


Figure 2-2 A flow chart demonstrating the process of rating the degree of certainty to the findings of each pairwise combination within a network meta-analysis (GRADE).

This rating process involves risk of bias assessment, assessment of indirectness (heterogeneity), inconsistency/incoherence, imprecision, and publication bias. As described in Figure 2-2, if the result of the assessment for a certain pairwise combination/outcome measure is high certainty and the direct evidence dominates the indirect evidence, then measures to rate the network estimate can be performed without the need for rating the certainty of the indirect estimate. Otherwise, the certainty of the indirect estimate is assessed by comparing the ratings of the two direct comparisons that form the most dominant first order loop, as well as for intransitivity. Rating the certainty of the overall network estimate considers the ratings of the direct and indirect ratings and well as assessment of incoherence and imprecision. Additionally, each stage can result in an upgrade in confidence if there is a large magnitude of effect or if all plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed. The methods of each domain of the GRADE assessment are described in turn, as follows:

Risk of bias assessment was performed using the Newcastle-Ottawa Scale for cohort studies (78). This is a system with which studies are assessed across the domains of Patient selection, Comparability and Outcome, for risk of bias. The Comparability domain requires assessment on whether studies control for possible confounding variables which are specific to the clinical context of the review. For this review, variation in infrarenal neck length and physiological fitness between treatment arms were selected as the two confounding variables for the Comparability domain assessment.

Heterogeneity refers to variation in outcome between studies conducting the same direct pairwise comparison. For this network meta-analysis, heterogeneity was assessed for each possible direct pairwise comparison using the I^2 statistic.

Incoherence refers to inconsistency within the network estimate. Assessing statistical consistency is paramount to having confidence in the assumption of transitivity for the network. Transitivity assumes that one can estimate the difference in the effect of two treatments by subtracting the difference in the effects of the two treatments relative to a common comparator. In Figure 2-1, transitivity is the assumption that an "indirect" effect size can be calculated for A vs C based on the two direct observations. Statistical consistency refers to the similarity between the result of direct comparison with that of indirect comparison for the same two treatments in the same network. Evidence of inconsistency would violate the assumption of transitivity. To assess consistency, a node-splitting technique was performed. Node-splitting involved removing direct comparisons between the pair of interest and running the NMA model such that an indirect effect size estimates between that pair of treatments was produced. The indirect effect size estimate was then compared to the direct and network estimates.

Publication bias was assessed by statistical analysis of a funnel plot (treatment effect vs standard error). The following hypothesis was tested: that smaller studies (higher standard error) would be asymmetrically distributed around the zero-effect line in the funnel plot. This is based on the assumption that smaller studies with non-significant results are less likely to be published. Statistical significance was tested using Egger's test.

With regards to assessment of intransitivity, indirect relationship calculations can only be considered valid if confounding variables (effect modifiers) are shown to be similar across studies being pooled. These potential effect modifiers were investigated with visual interpretation of patient characteristic plots for age, hypertension, diabetes, baseline renal failure and ischaemic heart disease.

Imprecision was assessed by visually inspecting the positioning and width of a confidence interval on a forest plot. Where the 95% CI crosses the No effect line only, or the clinically important effect sizes only, there is no concern. Where the 95% CI crosses the No effect line and the threshold for a clinically important effect size, there is some concern for imprecision.

Where the 95% CI crosses both thresholds of clinically important effect size, there is major concern. This is summarised in Figure 2-3.

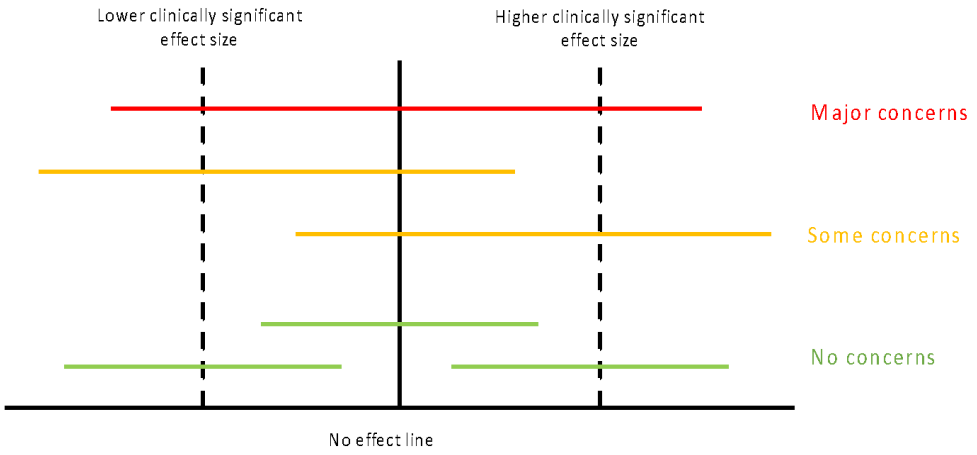


Figure 2-3 Diagrammatic representation of 95% confidence interval interpretation with respect to imprecision assessment.

2.3 Results

2.3.1 Search Results and Included Studies

The search identified 1190 abstracts after de-duplication and 24 studies, on 7854 patients, met the final inclusion criteria for the review (79-102) (Figure 2-4).

All studies employed a retrospective cohort design. All studies compared at least two of: OSR, FEVAR, EVAR off-IFU and ChEVAR. There were no comparative studies including EVAR reinforced with endoluminal screws that met inclusion criteria (Table 2-1).

Of the 24 studies, 19 reported comparative outcomes for the repair of juxtarenal and/or pararenal aneurysms (i.e. had inclusion criteria based on absent/short neck length alone) (81-83, 85, 87-95, 97-102), 4 studies included patients if they met one of several adverse neck morphology criteria (i.e. cases with one or more "off-IFU" characteristic) (79, 80, 86, 96) and one study included cases only if "massive neck atheroma" was present (84). These details, adverse neck feature definitions, and methods of accounting for confounders are presented in Table 2-2. The study including only cases of neck thrombus was excluded from quantitative analysis (84). As all other studies either exclusively included, or included as a majority, cases with a short or absent infrarenal neck, they were included in the NMA.

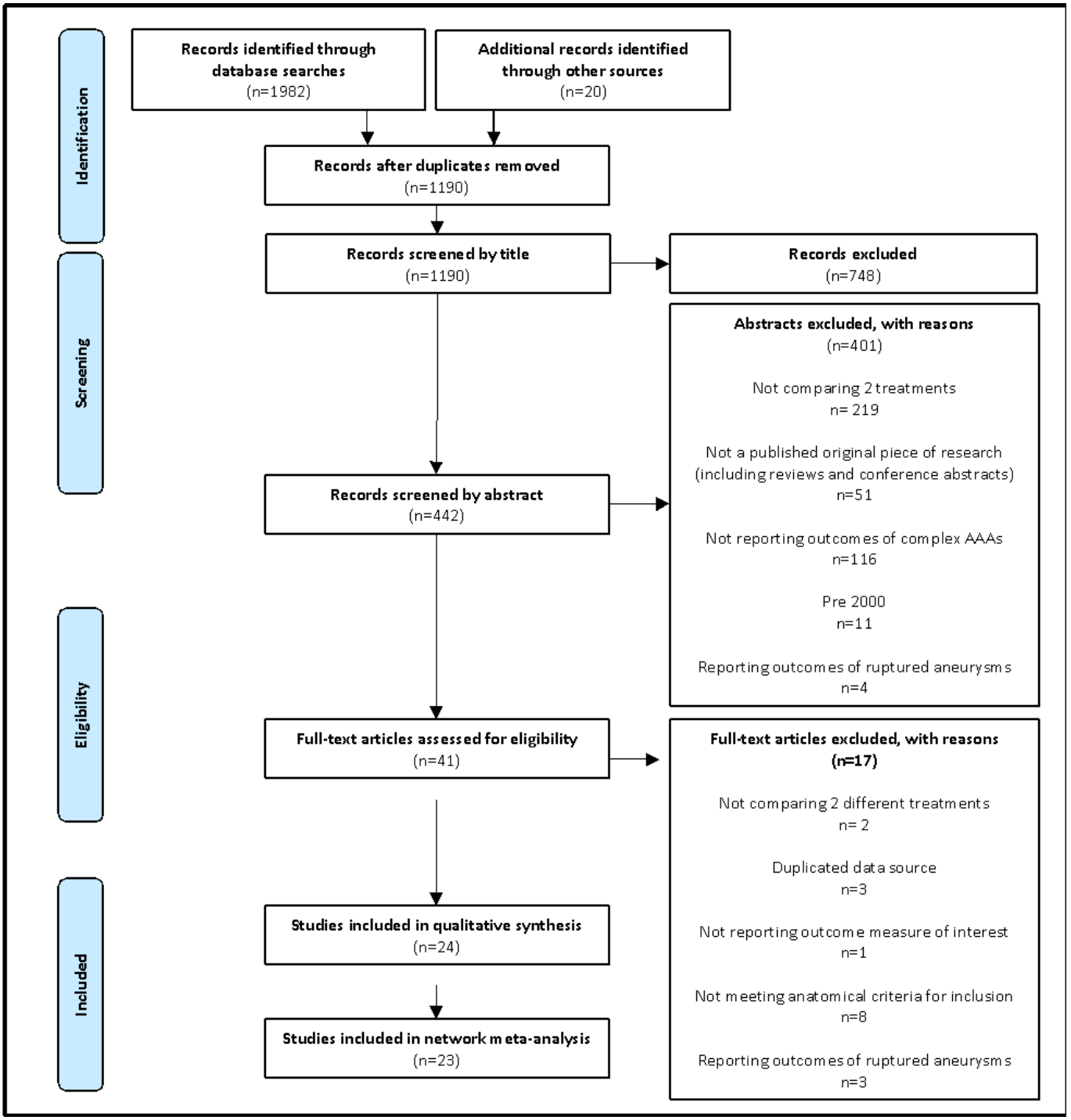


Figure 2-4 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of identification, screening, eligibility, and inclusion phases of the systematic search for studies providing comparative outcomes between methods of complex aneurysm repair.

Table 2-1 Study Characteristics for included studies from the systematic search.

Author	Publication Year	Country (of patients)	Data Source	Case capture Start	Case capture End	Follow-up (months)	n Total	n Open	n FEVAR	n EVAR off-IFU	n ChEVAR
Taneva(102)	2020	Germany	Single Centre	Jan-13	Jan-17	37.2	148	0	37	0	111
O'Donnell(101)	2020	USA/Canada	VQI Database	Jan-12	Dec-18	24	2572	1894	678	0	0
Soler(100)	2019	France	Single Centre	Jan-05	Dec-15	27	191	134	57	0	0
Locham(99)	2019	USA	NSQIP Vascular Database	Jan-12	Dec-16	1	1191	865	162	0	164
Fiorucci(98)	2019	Italy	Multicentre	Jan-98	Mar-16	48	143	102	41	0	0
Chinsakchai(97)	2019	Thailand	Single Centre	Jan-10	Dec-16	36.7	75	32	20	0	23
Charbonneau(96)	2019	Canada	Multicentre	Apr-03	Aug-16	63.6	426	224	0	202	0
Michel(89, 95)	2015 + 2018	France	WINDOWS + PMSI Databases	Sep-09	Dec-12	24	1566	1382	184	0	0
Manunga(94)	2018	USA	Single Centre	Jan-10	Feb-17	31	153	69	84	0	0
Deery(93)	2018	USA	Single Centre	Jan-10	Sep-15	26	116	98	18	0	0
Wooster(92)	2017	USA	Single Centre	Jan-10	Jun-15	10.3	93	0	39	0	54
Shahverdyan(91)	2015	Germany	Single Centre	Apr-99	Jul-14	45.5	69	34	35	0	0
Saratzis(90)	2015	UK	Single Centre	Jan-08	Oct-14	20.5	116	58	58	0	0
Raux(88)	2014	France/USA	Dual Centre	Jul-01	Aug-12	1	189	147	42	0	0
Lee(87)	2014	USA	Single Centre	Sep-09	Mar-13	6	30	0	15	0	15
Barilla(86)	2014	France/Italy	Dual Centre	Jan-06	Dec-10	not stated	100	50	50	0	0
Canavati(85)	2013	UK	Single Centre	Jan-06	Dec-10	1	107	54	53	0	0
Hoshina(84)	2012	Japan	Dual Centre	Jan-03	Nov-10	42	50	22	0	28	0
Freyrie(83)	2012	Italy	Single Centre	Jan-05	Dec-09	26.2	82	44	0	38	0

Donas(82)	2012	Germany	Single Centre	Jan-08	Dec-10	14.2	90	31	29	0	30
Sultan(81)	2011	Ireland	Single Centre	Oct-01	Oct-09	32.5	118	66	0	52	0
Bruen(80)	2011	USA	Single Centre	Jan-08	Dec-09	1	42	21	0	0	21
Chisci(79)	2009	Italy/Sweden	Multicentre	Jan-05	Dec-07	19.5	187	61	52	74	0

FEVAR – fenestrated endovascular aneurysm repair, EVAR Off-IFU – endovascular aneurysm repair off instructions-for-use, ChEVAR – chimney endovascular aneurysm repair, VQI – Vascular Quality Initiative, NSQIP – National Surgical Quality Improvement Program (American College of Surgeons), PMSI – Programme de medicalisation des systemes d'information (national hospital discharge database).

Table 2-2 Anatomical inclusion criteria with definitions, and methods employed to account for confounding across included studies from the systematic search.

			Absent/Short Neck (Para/Juxtarenal)	**Angulated**	**Calcified**	**Thrombus**	**Conical**	**Large diameter**
Author	**Comparison**	**Method of addressing confounding**	**Included, with definition [Mean/Median neck length]**	**Included, with definition**	**Included, with definition**	**Included, with definition**	**Included, with definition**	**Included, with definition**
Taneva(102)	FEVAR vs ChEVAR	Nil	3-9mm	Not included	Not included	Not included	Not included	Not included
O'Donnell(101)	Open vs FEVAR	Propensity Weighted Adjustment	Proximal extent at/below highest RA	Not included	Not included	Not included	Not included	Not included
Soler(100)	Open vs FEVAR	Nil	Up to interrenal aorta (as per Ayari et al (103))	Not included	Not included	Not included	Not included	Not included
Locham(99)	Open vs FEVAR vs ChEVAR	Nil	As listed in NSQIP database	Not included	Not included	Not included	Not included	Not included
Fiorucci(98)	Open vs FEVAR	Propensity Matching	Not provided	Not included	Not included	Not included	Not included	Not included
Chinsakchai(97)	Open vs FEVAR vs ChEVAR	Nil	No normal aorta available for infrarenal clamp [7.5mm Open, 1mm FEVAR, 4mm ChEVAR]	Not included	Not included	Not included	Not included	Not included
Charbonneau(96)	Open vs EVAR Off-IFU	Propensity Weighted Adjustment	4-14mm	>60°	Not included	Not included	Not included	33-34mm

Michel(89, 95)	Open vs FEVAR	Nil	Suprarenal clamp w/o visceral vessel reconstruction	Not included	Not included	Not included	Not included	Not included
Manunga(94)	Open vs FEVAR	Nil	Not provided	Not included	Not included	Not included	Not included	Not included
Deery(93)	Open vs FEVAR	Nil	Not provided	Not included	Not included	Not included	Not included	Not included
Wooster(92)	FEVAR vs ChEVAR	Nil	<4mm [3mm FEVAR, 5mm ChEVAR]	Not included	Not included	Not included	Not included	Not included
Shahverdyan(91)	Open vs FEVAR	Nil	≤10mm or requiring a suprarenal clamp	Not included	Not included	Not included	Not included	Not included
Saratzis(90)	Open vs FEVAR	Case matching	Not provided [8mm FEVAR, 9mm Open]	Not included	Not included	Not included	Not included	Not included
Raux(88)	Open vs FEVAR	Propensity Matching	Requiring suprarenal (or higher) clamp	Not included	Not included	Not included	Not included	Not included
Lee(87)	FEVAR vs ChEVAR	Nil	Not provided [4.5mm FEVAR, 1.1mm ChEVAR]	Not included	Not included	Not included	Not included	Not included
Barilla(86)	Open vs FEVAR	Case matching	<10mm	≥60°	>50%	>50% circumference	Included but no definition provided	>31mm
Canavati(85)	Open vs FEVAR	Risk adjustment (V-POSSUM)	<10mm	Not included	Not included	Not included	Not included	Not included
Hoshina(84)	Open vs EVAR Off-IFU	Nil	Not included	Not included	Not included	≥5mm thickness AND ≥75% circumference AND length ≥5mm	Not included	Not included
Freyrie(83)	Open vs	Nil	≤10mm	Not included	Not included	Not included	Not included	Not included

	EVAR Off-IFU		[7.1mm Open, 8mm EVAR]					
Donas(82)	Open vs FEVAR vs ChEVAR	Nil	<9mm or extension to interrenal aorta	Not included	Not included	Not included	Not included	Not included
Sultan(81)	Open vs EVAR Off-IFU	Nil	Requiring suprarenal clamp and infrarenal anastamosis	Not included	Not included	Not included	Not included	Not included
Bruen(80)	Open vs ChEVAR	Nil	Included but no definition provided [3mm Open, 0mm ChEVAR]	Included but no definition provided	Not included	Not included	Included but no definition provided	Not included
Chisci(79)	Open vs FEVAR vs EVAR Off-IFU	Nil	≤15mm [9mm Open, 10mm EVAR, 7.5mm FEVAR]	≥60°	Not included	>50% circumference	≥2mm diameter increase over 10mm length	≥28mm

FEVAR – fenestrated endovascular aneurysm repair, EVAR Off-IFU – endovascular aneurysm repair off instructions-for-use, ChEVAR – chimney endovascular aneurysm repair.

2.3.2 Primary Outcome Measure

Perioperative mortality

Some 22 studies reported perioperative mortality, defined either as death within 30 days of the aneurysm repair or death during the same admission as the primary procedure. A total of 7804 patients (18 two-arm studies and 4 three-arm studies) were included in this NMA, with 309/7804 (4%) deaths reported in this network (Figure 2-5 A).

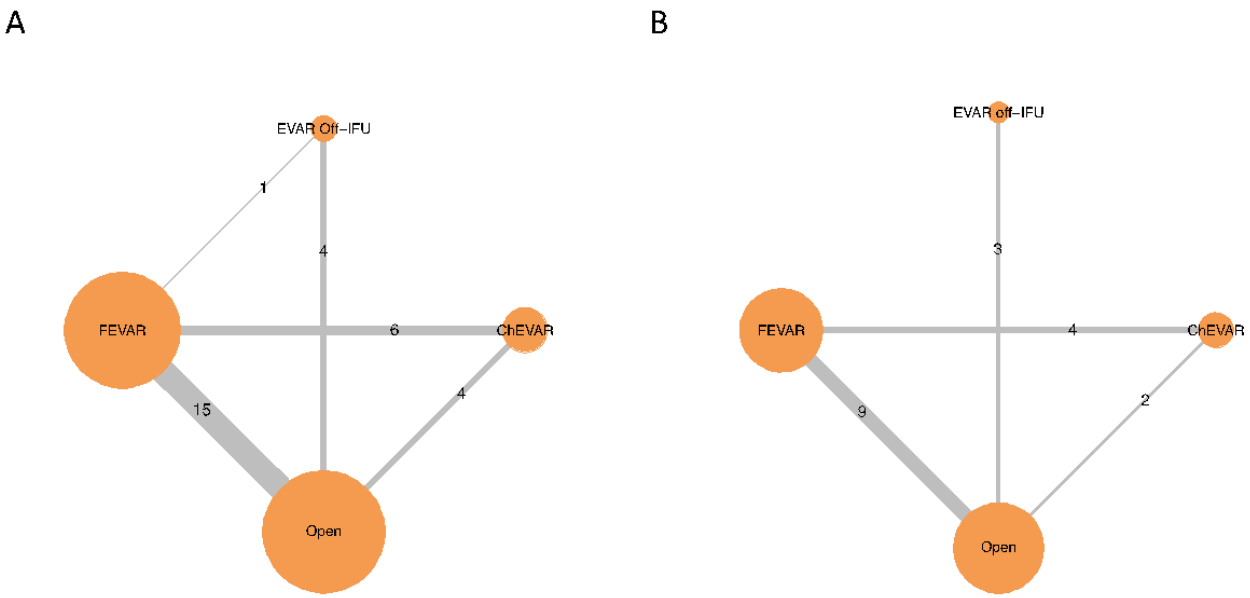


Figure 2-5 Literature summary network plots for all-cause mortality at A) Perioperative (7804 patients across 22 studies) and B) Mid-term follow-up (3481 patients across 16 studies) timepoints.

The size of each orange node corresponds to the number of study arms included for a treatment across all comparisons. Figure 2-5 A: Open=19 arms, FEVAR=18 arms, ChEVAR=7 arms, EVAR Off-IFU=4 arms. Figure 2-5 B: Open=13 arms, FEVAR=12 arms, ChEVAR =5 arms, EVAR Off-IFU=3 arms. The width of each grey line corresponds to the number of studies comparing the two interventions directly, and this number is superimposed on the line. FEVAR = fenestrated endovascular aneurysm repair, EVAR Off-IFU = endovascular aneurysm repair off instructions-for-use, ChEVAR = chimney endovascular aneurysm repair.

Unweighted pooled perioperative mortality rates were 4.4% (235 deaths/5366 patients) for OSR, 3.1% (52 deaths/1654 patients) for FEVAR, 4.8% (20 deaths/418 patients) for ChEVAR and 0.5% (2 deaths/366 patients) for EVAR Off-IFU. Results of the NMA show that both EVAR off-IFU (Relative Risk 0.10, 95%CI 0.01-0.41) and FEVAR (Relative Risk 0.62, 95%CI 0.32-0.94) were associated with lower perioperative mortality compared to OSR. Compared to FEVAR, EVAR off-IFU was associated with lower perioperative mortality (Relative Risk 0.17, 95%CI 0.02-0.74). There was no statistically significant difference in perioperative mortality between OSR and ChEVAR (Relative Risk 1.15 95%CI 0.50-2.44) (Figure 2-6 A and Figure 2-7 A).

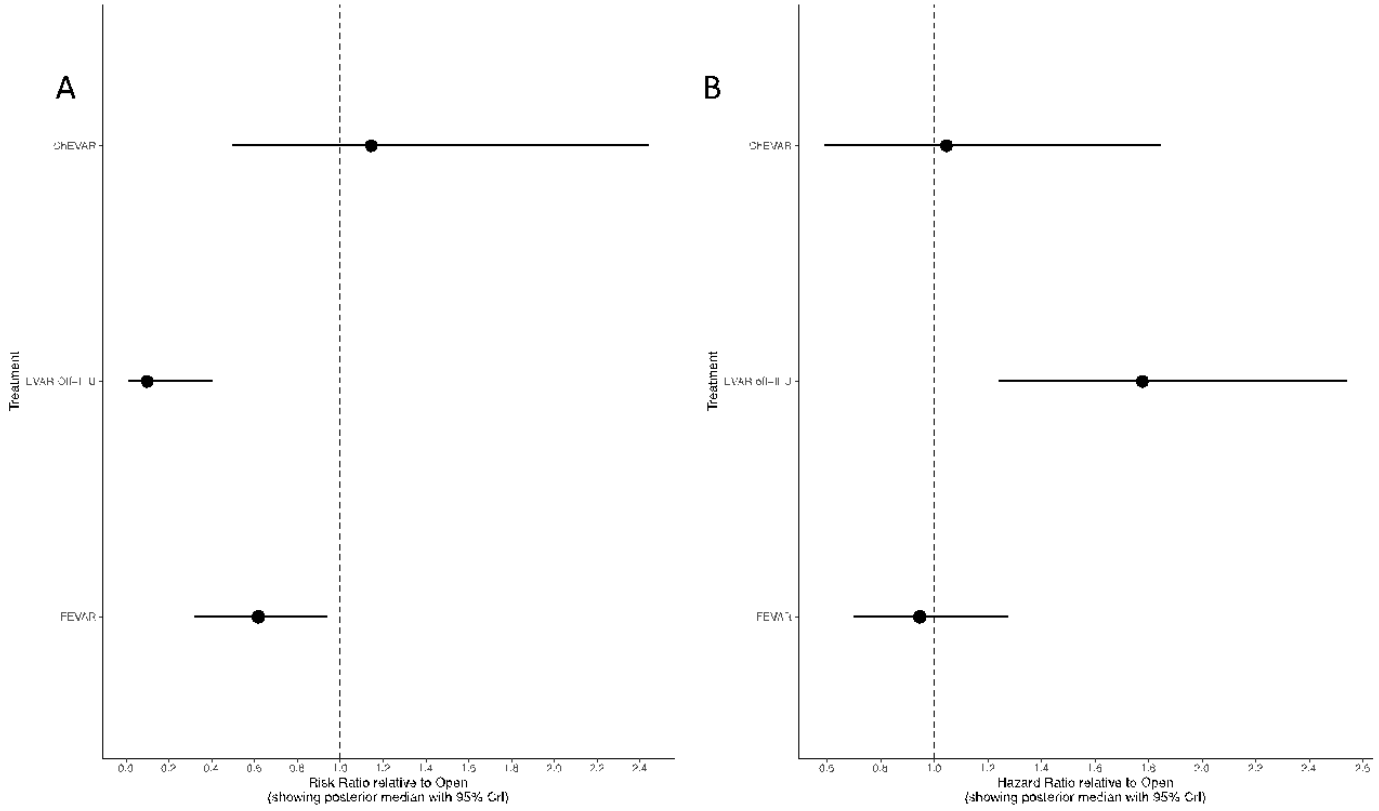


Figure 2-6 Forest plots for comparative all-cause mortality network meta-analysis at A) Perioperative (7804 patients across 22 studies) and B) Mid-term follow-up (3481 patients across 16 studies) timepoints.

2-6 A: Open Surgery 5366 patients, FEVAR 1654 patients, ChEVAR 418 patients, EVAR off-IFU 366 patients. 2-6 B: Open Surgery 2266 patients, FEVAR 699 patients, ChEVAR 224 patients, EVAR Off-IFU 292 patients. Reference comparator is Open Surgery. FEVAR = fenestrated endovascular aneurysm repair, EVAR Off-IFU = endovascular aneurysm repair off instructions-for-use, ChEVAR = chimney endovascular aneurysm repair. Perioperative results (Figure 2-6 A) are presented as Relative Risks and mid-term results (Figure 2-6 B) are presented as Hazard Ratios. Error bars represent 95% credibility intervals. Mean mid-term follow up = 30.63 months.

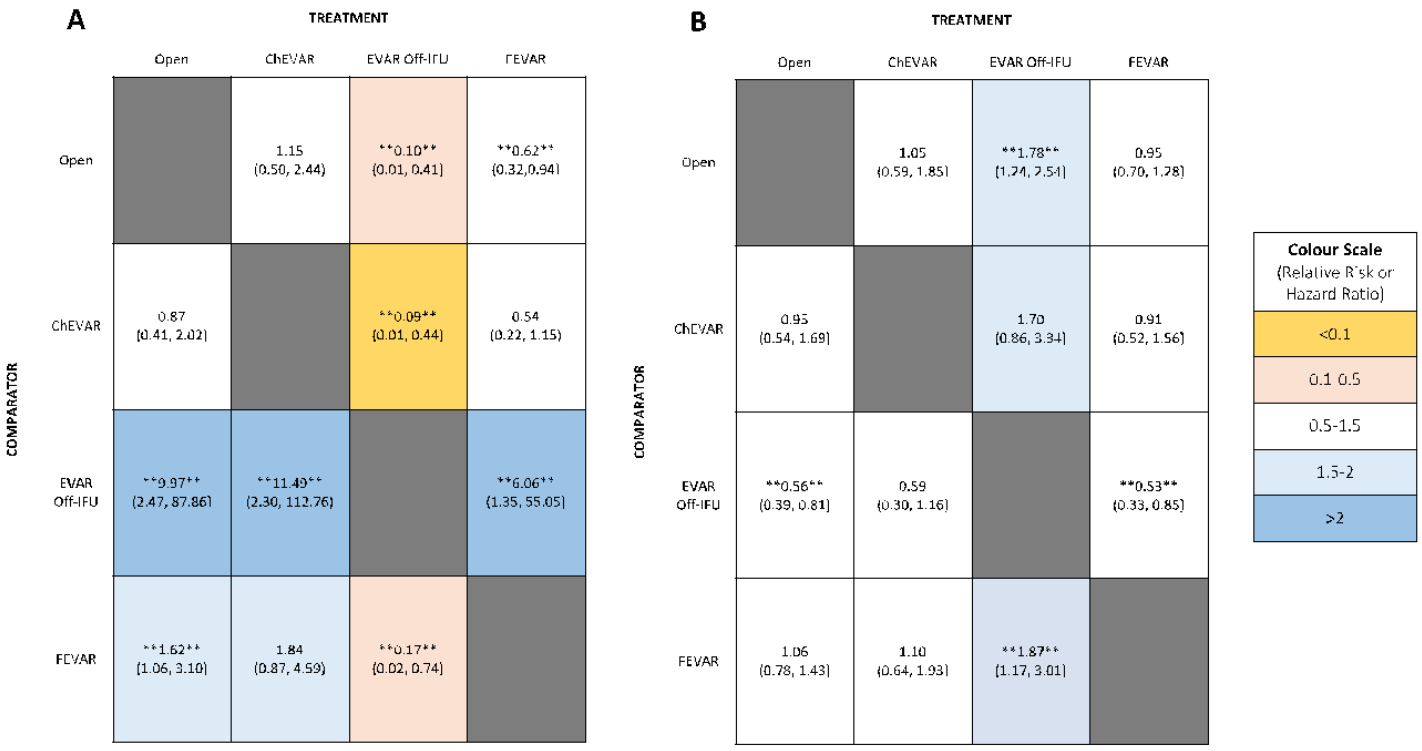


Figure 2-7 Heat plot matrices for comparative all-cause mortality network meta-analysis at A) Perioperative (7804 patients across 22 studies) and B) Mid-term follow-up (3481 patients across 16 studies) timepoints.

*2-7 A: Open Surgery 5366 patients, FEVAR 1654 patients, ChEVAR 418 patients, EVAR off-IFU 366 patients. 2-7 B: Open Surgery 2266 patients, FEVAR 699 patients, ChEVAR 224 patients, EVAR Off-IFU 292 patients. A colour scale is used to represent the size of relative treatment effects as shown. Perioperative results (Figure 2-7 A) are presented as RR (95% CI) and mid-term results (Figure 2-7 B) are presented as HR (95% CI). "**" denotes statistically significant differences (p<0.050). FEVAR = fenestrated endovascular aneurysm repair, EVAR Off-IFU = endovascular aneurysm repair off instructions-for-use, ChEVAR = chimney endovascular aneurysm repair. Mean mid-term follow up = 30.63 months.*

Rankogram showed that EVAR off-IFU had the highest probability of being the safest intervention (99% at rank#1) (Figure 2-8 A). SUCRA scoring rated EVAR off-IFU as the intervention with the highest ranking for perioperative safety, followed by FEVAR as the next safest, followed by OSR. ChEVAR ranked bottom for perioperative safety. In a sensitivity analysis, there were no changes to these findings (Appendix 2).

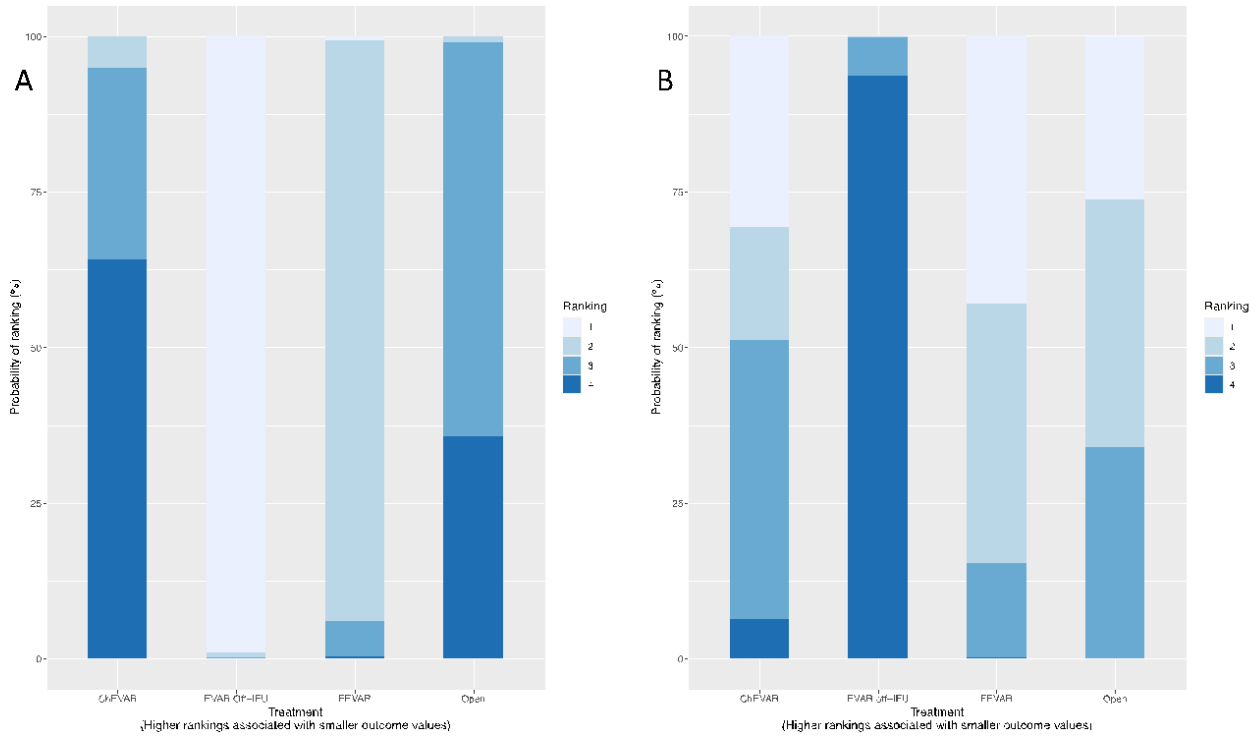


Figure 2-8 Rankograms for all-cause mortality NMA at A) Perioperative (7804 patients across 22 studies) and B) Mid-term follow-up (3481 patients across 16 studies) timepoints.

This displays the probability that each treatment is the nth best treatment. 2-8 A: Open Surgery 5366 patients, FEVAR 1654 patients, ChEVAR 418 patients, EVAR off-IFU 366 patients. 2-8 B: Open Surgery 2266 patients, FEVAR 699 patients, ChEVAR 224 patients, EVAR Off-IFU 292 patients. FEVAR = fenestrated endovascular aneurysm repair, EVAR Off-IFU = endovascular aneurysm repair off instructions-for-use, ChEVAR = chimney EVAR. Mean mid-term follow up = 30.63 months.

2.3.3 Secondary Outcome Measures

Mid-term all-cause mortality

Some 16 studies reported mid-term all-cause mortality. Mean follow-up time point was 30.63 months. A total of 3481 patients (15 two-arm studies and 1 three-arm study) were included in this NMA, with 536 deaths reported in this network (Figure 2-5 B).

Compared to OSR, EVAR off-IFU was associated with a higher mid-term all-cause mortality (HR 1.78, 95%CI 1.24-2.54). Compared to OSR, there was no difference in mid-term all-cause mortality with either ChEVAR (HR 1.05 95%CI 0.59-1.85) or FEVAR (HR 0.95 95%CI 0.70-1.28). Compared to EVAR off-IFU, FEVAR was associated with a lower mid-term all-cause mortality (HR 0.53, 95%CI 0.33-0.85) (Figure 2-6 B and Figure 2-7 B).

Rankogram showed that EVAR off-IFU had the highest probability of being the worst intervention for mid-term all-cause mortality (Figure 2-8 B). SUCRA scoring rated FEVAR as the intervention with the best (lowest) mid-term all-cause mortality, followed by OSR, followed by ChEVAR followed by EVAR off-IFU.

Perioperative renal failure

Some 16 studies reported perioperative renal failure rates. Definitions of acute renal failure were varied and included a rise in creatinine of >0.5mg/dl, a rise to ≥1.5mg/dL, a two-fold increase in creatinine, a rise of >50% and a rise of >30%. A total of 5690 patients (14 two-arm studies and 2 three-arm studies) were included in this NMA, with 868 cases of renal failure reported in this network. There were no statistically significant differences in rates of renal failure between the 4 treatment options.

Perioperative myocardial infarction (MI)

Some 17 studies reported perioperative myocardial infarction rates. Definitions of myocardial infarction consistently included troponin rise with or without electrocardiographic changes of ischaemia, although exact troponin threshold values were rarely provided. A total of 6325 patients (16 two-arm studies and 1 three-arm study) were included in this NMA, with 246 MIs reported in this network.

Unweighted pooled perioperative MI rates were 4.2% for OSR, 2.5% for FEVAR, 3.8% for ChEVAR and 5.1% for EVAR Off-IFU. Both EVAR off-IFU (Relative Risk 0.42, 95%CI 0.12-0.89) and FEVAR (Relative Risk 0.37, 95%CI 0.16-0.62) were associated with lower risk of perioperative MI compared to OSR. There were no statistically significant differences in perioperative MI risk between any of the endovascular treatment modalities.

Perioperative reintervention

Some 9 studies reported perioperative reintervention rates. A total of 3890 patients (7 two-arm studies and 2 three-arm studies) were included in this NMA, with 358 events (cases of perioperative reintervention) reported in this network.

Unweighted pooled perioperative reintervention rates were 9.7% for OSR, 7.9% for FEVAR, 9.1% for ChEVAR and 5.8% for EVAR Off-IFU. There were no statistically significant differences in perioperative reintervention risk between any of the treatment modalities.

Mid-term reintervention

Some 11 studies reported on mid-term reintervention rates. Mean follow-up time point was 28.68 months. A total of 1336 patients (9 two-arm studies and 2 three-arm studies) were included in this NMA, with 135 mid-term reinterventions reported in this network. FEVAR had a higher rate of mid-term reintervention than OSR (HR 1.65, 95%CI 1.04-2.66). There were no statistically significant differences between any of the other combinations of complex AAA repair. Rankogram analysis suggested that OSR had the highest probability of being the intervention with the lowest reintervention risk, compared to all three endovascular techniques. SUCRA scoring ranked OSR as being the best treatment (lowest rate of reintervention) followed by EVAR off-IFU, followed by FEVAR, followed by ChEVAR. It is unclear whether late hernia repair was included as an indication for reintervention in most studies reporting on OSR (it was only explicitly mentioned in two studies). Intervention to type 2 endoleaks without sac enlargement was a rare occurrence, only described in 1/7 studies reporting on FEVAR, on one occasion. All 7 studies reporting on FEVAR described graft-related endoleaks and visceral stent complications as the principal indications for reintervention.

Mid-term aneurysm-related mortality

Some 11 studies reported aneurysm-related mortality, which was defined as any perioperative death around the primary aneurysm repair, any death within 30 days of a re-intervention to the aneurysm repair or any death from an aneurysm-related complication. Mean follow-up time point was 30.01 months. A total of 2987 patients (10 two-arm studies and 1 three-arm study) were included in this NMA, with 138 aneurysm-related deaths reported. There were no statistically significant differences in mid-term aneurysm-related mortality rates between the 4 treatment options.

Cost/Cost-effectiveness

As only three studies reported on cost or cost-effectiveness, it was not possible to perform a meaningful quantitative analysis. Taneva et al(102) performed a cost-analysis comparing FEVAR to ChEVAR. Cost of the primary procedure was €42,116 vs €22,171 respectively and total cost (including re-admissions and re-interventions) after 3 years was €42,128 vs €22,872. They concluded that FEVAR was more expensive than ChEVAR.

Michel et al(89) performed microcosting and cost-effectiveness analysis comparing OSR and FEVAR. For para/juxtarenal aneurysms, total costs (primary procedure and re-admissions) at 30 days were €14,907 and €34,425 respectively. In a later 2-year analysis(95), total costs were €21,142 and €41,786 respectively. It was found that FEVAR was not cost-effective with an incremental cost-effectiveness ratio (ICER) of €110,216,700 per death averted.

Sultan and Hynes(81) compared OSR to EVAR Off-IFU for pararenal aneurysms. Over 3 years, EVAR Off-IFU costs (including follow-up and re-intervention) averaged €20,375 per patient (0.90 QALY) and OSR costs averaged €23,928 per patient (0.86 QALY). It was concluded that EVAR Off-IFU was cost-effective.

2.3.4 GRADE Assessment

As all studies were non-randomised, the starting point for the GRADE process was at "Low". GRADE assessment for certainty of this primary outcome measure was performed, considering the following domains: Risk of bias, Heterogeneity, Incoherence, Indirectness, Imprecision, and publication bias.

Risk of bias

Risk of bias assessment was performed using the Newcastle-Ottawa Scoring system for cohort studies. Four of the 24 studies were assessed as having high bias risk, and 20 as having a moderate risk of bias. Overall, across studies there was poor compensation for selection bias arising from variation in physiological fitness and neck length between endovascular and open treatment arms, as well as between subtypes of endovascular treatment options (Table 2-3).

Table 2-3 Risk of bias assessment using the Newcastle-Ottawa scoring system for cohort studies(78).

		SELECTION				**COMPARABILITY**		**OUTCOME**				
		Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest is not present at start of study	Controls for neck length between groups	Controls for physiological variation between groups	Assessment of outcome	Adequate follow up	Adequacy of follow up of cohorts	**Total Score**	**Risk of Bias**
Taneva(102)	2020	1	1	1	0	0	0	1	1	1	6	Moderate risk
O'Donnell(101)	2020	1	1	1	0	0	1	1	1	1	7	Moderate risk
Soler(100)	2019	1	1	1	0	0	0	1	1	1	6	Moderate risk
Locham(99)	2018	1	1	1	0	0	0	1	1	1	6	Moderate risk
Fiorucci(98)	2018	1	0	1	0	0	1	1	1	1	6	Moderate risk
Chinsakchai(97)	2019	1	1	1	0	0	0	1	1	1	6	Moderate risk
Charbonneau(96)	2019	1	1	1	0	0	1	1	1	1	7	Moderate risk
Michel(89, 95)	2018	1	0	1	0	0	0	1	1	1	5	High risk
Manunga(94)	2018	1	1	1	0	0	0	1	1	1	6	Moderate risk
Deery(93)	2018	1	1	1	0	0	0	1	1	1	6	Moderate risk
Wooster(92)	2017	1	1	1	0	0	0	1	1	1	6	Moderate risk
Shahverdyan(91)	2015	1	1	1	0	0	0	1	1	1	6	Moderate risk
Saratzis(90)	2015	1	1	1	0	0	1	1	1	1	7	Moderate risk
Raux(88)	2014	1	0	1	0	1	1	1	1	1	7	Moderate risk
Lee(87)	2014	1	1	1	0	0	1	1	1	1	7	Moderate risk
Barilla(86)	2014	1	0	1	0	0	0	1	1	1	5	High risk
Canavati(85)	2013	1	1	1	0	0	1	1	1	1	7	Moderate risk

Hoshina(84)	2012	1	0	1	0	0	0	1	1	1	5	High risk
Freyrie(83)	2012	1	1	1	0	1	0	1	1	1	7	Moderate risk
Donas(82)	2012	1	1	1	0	0	0	1	1	1	6	Moderate risk
Sultan(81)	2011	1	1	1	0	0	0	1	1	1	6	Moderate risk
Bruen(80)	2011	1	1	1	0	1	0	1	1	1	7	Moderate risk
Chisci(79)	2009	1	0	1	0	0	0	1	1	1	5	High risk

Heterogeneity

Heterogeneity refers to variation in outcome between studies conducting the same direct pairwise comparison. For this network meta-analysis, heterogeneity was assessed for each possible direct pairwise comparison. There are 6 possible direct comparisons in the network for 4 different treatments. It was possible to investigate heterogeneity for 4/6 direct comparisons (Figure 2-9). This was not possible for 2/6 pairwise comparisons: FEVAR vs EVAR Off-IFU could not be assessed as there was only 1 direct comparison in the network meta-analysis. EVAR OFF-IFU vs ChEVAR could not be assessed as there were 0 direct comparisons in the network meta-analysis. Heterogeneity was found to be low across all pairwise comparisons in the network that were analysed (Table 2-4).

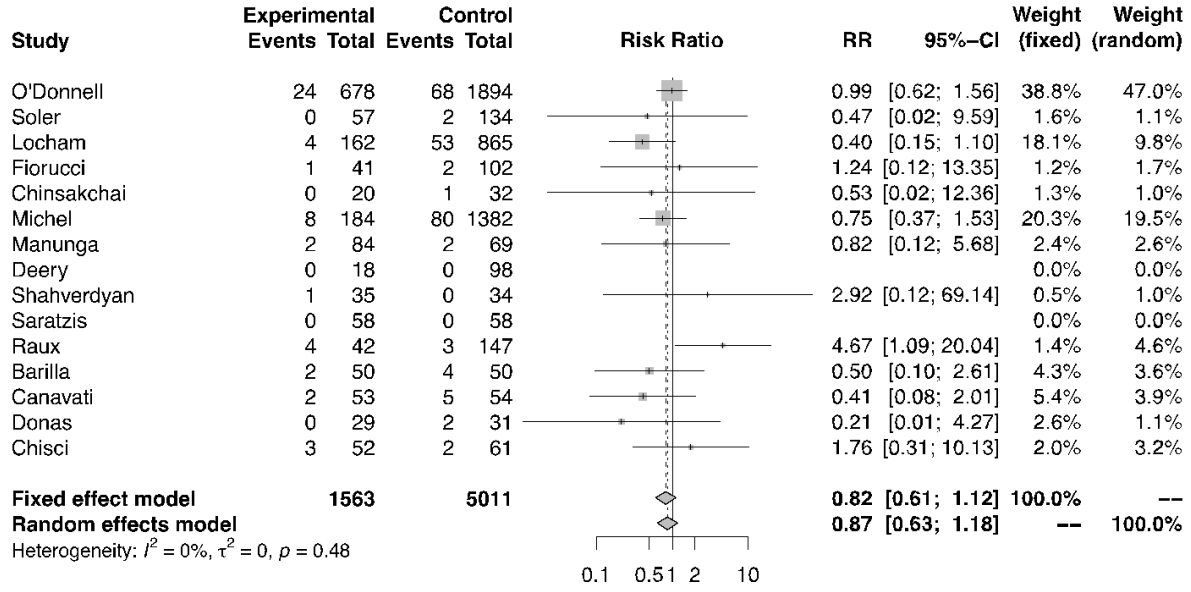


Figure 2-9 Forest plot for meta-analysis of studies directly comparing Open surgery (control) vs FEVAR (experimental).

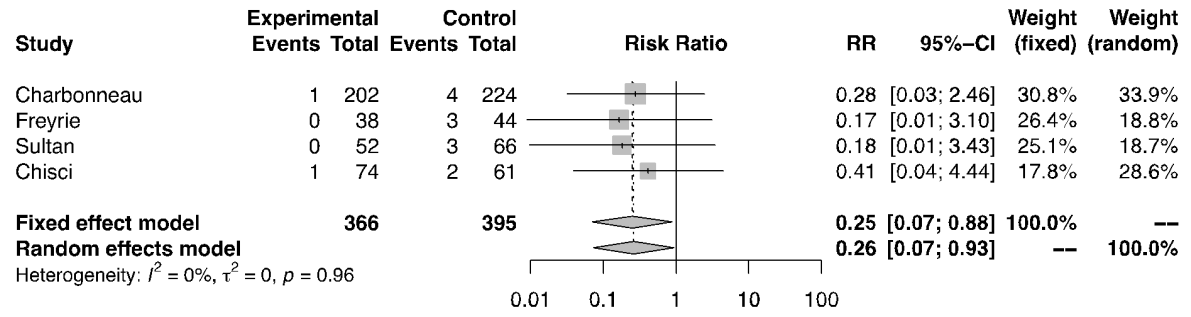


Figure 2-10 Forest plot for meta-analysis of studies directly comparing Open surgery (control) vs EVAR off-IFU (experimental).

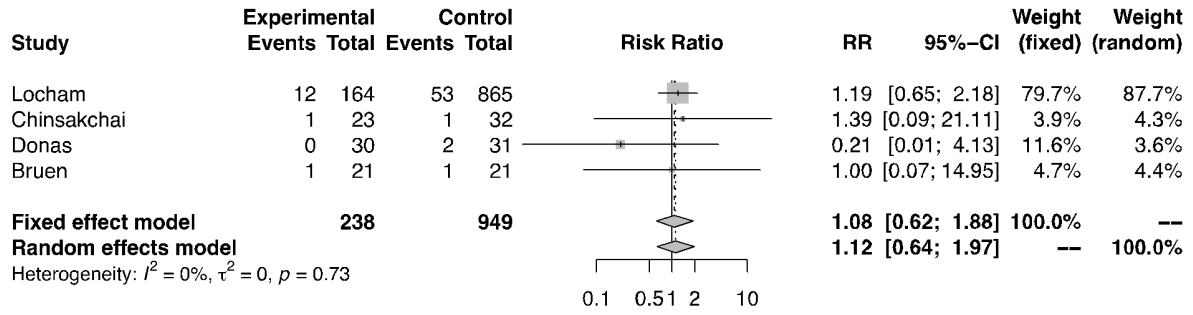


Figure 2-11 Forest plot for meta-analysis of studies directly comparing Open surgery (control) vs ChEVAR (experimental).

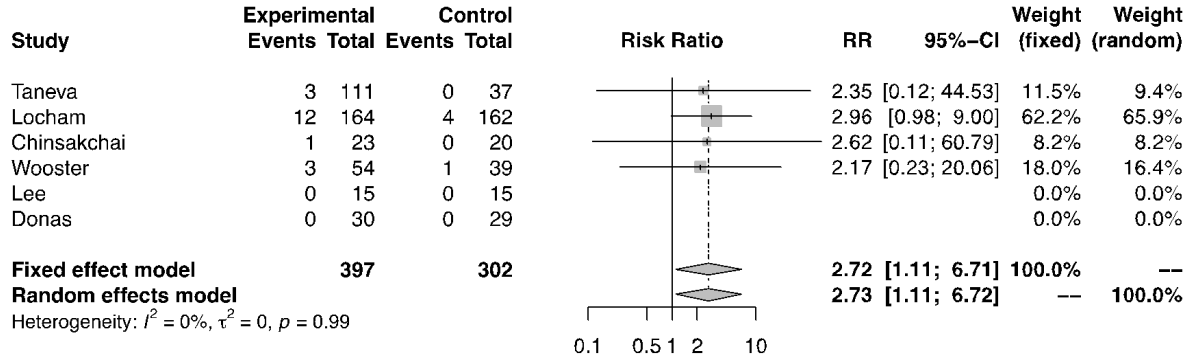


Figure 2-12 Forest plot for meta-analysis of studies directly comparing FEVAR (control) vs ChEVAR (experimental).

Table 2-4 Overall summary of quantitative heterogeneity assessment.

Comparison	I^2	Cochran's Q	p-value
Open vs FEVAR	0%	11.59	0.479
Open vs EVAR off-IFU	0%	0.3	0.959
Open vs ChEVAR	0%	1.32	0.725
FEVAR vs ChEVAR	0%	0.07	0.995

Incoherence

Incoherence refers to inconsistency within the network estimate. This refers to similarity between the result of the direct comparison with that of the indirect comparison for the same two treatments in the network. A node-splitting technique was performed for assessment of incoherence. This involved breaking down the NMA result into its separate direct and indirect components and to compare the two to the network estimate. Node splitting demonstrated consistency between the direct, indirect and network estimates by the fact that all 3 confidence intervals overlap across all the comparisons (Figure 2-13, Table 2-5).

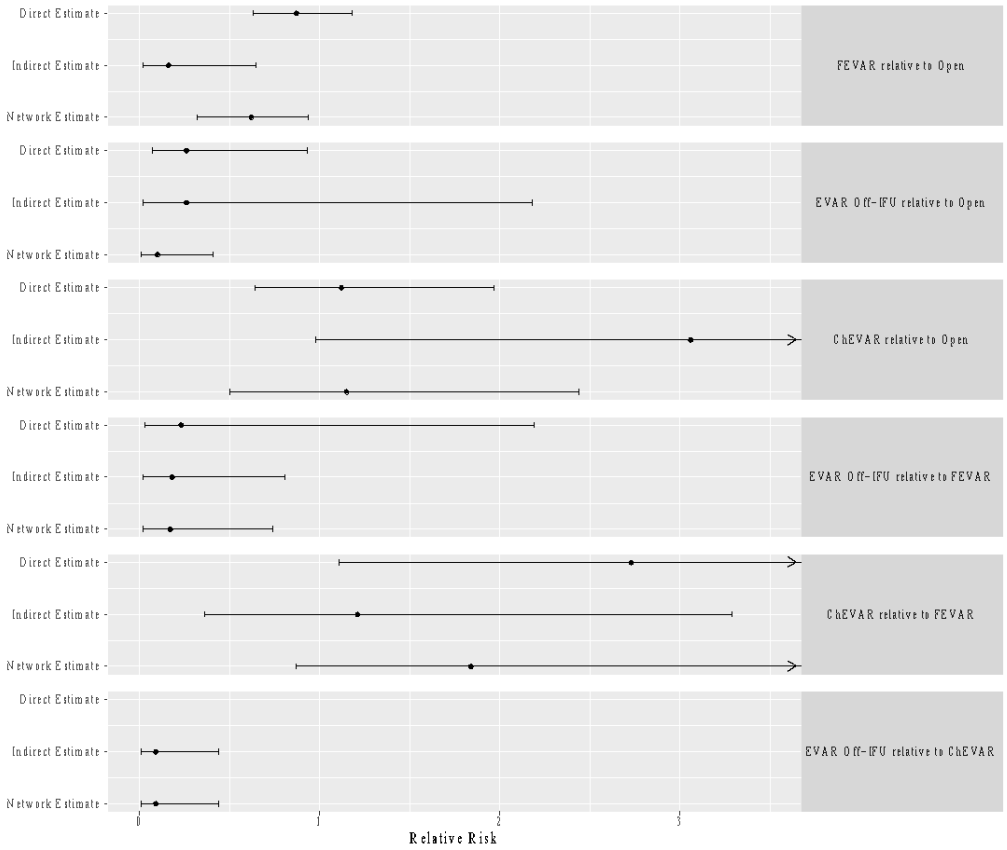


Figure 2-13 Node splitting forest plot showing direct, indirect and network estimates for all 6 possible comparisons.

Table 2-5 Node splitting results providing direct, indirect and network estimates of relative risk, presented with 95% confidence intervals.

Comparison	estimate	RR	Lower CI	Upper CI
FEVAR relative to Open	Network Estimate	0.62	0.32	0.94
	Indirect Estimate	0.16	0.02	0.65
	Direct Estimate	0.87	0.63	1.18
EVAR Off-IFU relative to Open	Network Estimate	0.10	0.01	0.41
	Indirect Estimate	0.26	0.02	2.18
	Direct Estimate	0.26	0.07	0.93
ChEVAR relative to Open	Network Estimate	1.15	0.5	2.44
	Indirect Estimate	3.06	0.98	12.09
	Direct Estimate	1.12	0.64	1.97
EVAR Off-IFU relative to FEVAR	Network Estimate	0.17	0.02	0.74
	Indirect Estimate	0.18	0.02	0.81
	Direct Estimate	0.23	0.03	2.19
ChEVAR relative to FEVAR	Network Estimate	1.84	0.87	4.59
	Indirect Estimate	1.21	0.36	3.29
	Direct Estimate	2.73	1.11	6.72
EVAR Off-IFU relative to ChEVAR	Network Estimate	0.09	0.01	0.44
	Indirect Estimate	0.09	0.01	0.44
	Direct Estimate	NA	NA	NA

Indirectness/Intransitivity

Assessing indirectness of the direct estimate alone (intransitivity) involved a global assessment of whether methods and populations were standardised between studies of the same pairwise comparisons. This review had strict anatomical inclusion criteria and excluded studies on that basis. However, there was still potential for variation across studies with regards to baseline characteristics and treatment indications. Although we excluded ruptured aneurysms, some studies included urgent cases and re-do surgery whereas most did not. Overall, there would be some concern for indirectness of all direct estimates for this reason.

Potential effect modifiers were investigated with visual interpretation of patient characteristic plots. Patient characteristic plots for age, hypertension, diabetes, baseline renal failure and ischaemic heart disease are provided in Appendix 2. Studies seemed to be consistent with regards to baseline age (approximately 70-80) , incidence of hypertension (approximately 70-90%), incidence of diabetes (approximately 10-30%) and incidence of CKD (approximately 10-30%). There was concern regarding variable incidence of ischaemic heart disease (IHD) in the populations undergoing ChEVAR and FEVAR across studies. Visual interpretation of the patient characteristic plot for IHD alone raises concern for violation of transitivity, however this may be due to variation in definition of IHD across studies as opposed to variation in incidence (Appendix 3).

Imprecision

Imprecision was assessed by visually inspecting the positioning and width of the confidence intervals provided in the node splitting forest plots generated for the assessment of incoherence (Figure 2-13). A guide for interpretation was shared in Figure 2-3. This generated some concern for imprecision within the forest plots for Open vs ChEVAR and ChEVAR vs FEVAR comparisons.

Publication Bias

Publication bias was assessed by statistical analysis of a funnel plot (treatment effect vs standard error). The result is represented on a funnel plot, with symmetry around the zero-effect line (Figure 2-14). This coupled with a Egger's test result of p=0.9825 suggests the absence of publication bias.

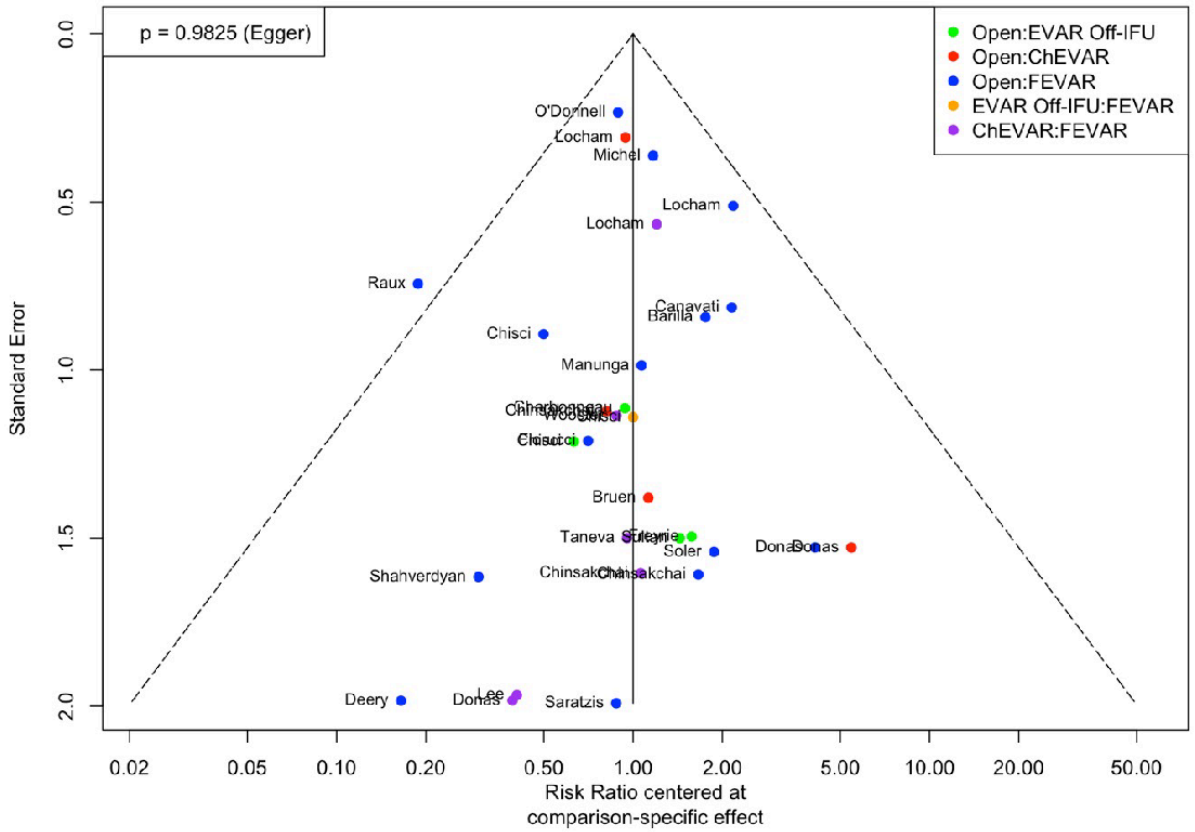


Figure 2-14 Funnel Plot to assess for publication bias in the network.

The final GRADE assessment for each pairwise comparison network estimate is shown in full in Appendix 4. A summary of the final ratings are as follows:

Open vs FEVAR: Low

Open vs EVAR off-IFU: Moderate

Open vs ChEVAR: Very Low

FEVAR vs ChEVAR: Very Low

FEVAR vs EVAR off-IFU: Low

EVAR off-IFU vs ChEVAR: Very Low

2.4 Discussion

This is the first systematic review that included a network meta-analysis that compares different treatments for the repair of juxtarenal and complex-neck AAAs, namely OSR, FEVAR, ChEVAR and EVAR Off-IFU. The main finding is that EVAR Off-IFU and FEVAR have lower perioperative mortality compared to OSR for the repair of AAAs with short or absent infrarenal necks (10-fold and 6-fold reduction respectively), with or without other complex-neck features.

This difference could be due to a difference in perioperative MI, as the NMA also revealed significantly lower incidence of MI after both EVAR Off-IFU and FEVAR as compared to OSR. However, MI was the most commonly reported complication across studies and therefore amenable to NMA. Other complications not analysed in this work may be contributing to the treatment effect. There was no difference in the incidence of acute kidney injury between treatment methods although this finding should be seen with caution given the heterogeneity of definitions used across studies. These perioperative findings would mirror randomised controlled trial evidence of standard EVAR vs OSR for the repair of standard infrarenal aneurysms (37).

ChEVAR had equivalent perioperative survival compared to OSR, although the precision of this estimate is low. Although studies reporting on ruptured aneurysms were excluded from this analysis, ChEVAR cohorts included urgent operations, reflecting an "off-the-shelf" solution. This may explain the apparent loss of perioperative survival benefit, which is expected with endovascular techniques over OSR. ChEVAR also carries the risk of specific complications that could elevate mortality rate; this includes stroke, which was not amenable to NMA due to inconsistent reporting across treatment arms.

This NMA shows a "catch-up" in all-cause mortality between OSR and FEVAR (equivalent survival at 2.5 years). However, EVAR off-IFU had worse mid-term survival as compared to OSR (HR 1.78 95%CI 1.24-2.54). Due to the non-randomised nature of all studies included in this analysis, this is likely to reflect confounding from variation in baseline physiological fitness between the two groups. It is possible that clinicians choose to offer EVAR Off-IFU as a simpler solution to their least fit patients. Unfortunately, adequate data regarding functional measures of fitness were lacking to permit testing of this supposition.

FEVAR carries a higher re-intervention rate than OSR at 20 months follow-up. Coupled with its high cost, there is potential concern for re-interventions to contribute to poor cost-effectiveness when compared to OSR (95). It should be noted however, that detail on reinterventions after OSR were often lacking. Although 3/7 studies seemed to provide details regarding hernia repairs and amputations in mid-term follow-up, 4/7 studies provided no such reassurance that these cases were counted.

This systematic review and NMA attempted to remedy several limitations of the existing literature. First, original comparisons and meta-analyses have often produced results that are difficult to interpret due to anatomical heterogeneity (104-107). Anatomical heterogeneity was minimised by only searching for studies reporting on cases with adverse infrarenal neck features (including juxtarenal aneurysms) but excluded TAAAs and those affecting the visceral aorta (at the level of the coeliac artery). Additionally, only studies reporting on short/absent infrarenal necks were included in the quantitative NMA.

Second, meta-analyses have often focussed on OSR versus FEVAR alone, neglecting other commonly used methods of complex aneurysm repair, and pooling case series data with data from comparative studies, thus introducing significant bias (72, 73). Occasionally, comparative studies and meta-analyses have included other methods of repair but have combined all endovascular treatment techniques together and compared them to OSR (70, 108). This is of limited value as each treatment technique is distinct, with its unique advantages and disadvantages. This network meta-analysis avoided such 'combined cohorts' and considered OSR, FEVAR, ChEVAR and EVAR Off-IFU as distinct treatment modalities.

Finally, most published meta-analyses included studies published up to 2000-2010 (72, 73). This systematic search provides a more contemporaneous assessment, with 14/24 studies published in and beyond 2015, and these findings are therefore less likely to suffer from a learning curve effect.

There are several limitations that should be noted when interpreting the findings of this network meta-analysis. All studies provided non-randomised comparisons between treatment methods and are therefore subject to selection bias based on variations in physiological fitness and exact anatomy of the infrarenal neck. For example, FEVAR was often only offered if patients were unfit for OSR, and ChEVAR was only offered if FEVAR was anatomically not possible or if the

cases were urgent. Only 7/24 studies attempted to account for such confounding with a form of statistical adjustment. Although anatomical heterogeneity was limited by excluding studies reporting on TAAAs and visceral segment aneurysms at the level of the coeliac artery, there was often no detail provided on exact neck length or the comparative incidence of other adverse neck features between treatment groups. This does introduce the possibility of neck length variation between treatment groups. Indeed, the definitions of a short neck did vary slightly across studies (Table 2), and so the OSR group may be heterogenous with respect to clamp level. Additionally, 5/24 studies reported "re-do" cases as a small proportion of their study population, with a predominant use of ChEVAR in this situation.

From a statistical point of view, the network meta-analysis was valid with non-violated transitivity and consistency on assumption testing, low heterogeneity, low concern for imprecision in most comparisons, and no suggestion of publication bias. However, GRADE rating for certainty of evidence was overall "Low" for the majority of pairwise comparisons, reflecting the inherent biases carried by non-randomised observational studies.

Although the original aim was to analyse comparative outcomes for the repair of a wide variety of complex aneurysm subtypes (a wide range of adverse neck features), the results of the search meant that pragmatically, NMA was only possible for the repair of juxtarenal aneurysms and not AAAs with adverse neck features other than short/absent length. Analysis was also limited to OSR, FEVAR, EVAR Off-IFU and ChEVAR, as comparative outcomes of Standard EVAR with adjunctive endoluminal screws were not available. This would be of interest as it is a licenced technique for short neck aneurysms.

The findings of this NMA reconfirm the widely accepted observation that endovascular techniques are associated with significantly lower perioperative mortality compared to OSR for complex aneurysms. Recommendation 96 in the European Society of Vascular Surgery (ESVS) guidelines states that "In complex endovascular repair of juxtarenal abdominal aortic aneurysm, endovascular repair with fenestrated stent grafts should be considered the preferred treatment option when feasible"(5). However, this is allocated a Class II rating: that there is "conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure". Meaningful take-home messages around complex aneurysm repair are hindered by inconsistent reporting of baseline characteristics and outcomes. New reporting standards and guideline definitions would increase confidence when interpreting pooled data.

Lack of equipoise around perioperative safety explains reluctance among practicing clinicians to support an RCT comparing open and endovascular treatments for complex AAAs. An acceptable alternative may be a large-scale study that compares all treatment methods currently being used in a "real-world" analysis, that rigorously adjusts for physiological risk between groups and accurately stratifies cases by exact neck length and morphology.

3 Methodology For A Cohort Study Comparing Different Treatments For The Repair Of Juxtarenal And Complex-neck Aneurysms

3.1 Design Considerations

This chapter describes the methods for an observational cohort study comparing different strategies for the repair of juxtarenal and complex-neck AAAs. When considering the study design for this comparison, consideration was paid to existing deficiencies in the literature as highlighted by the systematic review and network meta-analysis in chapter 2. These included the following:

1) There is considerable anatomical heterogeneity in previous study populations. Pooling complex-neck aneurysms, juxtarenal aneurysms and thoracoabdominal aortic aneurysms into one population limits clinical interpretation of any results.
2) There has been consistent failure to adjust for baseline indication biases, primarily that open surgery is often reserved for the fittest patients, whereas endovascular treatments tend to be offered to patients across the whole spectrum of physiological risk, even the least fit.
3) Capture of cases into existing comparative studies is usually reliant on coding processes for specific databases. This provides very limited detail on exact anatomical features to the AAA and on occasion, it is the listing by operative technique that drives groupings without any attention paid to anatomy. In studies where anatomical profiles are described in any detail, numbers are low as they have tended to represent single-centre experience.
4) There has been a large focus on open surgery and fenestrated EVAR (FEVAR) as the two principal methods of repairing juxtarenal aneurysms. However, a study (including a potential randomised controlled trial design) only focussing on these two techniques would fail to provide a real-world assessment of practice in which there are additional treatment options in routine use, including off-label EVAR and EVAR with adjuncts.

Additionally, pertinent information regarding study design was gleaned by my supervisor at a study design workshop in 2015, which was attended by representatives from every centre with a FEVAR programme in the United Kingdom, together with other academic leaders in the field. There was no willingness to recruit patients into a randomised controlled trial with an

expectation of a substantially lower perioperative mortality after FEVAR compared to open surgery being the stated reason for a lack of equipoise [unpublished data]; this bias in favour of endovascular techniques was being driven by the results of comparative studies for standard infrarenal aneurysms (37) as well as large case series detailing favourable early experiences with newer endovascular techniques (59).

Therefore, a pragmatic solution considering all of the above was found: a large cohort comparison study of all available techniques, capturing all juxtarenal and complex-neck aneurysms on a national basis, utilising large routinely-collected datasets, and incorporating propensity score methods to adjust for potential confounders.

3.2 Data Sources

This study was based on routinely-collected data. A comprehensive set of demographic, diagnostic, health, procedural, follow-up and survival data were retrieved from multiple sources, and linked. Further information on the data fields and various sources are shown in Appendix 2. When the same information was available from multiple sources, data were triangulated to improve completeness and to remove any duplication.

Data sources were:

1) Hospital Episode Statistics (HES)

Provided by National Health Service Digital (NHS Digital), this is a warehouse of administrative data containing details of all care provided at National Health Service (NHS) hospitals in England, serving as a documented record of activity for patients during every hospital presentation. It comprises different datasets for activity at outpatient appointments, emergency department presentations, diagnostic imaging as well as all activity with an inpatient stay. Data is in the form of codes as listed in the Office of Population Conseuses and Surveys (OPCS-4), International Classification of Diseases (ICD-10) and NHS Digital's in-house classification systems. It is the only complete database for Vascular Surgery in the U.K. that allows linkage of different episodes across a patient journey and can also be linked to long-term mortality data (109).

2) The National Vascular Registry (NVR)

This is a quality improvement audit in England and Wales that includes a wide range of health and technical data for several different aspects of Vascular Surgery, including the repair of AAAs. It is run by the Clinical Effectiveness Unit of the Royal College of Surgeons of England and has been shown previously to consistently have approximately 95% case ascertainment for elective AAA cases (26). The NVR includes a wide range of data relevant to this study, including records of patient demographics, baseline comorbidity, preoperative assessment, intraoperative detail, as well as outcomes within 30 days of surgery including mortality, postoperative complications, duration of hospital stay and critical care use for all types of AAA repair.

3) The Office for National Statistics (ONS)

The ONS records all deaths, their date and their causes as documented on a patient's death certificate, for individuals who have died in the United Kingdom. Official linkage with all individuals featuring in HES datasets is possible.

4) Anatomical and procedural imaging analysis data

These data were generated by a Corelab (further detail in Chapter 4), specially designed for the study, which received imaging data (pre-procedural computerised tomography scans and intra-operative angiography for endovascular procedures) via a secure internet exchange portal linked to the Picture Archival and Communication System (PACS) of all of hospitals in the country.

3.3 Identification of Patients for Inclusion

In this cohort study, the intention was to include all repairs of juxtarenal and complex-neck AAA performed in England between 1st November 2017 and 31st October 2019. There is no central repository of juxtarenal and complex-neck AAAs specifically and all known datasets lack the granularity to accurately distinguish standard infrarenal aneurysms from juxtarenal and complex-neck AAAs. They also fail to distinguish between the subtypes of juxtarenal and complex-neck AAAs, a requirement for this cohort study. Therefore, identification of patients for this study was through first-hand interpretation of pre-operative computerised tomography (CT) scans of all AAAs, with strict inclusion criteria based on morphological characteristics of the infrarenal aortic neck (further detail in Chapter 4).

Therefore, all AAA repairs (encompassing all anatomical variations and treatment methods used) were identified from the HES Admitted Patient Care (APC) dataset. This specific dataset of HES provides OPCS-4 codes for operative procedures undertaken in hospital. A set of codes for the repair of abdominal aortic aneurysm (Appendix 2) was utilised to capture all cases of AAA repair in England between the inclusion dates of 1st November 2017 and 31st October 2019.

For patients meeting these coded criteria, the type, hospital and date of their pre-operative CT scan was identified in the NHS Digital Diagnostic Imaging Dataset (DID), a dataset linked to HES (Appendix 2 for imaging codes). DID is a collection of data on diagnostic imaging tests taken from NHS providers' radiological information systems. It does not include the images that are produced as a result of these tests, but rather the information about referral source, details of the test (type of imaging, body part etc), storage location and waiting times amongst others.

CT scan images are stored in a Digital Imaging and Communications in Medicine (DICOM) format. The DICOM files for the pre-operative CT scans of all AAA patients identified were retrieved via the NHS Picture Archiving Communication System (PACS) over a secure Internet Exchange Portal (IEP). Upon receipt, CT scan images were irreversibly pseudonymised: this refers to physical deletion of patient identifiable information tagged onto the scan, and replacement with a unique study ID. This process was initially carried out using Carestream Vue PACS v11.4.1.1011 software (Carestream Health, Rochester, NY, USA), but later Osirix MD (Osirix, Geneva, Switzerland) was used for faster processing. The pseudonymised scans were then securely stored for blinded Corelab analysis.

The term "Corelab" refers to a combination of infrastructure and methodology of image analysis according to predetermined reporting standards and definitions. The Corelab functioned to a pre-designed measurement protocol that was approved by an expert "Clinical Consensus Group". A focus on the Corelab protocol, its design and its validation are the focus of Chapter 4 in this thesis.

Patients were therefore included based on accurate analysis of the infrarenal aortic neck on the latest CT scan in the 6 months prior to the date of surgery. It has previously been described in this thesis, how certain morphological characteristics to the infrarenal neck preclude standard endovascular aneurysm repair (EVAR) (Table 1-1). The definition of juxtarenal and complex-neck aneurysms is therefore pragmatically reflective of the instructions-for-use (IFU)

document supporting the stent-grafts implanted as part of standard EVAR. As such, inclusion and exclusion criteria for the cohort study were finalised as shown in Table 3-1.

Table 3-1 Inclusion and Exclusion criteria for a cohort study (based on pre-operative CT scan anatomy).

<table>
<tr><th>Inclusion Criteria</th><th>Exclusion Criteria</th></tr>
<tr><td>Neck length <10mm ("juxtarenal AAA")</td><td>Maximum AAA Diameter <55mm (inc. small saccular aneurysms)</td></tr>
<tr><td rowspan="4">Neck length ≥10mm AND the presence of ≥1 of the following adverse neck features (complex-neck AAA"):
- Beta (β) angle >90°
- Conicality (>10% change in diameter along 15mm length of neck)
- Thrombus lining >1/3 circumference of the neck OR filling 1/3 the surface area of the neck along a 3mm length of neck
- Calcium load in the wall of the neck affecting >1/3 circumference of the neck along a 3mm length of neck</td><td>Ruptured AAA</td></tr>
<tr><td>Standard Infrarenal AAA (by IFU criteria)</td></tr>
<tr><td>Thoracic/Thoracoabdominal Aneurysm</td></tr>
<tr><td>Visceral Aortic Aneurysm
(Aortic diameter at level of SMA ≥30mm)</td></tr>
<tr><td>"Ambiguous" neck AAA (cases where complex-neck definitions satisfy criteria for some stent-grafts but not others), for example:
- Beta (β) angle 61°-90°
- Neck length 10-14mm
- Alpha angle >45°</td></tr>
</table>

The first inclusion criterion is for juxtarenal AAA, as defined by a neck length of <10mm; the use of any commercially available stent-graft at the time of study design in such a patient would constitute off-label use. The second inclusion criterion is for complex-neck AAA, as defined by a neck length of ≥10mm accompanied by the presence of at least one adverse neck feature (from beta angulation >90°, conicality, excessive thrombus-lining and excessive calcification), such that the use of any commercially available stent-graft at the time of study design in such a patient would constitute off-label use.

Exclusion criteria included AAAs that were <55mm in maximal diameter on the latest CT angiogram prior to repair. An infrarenal aortic diameter of 55mm is the threshold at which an enlarging aneurysm should be considered for repair according to international guidelines (5). At sizes smaller than this, repair has not been demonstrated to be beneficial compared to conservative management (19). Aneurysms may be repaired at smaller sizes in women, in cases

where the diameter is increasing at an abnormally fast rate and if the morphology of the aneurysm sac is abnormal (termed saccular, as opposed to fusiform); however, these practices are not standard around the globe, and this subset of aneurysm repairs is relatively small. It was therefore decided to exclude these cases to maintain as much external validity to the findings as possible. Ruptured AAA should have been excluded based on the list of identifying OPCS-4 codes used to generate the list of elective AAA repairs at the outset. However, in the case of miscoding, identification of a ruptured AAA on the pre-operative CT scan was an indication for exclusion. Other anatomical variants of AAA were to be excluded to minimise the significant heterogeneity seen in previous studies. Standard infrarenal aneurysms (on-label for standard infrarenal stent-grafts) have previously been studied to a large extent and are not the focus of this work. Thoracic, thoracoabdominal and visceral aortic aneurysms are considered complex in nature but are distinct from juxtarenal and complex-neck aneurysms in terms of anatomical body cavity involvement (often involve the thorax instead of or in addition to the abdomen) and therefore have different treatment options and clinical outcomes. For that reason, all of the above would be excluded after identification on CT analysis.

The final exclusion criterion refers to complex-neck aneurysms that satisfy complexity criteria for certain endovascular stent-grafts, but not others. Specific hypothetical examples of what is referred to as an "ambiguous" neck, would be:

- A neck length of 13mm with no other adverse features: this aneurysm would be repaired on-label with a Endurant II stent-graft (Medtronic Inc, USA) but off-label with a Zenith stent-graft (Cook Medical, USA)
- A beta angle of 80° with no other adverse features: this aneurysm would be repaired on-label with an Anaconda stent-graft (Terumo Aortic, UK) but off-label with a Medtronic Endurant II stent-graft (Medtronic Inc, USA).
- An alpha angle of 70° with no other adverse features: this aneurysm would be repaired on-label with a Gore Excluder stent-graft (W.L. Gore & Associates, USA) but off-label with a Medtronic Endurant II stent-graft (Medtronic Inc, USA).

As neck complexity was defined by the IFU of commonly used stent-grafts, it was considered appropriate for the study to only include cases that are off-IFU for all commercially available stent-grafts. "Ambiguous" necks are therefore excluded from the analysis and may be the subject of further work.

3.4 Methods Of Repair To Be Compared In The Study Population

Four distinct treatment options are offered throughout England for the repair of juxtarenal and complex-neck AAA. They include:

1) Open Surgical Repair (OSR).
   This involves sutured anastomosis of a surgical conduit, usually by one of two surgical approaches: transperitoneal (from front of abdomen to the back, passing through the main abdominal cavity and its associated organs) or retroperitoneal (from the flank, avoiding the main abdominal cavity and its associated organs).

2) Fenestrated Endovascular Aneurysm Repair (FEVAR)
   This is a customised pre-ordered stent-graft system for which there were 3 commercial devices available to England during the study period. They were Zenith Fenestrated (Cook Medical, USA), Anaconda Fenestrated (Terumo Aortic, UK) and Jotec Extra-design Service (Jotec, UK).

3) Off-label standard endovascular aneurysm repair (EVAR)
   This refers to an off-the-shelf unmodified commercial stent-graft implanted outside of instructions-for-use (IFU) in relation to infrarenal neck anatomy.

4) Standard EVAR with adjuncts
   This refers to the use of an off-the-shelf commercial stent-graft (standard EVAR) combined with one of two adjunctive technologies: endoluminal screws/Heli-FX EndoAnchor System (Medtronic Inc, USA) or parallel stent-grafts (also known as a chimney or snorkel configuration of stent-grafts).

The type of repair undertaken for all included patients was determined by triangulation of three separate data sources, namely 1) Hospital Episodes Statistics Admitted Patient Care dataset 2) the National Vascular Registry and 3) visual interrogation of the intraprocedural images (for endovascular cases) utilising the same pathway of image acquisition as described earlier for pre-operative anatomy assessment.

3.5 Anatomical and Physiological Stratification

Previous studies have failed to account for baseline indication biases in terms of both anatomical variation and physiological risk. A clinical consensus group was convened on 16th December 2019 in London United Kingdom to ensure that this was addressed in the study design. Participants were Vascular Surgeons and relevant multidisciplinary experts from around the United Kingdom (see Acknowledgments for a list of members). Those unable to attend in person were able to join by teleconference. The meeting had two functions:

1) To gather approval for a measurement protocol for the study Corelab (further details in Chapter 4 of this thesis).

2) To conduct a clinical consensus exercise for anatomical and physiological stratification to produce subgroups of clinical relevance for statistical analysis.

Suggestions and discussion were undertaken in a focus group format with opportunity for all to express opinion before reaching consensus through voting. It was decided that neck length is the morphological feature of most interest with regards to complex aneurysms. This replicated a published Delphi consensus exercise undertaken in Italy on the same topic (48). Grouping by neck length in mm would provide clinical relevance to the findings and limit anatomical heterogeneity. Furthermore, the degree to which an infrarenal neck is short will influence which specific endovascular techniques are likely to be employed as well as whether the aortic clamp during OSR can be placed below the renal arteries. In broad terms, infrarenal clamping was thought to be possible for a neck at least 5mm long. Furthermore, experts were unlikely to employ off-label EVAR (with or without adjuncts) in a neck <5mm in length and would consider FEVAR the only reasonable endovascular option.

Therefore, the following primary anatomical stratification across three groups was recommended:

Group 1: neck length 0-4mm ("juxtarenal" aneurysms)
Group 2: neck length 5-9mm ("short-neck" aneurysms)
Group 3: neck length ≥10mm AND unsuitable for standard EVAR within IFU ("complex-neck" aneurysms)

Within group 3, it is appreciated that there will be a variety of adverse neck features present other than neck length (conicality, angulation, thrombus burden and calcification). The potential to separate these depending on the numbers included was recognised, but the *a priori* analysis plan was to group these cases.

Large neck diameter is an adverse neck feature that has been shown to be correlate with poor outcomes. It was felt that 30mm should be the distinction between normal aortic neck and aneurysmal aorta given traditional definitions of an aneurysm, despite IFU criteria "permitting" standard EVAR for uniform necks up to 32mm in diameter. Some centres do not consider standard EVAR appropriate at diameters even smaller than this (above 28mm). It was recognised that cases of uniform infrarenal aorta with adequate length but large diameter (≥30mm) would technically be classified in Group 1 (0-4mm necks), as by protocol they would have a neck length of 0mm. It was felt most appropriate for these cases to be removed from the analysis.

The British Aneurysm Repair (BAR) Score will be used for risk-adjustment. This is a risk prediction model generated through prospectively collected data for over 11,000 patients who underwent AAA repair between 2008 and 2011 (23). Its primary function was to risk-adjust perioperative mortality rates for UK elective AAA repair. It is currently employed for this purpose in the National Vascular Registry to provide comparable mortality rates between hospitals and surgeons, considering variations in case-mix. It is recalibrated annually based on the latest input of data from the previous year's registry submission. The model requires input of 11 different variables across patient medical history, demographics, medication, anatomy, and pre-operative investigation results (Table 3-2). All values are available in the NVR dataset. Other risk predictive models were considered, namely the Medicare model and Vascular Governance Northwest (VGNW) model, but the BAR score has previously been shown to have advantages over these other options (24) and so was considered the preferred model.

Table 3-2 The 11 parameters of The British Aneurysm Repair Score.

Type of repair (Open vs EVAR)	Abnormal ECG (Yes/No)
Age (Continuous)	Previous aortic surgery/stent (Yes/No)
Abnormal Sodium <135 or >145 mmol/L (Yes/No)	Creatinine >120μmol/L (Yes/No)
Abnormal White cell count <3 or >11 $x10^9$ (Yes/No)	Maximal AAA diameter (cm)
Ischaemic Heart Disease or Heart Failure (Yes/No)	Sex (Male or Female)
ASA Grade (I,II, III or ≥IV)	

It was recognised that BAR Score was developed for the full range of anatomical complexity and physiological fitness seen in AAA patients and not specific to patients meeting the inclusion criteria of this study. However, this was not considered a significant limitation as the tool is recognised to demonstrate excellent discrimination throughout a wide range of anatomical complexity and physiological fitness. The purpose of BAR Score in this study was to group patients with comparable levels of risk as opposed to accurately predicting risk for individual patients. As such, subgroups were generated based on BAR score discrimination as follows:

1) **Standard Risk**: Lower 75 percentile of the operated cohort (by BAR score)
2) **High Risk**: Highest 25 percentile of the operated cohort (by BAR score).

Therefore, a total of 6 subgroups were generated for analysis: 3 anatomical groups (1, 2 and 3 as described earlier), and for each anatomical subgroup, there was a division into standard and high-risk groups based on BAR score.

3.6 Outcome Measures

Outcome measures will be described for both early (perioperative) and mid-term post-operative periods. Early or perioperative outcomes are those occurring within 30 days of the operation, or during the same admission as the operation (even if this exceeds 30 days). Late post-operative outcomes are those measured beyond the perioperative period through to the latest available follow-up time point of 3.5 years.

The primary outcome measure was perioperative mortality. This refers to death in hospital during the same admission as the primary operation, or within 30 days of the procedure. This is an accepted time point of clinical relevance for surgical trials in general, but more specifically, it has previously provided discriminatory outcomes between open surgery and endovascular

techniques in the context of standard infrarenal aneurysms. The source of this data was a combination of NVR record and a linked HES-ONS dataset.

Secondary outcome measures in the early post operative period include perioperative complication rates, secondary interventions, and critical care use. Perioperative complication rates comprise a wide range of conditions involving multiple organ systems, including neurological, cardiac, respiratory, renal, and peripheral vascular amongst others. A full list of relevant complications is provided in Appendix 2. These data were sourced from the NVR and HES-APC datasets. Perioperative secondary interventions refer to patients undergoing further interventions in the 30 days after the primary procedure, or within the index hospital admission. These may be directly associated with the aneurysm repair (e.g., return to theatre for bleeding or a wound complication) or may be indirectly associated with the aneurysm repair (e.g., emergency coronary stenting for a heart attack after the primary procedure). Secondary interventions were identified from the HES-APC dataset and further details can be found in Appendix 2. Critical care use data were collected for all patients in the study, specifically whether critical care was used or not and, if so, the duration of stay. This was provided by a combination of the NVR and HES-critical care datasets.

Secondary outcomes involving the follow-up period included overall survival, late all-cause mortality, mid-term aneurysm-related mortality, and mid-term aneurysm-related secondary intervention. Overall survival refers to patients staying alive during the follow-up period, i.e., freedom from death of any cause, from the date of operation through to the last point of follow-up. This is in contrast to late all-cause mortality which refers to death from any cause after the perioperative period through to the last point of follow-up. Mid-term aneurysm-related mortality is a composite outcome measure of death after the perioperative period from any aneurysm-related complication (as listed in ONS death certificate data) or within 30 days of an aneurysm-related secondary intervention. All death data were sourced from the HES-ONS dataset. Mid-term aneurysm-related secondary intervention is a reintervention directly related to the primary repair. These procedures were identified from code-based entries in the HES-APC dataset which required further cleaning with clinical interpretation providing a final judgement on whether an intervention was aneurysm-related. Codes used to screen for mid-term secondary interventions are provided in Appendix 2.

3.7 Statistical Considerations

Power estimates

The primary outcome measure is perioperative death. The primary efficacy parameter is odds ratio. The two primary comparisons of interest were FEVAR v OSR and Off-label EVAR v OSR. It was anticipated that 2000 patients would meet inclusion criteria, based on pilot data from Corelab analysis [unpublished]. Based on published evidence, the perioperative mortality rate for the treatment of juxtarenal/complex-neck AAA was expected to be 8% with OSR and 4% with endovascular strategies (equivalent to an odds ratio of 0.48) (59, 110). Based on detection of a 4% difference of mortality, a power in excess of 80% was estimated *a priori,* if the allocation between treatment strategies were relatively equal and preserved above 70%, even if one treatment strategy were used twice as much as the other two, with Bonferroni adjusted two-sided alpha level of 0.025.

Estimated survival rates at 1, 2 and 4 years are 90%, 80% and 70% respectively. All patients had a median of 3.5 years follow-up after entering this study. It is approximated that 2000 patients should then contribute approximately 550 events (all-cause mortality after 30 days/discharge). As the study is not designed to identify a difference in long-term overall survival, no power calculation is provided to detect some minimum clinically relevant difference. Instead, assuming the difference between two treatment arms to be measured using a log hazard ratio it is estimated that from 550 events, a standard error of approximately 0.085 will be observed. This translates to a 95% confidence interval of length of approximately 0.34. Here, a hazard ratio smaller than 0.71 or larger than 1.40 will be shown to be significant at a 5% level.

Propensity analysis

Statistical analyses of the primary outcome measure shall follow the principle of propensity score analysis. The overall statistical aim is to estimate the causal effect of a treatment approach. Theoretically, this can be achieved on a population level by creating two (or more) balanced sets of patients and then comparing their outcomes. Randomisation is the best tool available for achieving this balance as it would ensure that each individual in a study has an equal chance of receiving each treatment; but this is not always feasible. Therefore, when one cannot randomise then the use of unbalanced datasets is necessary. Propensity score analyses are a method of imposing balance on an unbalanced dataset. It is a method that can be utilised to balance out the

probability of receiving a particular treatment between groups, as well as accounting for known sources of confounding. It cannot account for unknown sources of confounding.

Propensity score refers to the conditional probability of an individual receiving one of the specific treatments being compared, given the measured pre-treatment covariates (111). Covariates are variables available for analysis in the study that are not the outcome, nor the exposure of interest; they may be confounders or not. Propensity score estimation is chosen for the analysis of the primary endpoint instead of multivariable regression techniques because it is considered the most appropriate means of accounting for selection bias at the low level of peri-operative death rates anticipated (112). The propensity score analysis can be broken down into four distinct steps:

1) Calculating the propensity score.

Propensity scores would be calculated for each individual in the study, i.e., what is the probability that the patient received open repair, EVAR +/- adjuncts or FEVAR, based on their known characteristics? This propensity model was constructed using multivariable multinomial regression techniques using a backwards step-wise procedure based on Akaike's information criterion with the treatment strategy being the propensity outcome and all baseline information and co-morbidities included as explanatory variables. Patients for whom a propensity score could not be calculated due to missing data were excluded. The multivariate propensity scores were then used to estimate each patient's chance of being offered each of the treatment strategies with significance set at ≥10%. These scores can be plotted on a graph as shown in Figure 3-1.

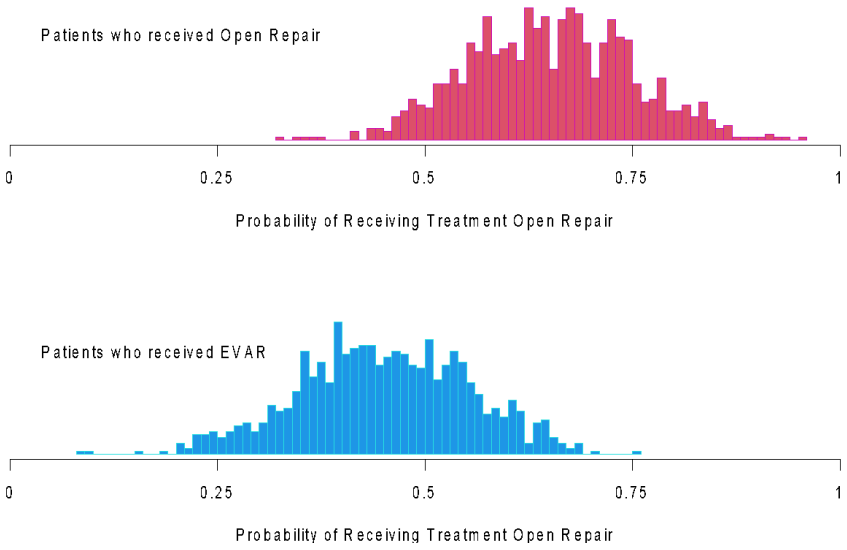


Figure 3-1 Histograms showing the distribution of propensity scores for 2 hypothetical populations. Red = a population who received open repair, Blue = a population who received EVAR. Both x-axes are the propensity scores for open repair, i.e., the likelihood that a patient would have had open repair given their baseline characteristics.

2) Selecting the population for whom a treatment comparison represents a valid question.

At this stage, it would become clear which patients were never realistically going to receive certain treatments. They were those estimated not to have a ≥10% chance of being offered more than one treatment strategy. These individuals would be excluded from the comparative analysis as it is not reasonable to compare treatments in a population of patients who only ever had one viable treatment option. They form the "unsupported regions" on a propensity score histogram, whereas those suitable for comparative analysis form the "region of common support" (Figure 3-2).

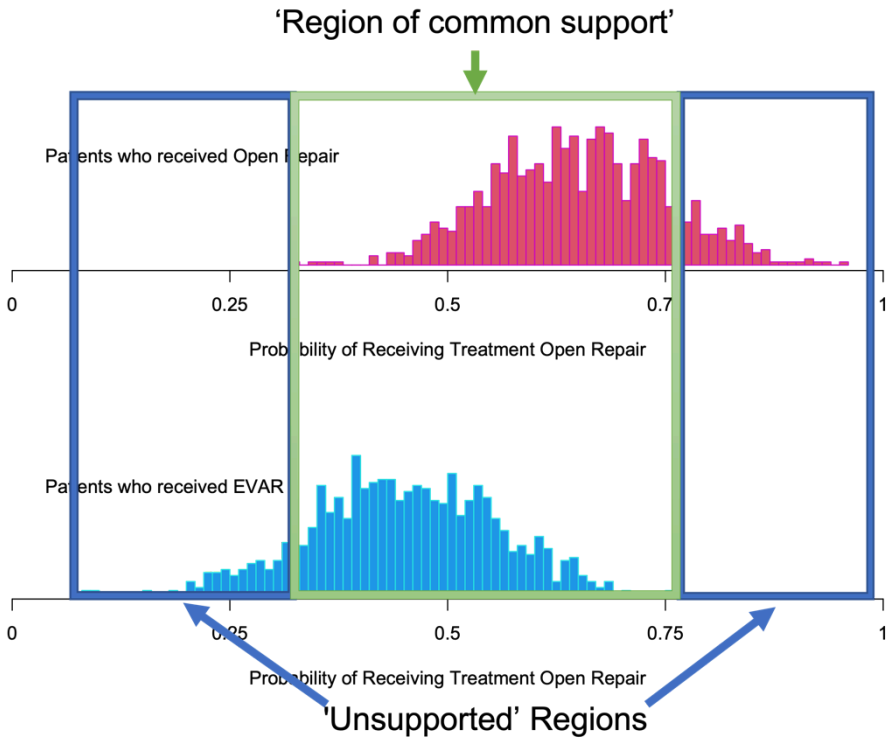


Figure 3-2 Demonstration of "region of common support" (green) and "unsupported regions" (blue) on a propensity score histogram.

The unsupported region on the left represents individuals who were only likely to receive EVAR and the unsupported region on the right represents those only likely to receive open repair. The central region of common support represents individuals who may have received either treatment, so can contribute to the comparative analysis.

3) Choosing a strategy for employing the propensity score.

In this study, the chosen methods of utilising the propensity score were stratification and covariate adjustment. This creates similar patients within smaller sub-groups or strata, as compared to comparing the entire "region of common support" in isolation. Prior to analysis it was confirmed that each stratum contained at least 20 observed perioperative deaths. If not, the

strata was combined with an adjacent strata level. Eventually, four distinct strata were created (Figure 3-3); one strata of patients who had a significant chance of being offered all three treatment strategies (OSR, FEVAR and FEVAR), and three strata each with a significant chance of being offered two treatment strategies (OSR and EVAR; OSR and FEVAR; EVAR and FEVAR). Analysis of the data were then performed using a conditional (stratified) logistic regression model. Included in this model are the stratification levels, the individual propensity scores, and the treatment identifier.

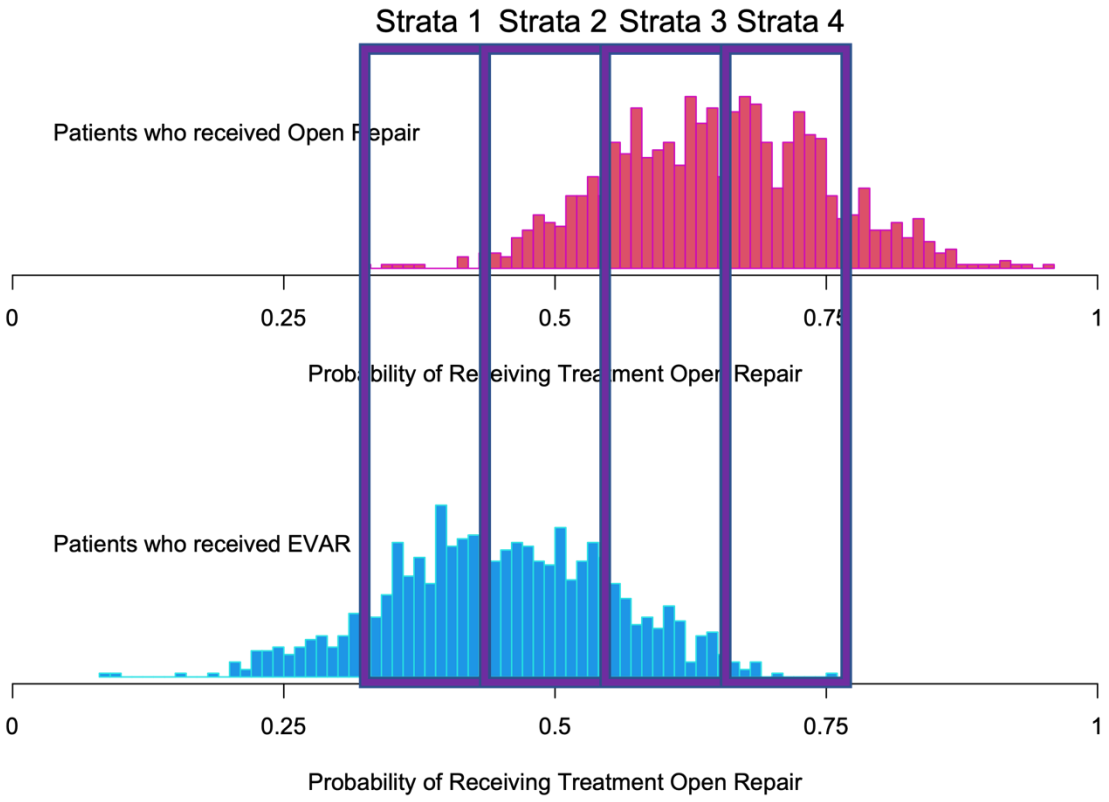


Figure 3-3 Demonstration of stratification for propensity analysis, creating strata within the region of common support.

4) Analysing the propensity score-based data

Comparative outcomes were first analysed within each of the 4 strata individually (Figure 3-4) and then pooled to provide an overall estimate of treatment effect. Analyses of the primary outcome were performed using conditional logistic regression conditioning on the defined strata and including the propensity scores as adjusting covariates. The key efficacy parameter of interest was an odds ratio presented with a 97.5% confidence interval. Analysis of the perioperative mortality was conducted using a Bonferroni adjusted alpha level of 0.25 to account for multiple

comparisons as is consistent with the study sample size estimate. All other comparisons use the $p<0.05$ level to determine statistical significance. Analysis was undertaken independently by two statisticians using R (Version 4) and SAS (Version 9).

Figure 3-4 Representation of propensity analysis being undertaken in each of the 4 strata.

Sensitivity analyses for the primary outcome measure

Sensitivity analyses were performed under a number of scenarios to assess the robustness of the study results to the analysis assumptions and to ensure the results are not sensitive to either the propensity model or the method of application. These scenarios included removal of propensity scores as adjusting covariates, addition of the BAR score as an adjusting covariate and the calculation of an alternative propensity score removing the covariates that represent patient comorbidities.

Secondary outcome measure analyses

Secondary categorical outcomes follow an analytical approach equivalent to that of the primary outcome (for perioperative complication rates, secondary interventions, and critical care use).

Analysis of time-to-event outcomes were performed using stratified Cox regression including propensity scores as adjusting covariates.

Missing data

Reports of HES data validation confirm high levels of completeness and accuracy. Therefore, missing data or inaccurate data is unlikely to be a significant problem. It was proposed *a priori* that covariates with small amounts of missing data (≤10%) will be included on a complete case basis and covariates with a large amount of missing data (>10%) will be excluded from the analysis.

4 A Protocol For Data Management, Anatomical Measurement And Internal Validation Of Computerised Tomography Scan Analysis For The Complex Aortic Neck

4.1 Introduction

The previous chapter introduced the methodology for a national cohort study comparing the different treatments offered in England for the repair of juxtarenal and complex-neck aneurysms. Although largely based on routinely-collected data sources, the study also required image interpretation for a large number of patients as a crucial component of the study design. This was performed in a study "Corelab", a fully digital and paper-free facility.

Clinical radiological interpretation is inherently subjective. However, because anatomical detail influences treatment decisions and clinical outcomes, interpretation of said imaging needs to be reproducibly standardised. A Corelab refers to a combination of infrastructure and methodology for image analysis according to predetermined reporting standards and definitions.

In this cohort study, the analysis of pre-operative computerised tomographic (CT) angiograms in the Corelab had two primary aims: 1) to aid in the identification of juxtarenal and complex-neck aneurysms from a wider pool of all AAAs repaired in England during the inclusion period, and 2) to aid in the stratification of included patients across 3 anatomical subgroups for separate analysis (Group 1: 0-4mm neck length, Group 2: 5-9mm neck length, Group 3: ≥10mm neck length but with other adverse morphological characteristics).

To ensure external validity to the eventual findings of the comparative analysis, it is crucial that the methods, utilised to identify the aneurysms of interest and to group them, are shown to be accurate and reproducible. This chapter will detail the Corelab standard operating procedure for data management, the design of the measurement protocol, and an internal validation exercise. Additionally, it will provide definitions of various anatomical parameters of the aneurysm that are adhered to by the Corelab.

4.2 CT Scan Management

CT scan management involves the retrieval, pseudonymization and upload of CT scans for Corelab analysis in line with regulatory approvals. It was performed by the 'Research PACS Clerk' who is a trained member of the study team and an employee of the host NHS trust. The process is conducted in compliance with the principles of The General Data Protection Regulation (GDPR), tailored by the Data Protection Act 2018, with appropriate training for all members of the study team.

The date and location of the most recent CT scan of the abdominal aorta, prior to the date of the patient's operation, is identified from the HES-DID dataset. This CT scan DICOM data is retrieved via the NHS PACS system utilising NHS number, date of birth and the date of specific CT scan in question, as provided by NHS Digital under a data sharing agreement. The transfer is conducted securely over an internet exchange portal (IEP) that is in routine clinical use throughout England. Legal basis was secured to access patient data without consent through the Secretary of State's Section 251 approval with Confidentiality Advisory Group (CAG) recommendation.

Upon receipt, the scan data were irreversibly pseudonymised, i.e., all patient identifying data as well as information regarding the performing institution were removed from the images. These data are replaced with a unique Study ID number which acts as pseudonym. It is not possible for the study team to re-identify any patient from this point. This process was initially carried out using Carestream Vue PACS v11.4.1.1011 software (Carestream Health, Rochester, NY, USA), but later Osirix MD (Osirix, Geneva, Switzerland) was used for faster processing.

The pseudonymised scans were then uploaded onto a research section of the local PACS server, entitled the "Vendor Neutral Archive" (VNA), accessible via a two-stage authentication process and only to members of the study team approved for Corelab analysis. Analysis of these scans is therefore blinded to the interpreting clinician researcher. It is possible to see the Study ID and date of scan acquisition when a CT is loaded for analysis, but not possible to re-identify a patient.

4.3 Development of Measurement Protocol

The Corelab protocol was initially devised by consensus between three researchers: a senior vascular surgeon (also the chief investigator of the study) and two clinical research fellows, following review of the literature and the instructions-for use (IFU) documents of all commonly

used commercial EVAR stent-grafts (Table 1-1); information regarding anatomical features of complexity with respect to the neck of abdominal aortic aneurysms was taken into consideration.

Only 2 studies described a Corelab process around the interpretation of CT angiograms of the aorta (113, 114). In the first, the context of the Corelab differed from that of this cohort study, in that it showed feasibility for both research and clinical use, and in addition it measured wider segments of the aorta, not just the infrarenal aortic neck. It suggested that measurements that relied on consistent anatomical landmarks were most reproducible, whereas assessment of angulation and calcification was subjective (113). The second involved validation and assessment of measuring both 2-dimensional and 3-dimensional CT series; it concluded that utilising 3-dimensional image reconstruction across multiple planes led to greater consistency and should be preferred for repeatable measurements of AAAs (114). This evidence was taken forward into the Corelab protocol for this study.

There are two aspects to consider with regards to the Corelab protocol. Firstly, the definitions agreed upon to form the basis of the morphological assessment. And secondly, the measurement process of the infrarenal neck itself. In general, with a paucity of information regarding Corelab set-up in the published literature, content around definitions was determined by consensus and subsequent approval by members of an expert clinical consensus group.

The meeting of the clinical consensus group has been described earlier (Chapter 3, Section 5). It was convened on 16th December 2019 in London, United Kingdom and participants were Vascular Surgeons and relevant multidisciplinary experts from around the United Kingdom. Those unable to attend in person were able to join by teleconference. Suggestions and discussion were undertaken in a focus group format, with reference to stent-graft IFUs, with opportunity for all to express opinion before reaching consensus through voting. The meeting had two functions:

1) To gather approval for study definitions that underpin the measurement protocol for the study Corelab (details to be provided in this chapter).
2) To conduct a clinical consensus exercise for anatomical and physiological stratification to produce subgroups of clinical relevance for statistical analysis (as previously detailed in Chapter 3, Section 5).

Definitions of the anatomical parameters measured in the Corelab were eventually set as presented in Table 4-1.

Table 4-1 Anatomical Definitions for the Corelab assessment of pre-operative CT angiograms of the aorta, as approved by an expert Clinical Consensus Group.

Measurement terminology	Unit of measurement	Definition
Total neck length	Millimetres (mm)	Distance between: a) Lowermost major renal artery and, b) - Point of abrupt change in calibre *(if the neck is parallel sided and <30mm diameter)* OR, - where the aorta reaches 30mm in diameter
Neck diameter	Millimetres (mm)	Orthogonal diameter of infrarenal neck at specified distances (0mm, 5mm, 10mm and 15mm) below the origin of the lowermost major renal artery (outer wall to outer wall diameter)
α neck angle	Degrees (°)	Angle between axis of suprarenal aorta and axis of infrarenal neck
β neck angle	Degrees (°)	Angle between axis of infrarenal neck and axis of aneurysm
Aneurysm Diameter	Millimetres (mm)	Maximum orthogonal diameter of aneurysm (outer-to-outer)
Excessive thrombus	Binary	Presence of thrombus lining >1/3 circumference of neck or filling >1/3 surface area of the axial slice, along a 3mm length of neck
Excessive calcification	Binary	Presence of calcium involving >1/3 circumference of neck in axial slices along a 3mm length of neck

4.4 The Corelab Measurement Protocol

Image analysis was initially performed using the multi-planar reconstruction function of Carestream Vue PACS v11.4.1.1011 software (Carestream Health, Rochester, NY, USA). After completion of measurement on approximately 3000/9000 scans, the host site installed an updated version of the same programme (v12.2.2.1025) for the measurement process of the remainder.

CT series of the abdominal aorta with arterial phase contrast are loaded in double-oblique multiplanar reconstructed (MPR) format. This will permit visualisation of the

aneurysm/aneurysm neck in axial, sagittal and coronal views. Contrast windowing and magnification are considered baseline adjustments prior to commencement of the measurement process, which is detailed below for specific measures:

1. Aneurysm diameter

Both the coronal and sagittal planes are aligned with the long axis of the aneurysm body (not the flow lumen) using double oblique adjustment. This allows orthogonal axial view of the aneurysm at its largest point. A ruler function is used to measure the maximal (outer to outer) diameter of the aneurysm in the axial plane (Figure 4-1).

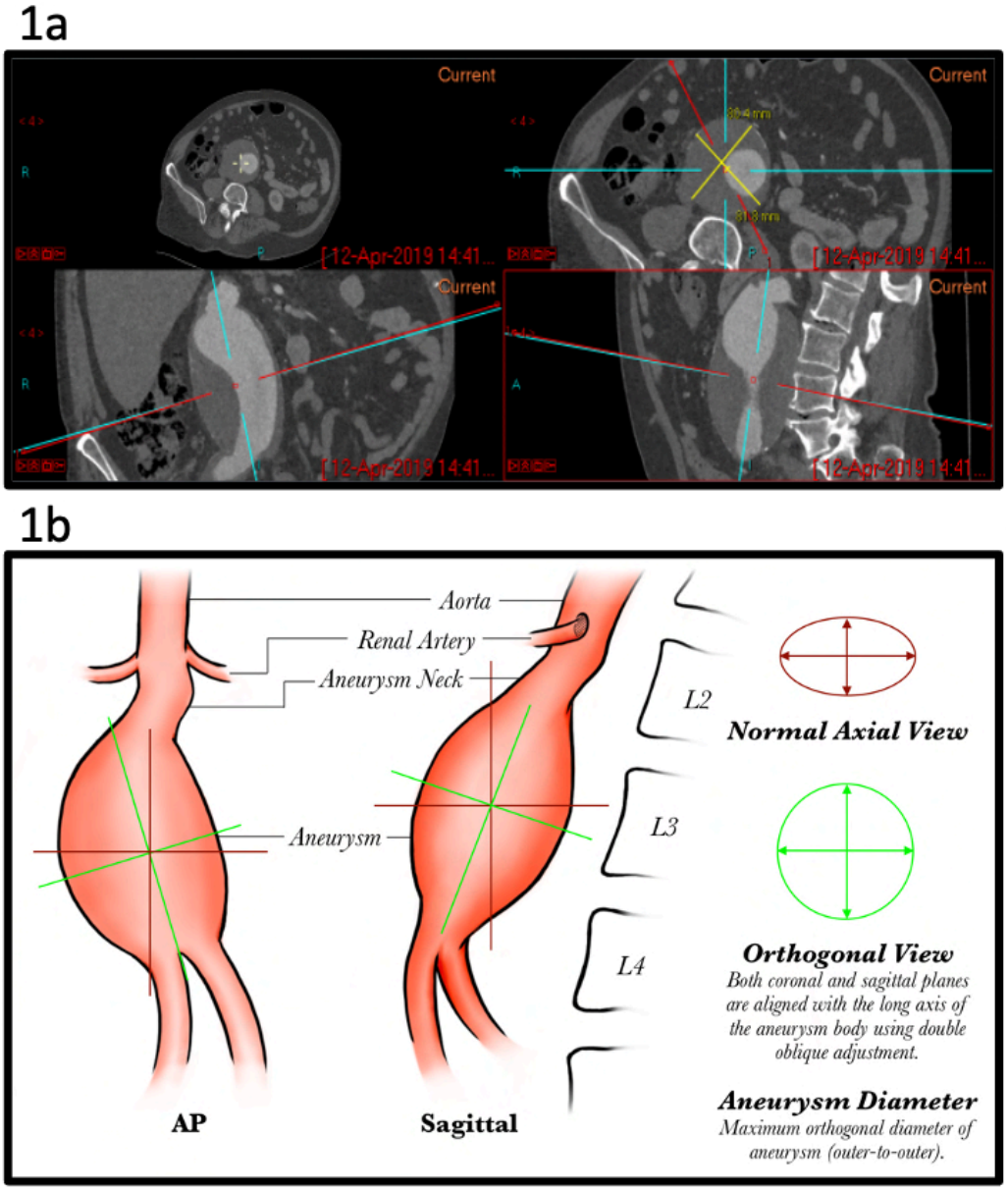


Figure 4-1 a) screenshot of a multiplanar reconstructed orthogonal view of AAA diameter measurement, b) diagrammatic representation of this measure.

2. Total neck length

Total neck length is defined as the distance between the inferior aspect of the lowermost main renal artery and the superior aspect of the aneurysm.

The superior aspect of the aneurysm is defined as:

- The transition between normal aorta and aneurysm, where the aneurysm commences abruptly (if the neck is parallel sided and <30mm diam), OR
- the point at which the neck diameter becomes 30mm in cases where the transition to aneurysm is not abrupt.

Long axis of the aneurysm neck is aligned to both coronal and sagittal planes and the distal margin of the lower most renal artery is profiled by aligning double-oblique planes to the renal artery ostium in the axial view. A ruler function is used to measure the neck length in both coronal and sagittal views (Figure 4-2).

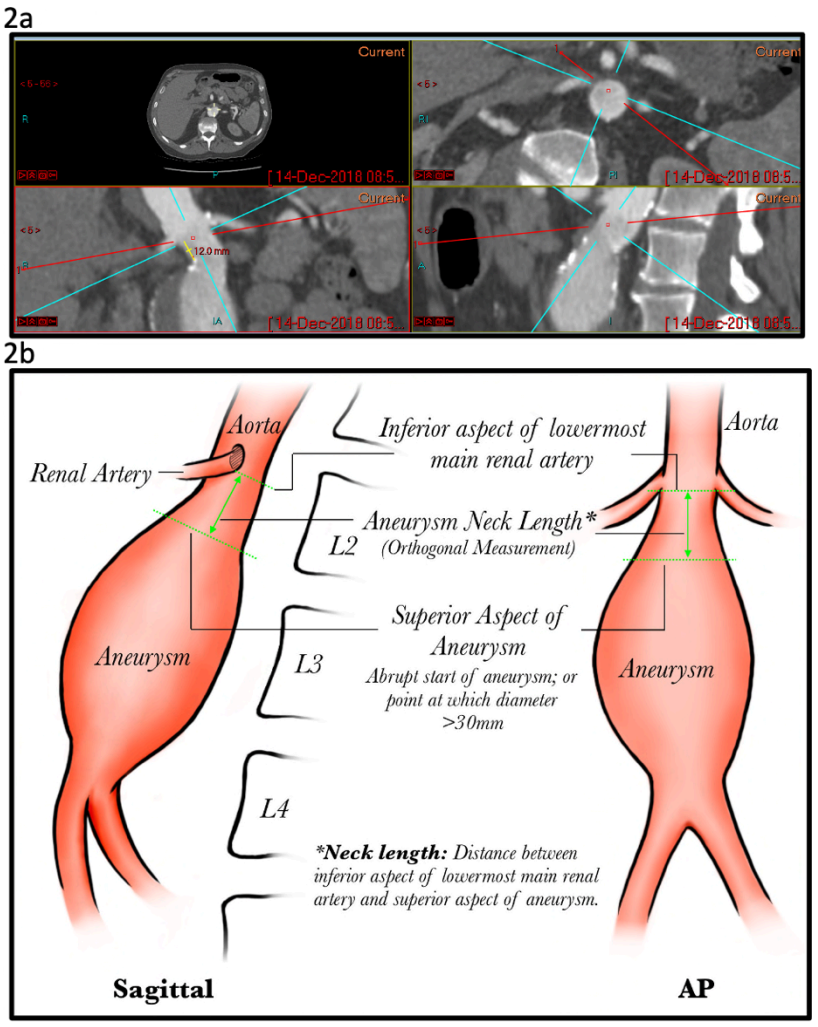


Figure 4-2 a) screenshot of a multiplanar reconstructed orthogonal view of AAA neck length measurement, b) diagrammatic representation of this measure.

3. β neck angle

Beta (β) neck angle refers to the angle between the axis of the neck and the axis of the aneurysm, measured in degrees.

The first step is to align both coronal and sagittal planes to the axis of the aneurysm neck. Tilting the double-oblique marker lines in the axial view will permit visualisation of the aneurysm axis in the coronal or sagittal views. The angle between the axis of the neck and the axis of the aneurysm is measured and subtracted from 180 to calculate the β neck angle (Figure 4-3).

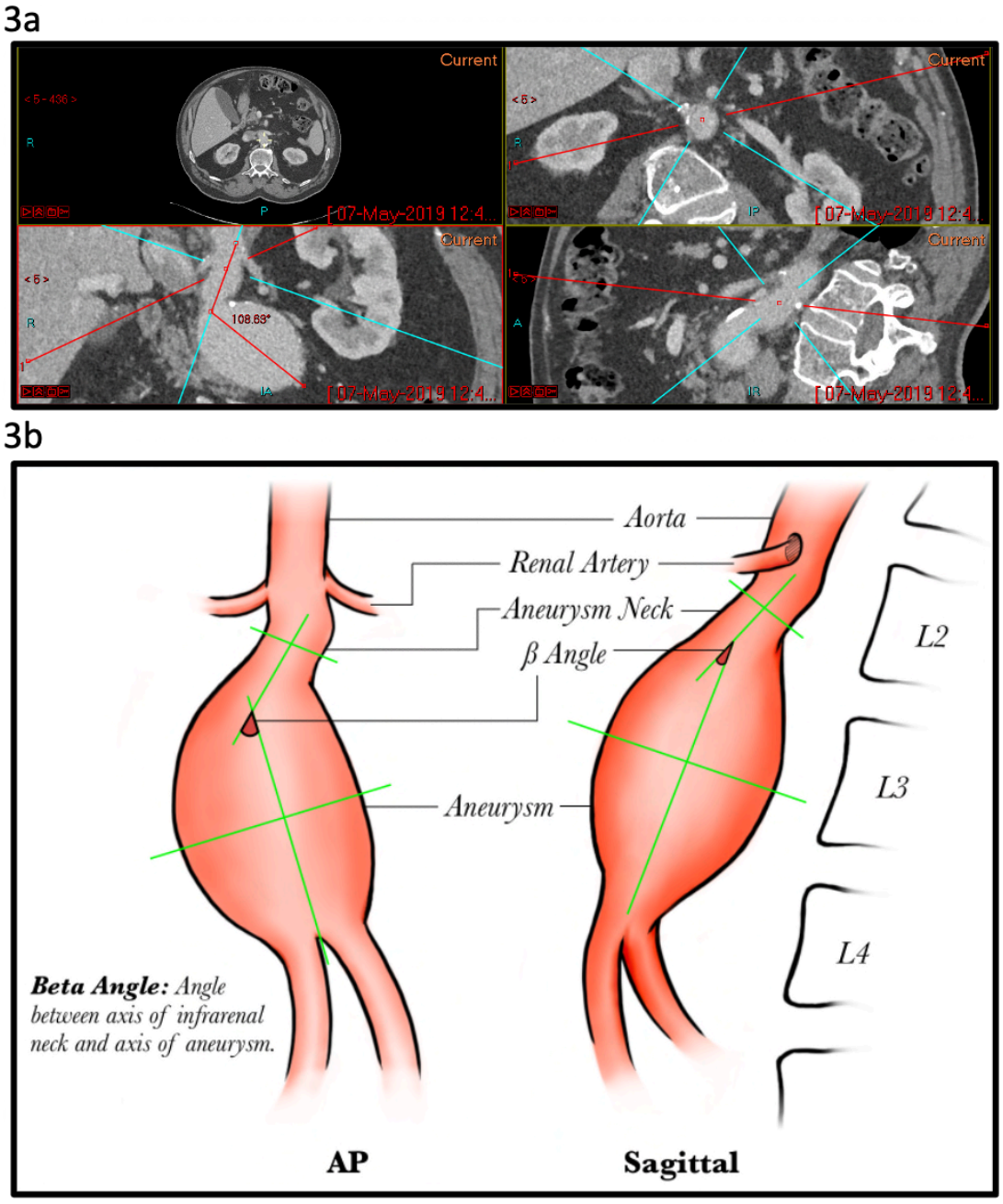


Figure 4-3 a) screenshot of a multiplanar reconstructed orthogonal view of AAA β-angle measurement, b) diagrammatic representation of this measure.

4. Neck Calcification

Excessive calcium load is defined as the presence of calcification affecting >1/3 circumference of the neck along a 3mm length of neck, either as 1 continuous "plate" of calcium, multiple plaques or as speckled coverage.

Measurement involves profiling the neck in both coronal and sagittal views, with subsequent assessment in the orthogonal axial over 3mm lengths of neck (Figure 4-4). Presence of excess calcification is determined based on a visual estimation of the 1/3 circumference threshold and recorded as binary outcome.

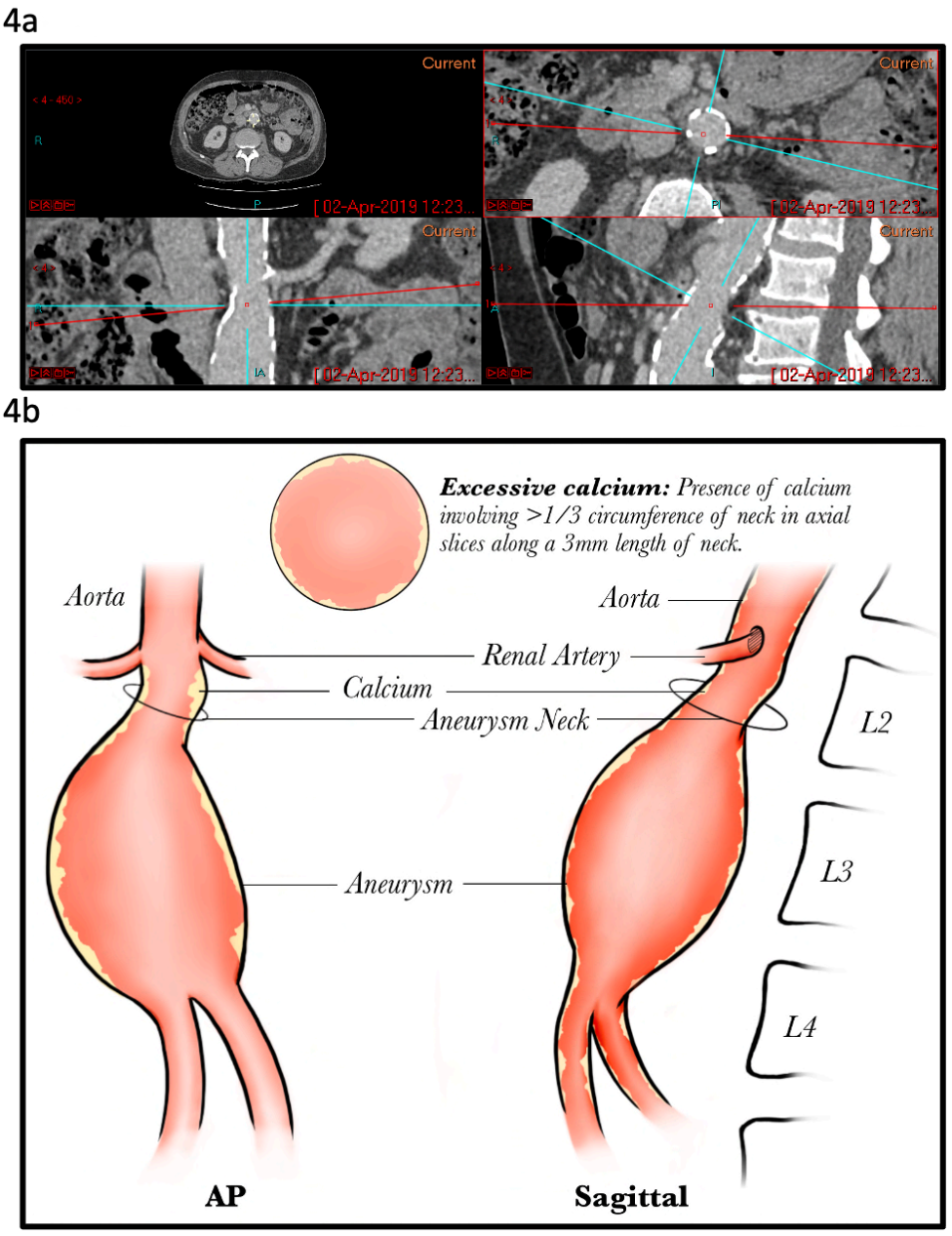


Figure 4-4 a) screenshot of a multiplanar reconstructed orthogonal view of AAA neck calcification assessment, b) diagrammatic representation of this measure.

5. Neck Thrombus Load

Excessive thrombus load is defined as the presence of thrombus within the lumen of the aortic neck, lining >1/3 circumference of the neck OR filling 1/3 the surface area of the neck in axial slices along 3mm of neck length.

Assessment involves profiling the neck in both coronal and sagittal views, with subsequent assessment in the orthogonal axial view. Thrombus load is assessed on visual estimation of the 1/3 circumference threshold or 1/3 surface area threshold across multiple axial views of the neck (Figure 4-5) and recorded as a binary outcome.

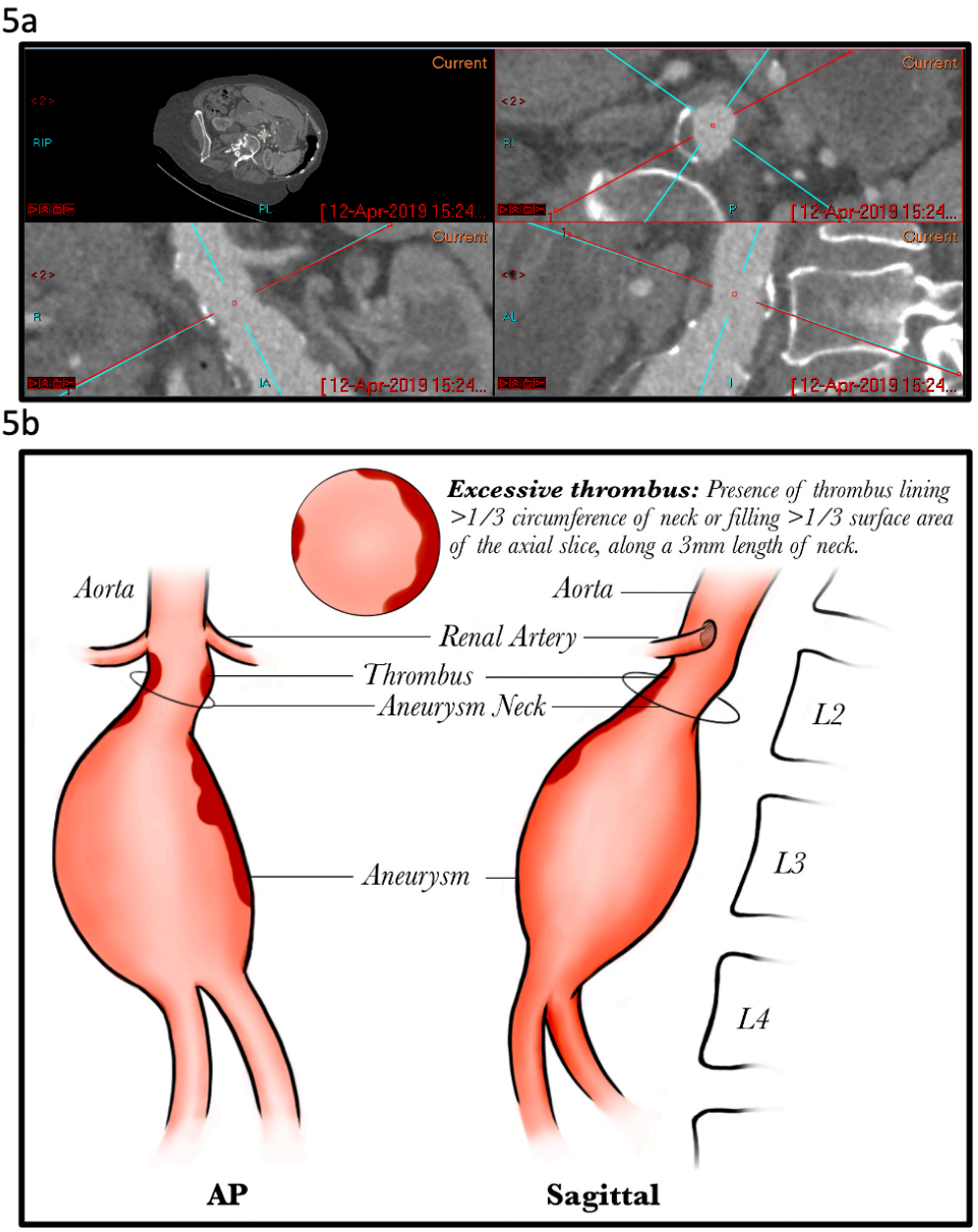


Figure 4-5 a) screenshot of a multiplanar reconstructed orthogonal view of AAA neck thrombus assessment measurement, b) diagrammatic representation of this measure.

6. Neck diameters

Neck diameter is defined as the maximal outer to outer diameter (mm) in orthogonal cross section. The aneurysm neck is profiled in both coronal and sagittal views with subsequent assessment in the orthogonal axial view. Neck diameters are measured at the level of the lowermost renal artery, at 5mm below this point, at 10mm below this point, and at 15mm below this point. The various positions along the length of the neck will be defined using the ruler function on the coronal view as seen in Figure 4-6. Where the neck is <15mm in length, a neck diameter measurement will additionally be taken at the most distal point of the neck.

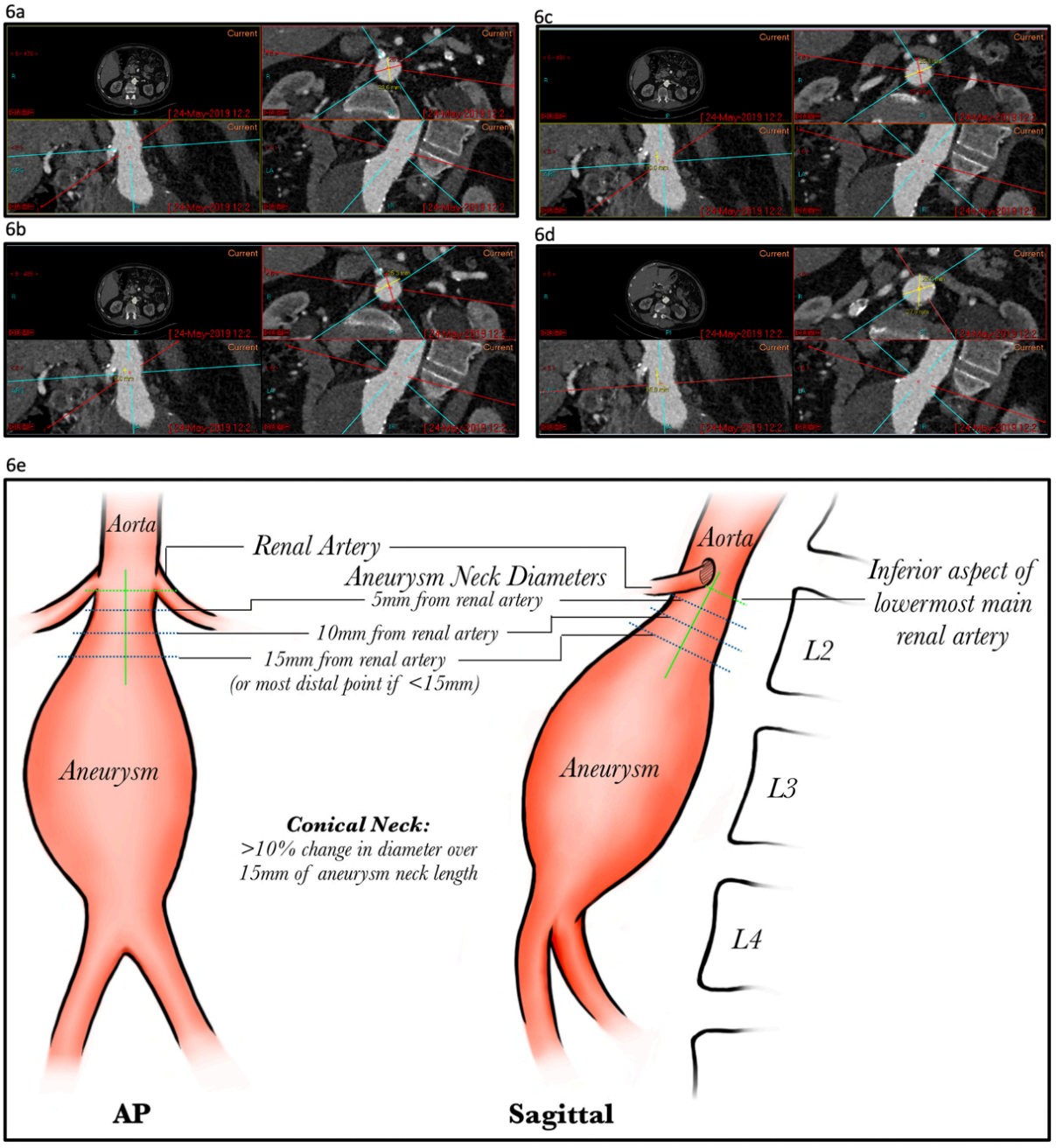


Figure 4-6 a-d) screenshots of a multiplanar reconstructed orthogonal view of AAA neck diameter measurements at 0,5,10 and 15mm below lowermost renal artery respectively, b) diagrammatic representation of this measure.

7. α neck angle

α neck angle refers to the angle, in degrees, between the axis of the suprarenal aorta and the axis of the infrarenal neck.

As there is often tortuosity of the suprarenal aorta making axis delineation unclear, only the 30mm of suprarenal aorta immediately proximal to the lowermost major renal artery will be used to create its axis. The first step of measurement is alignment of the axis of the neck in both coronal and sagittal planes. Tilting the double-oblique marker lines in the axial view in the next step will align the supra renal aorta in the coronal or sagittal views with the neck visible in the same field. The angle function is used to measure the angle between the neck and the suprarenal aorta and α neck angle is calculated by subtraction from 180 (Figure 4-7).

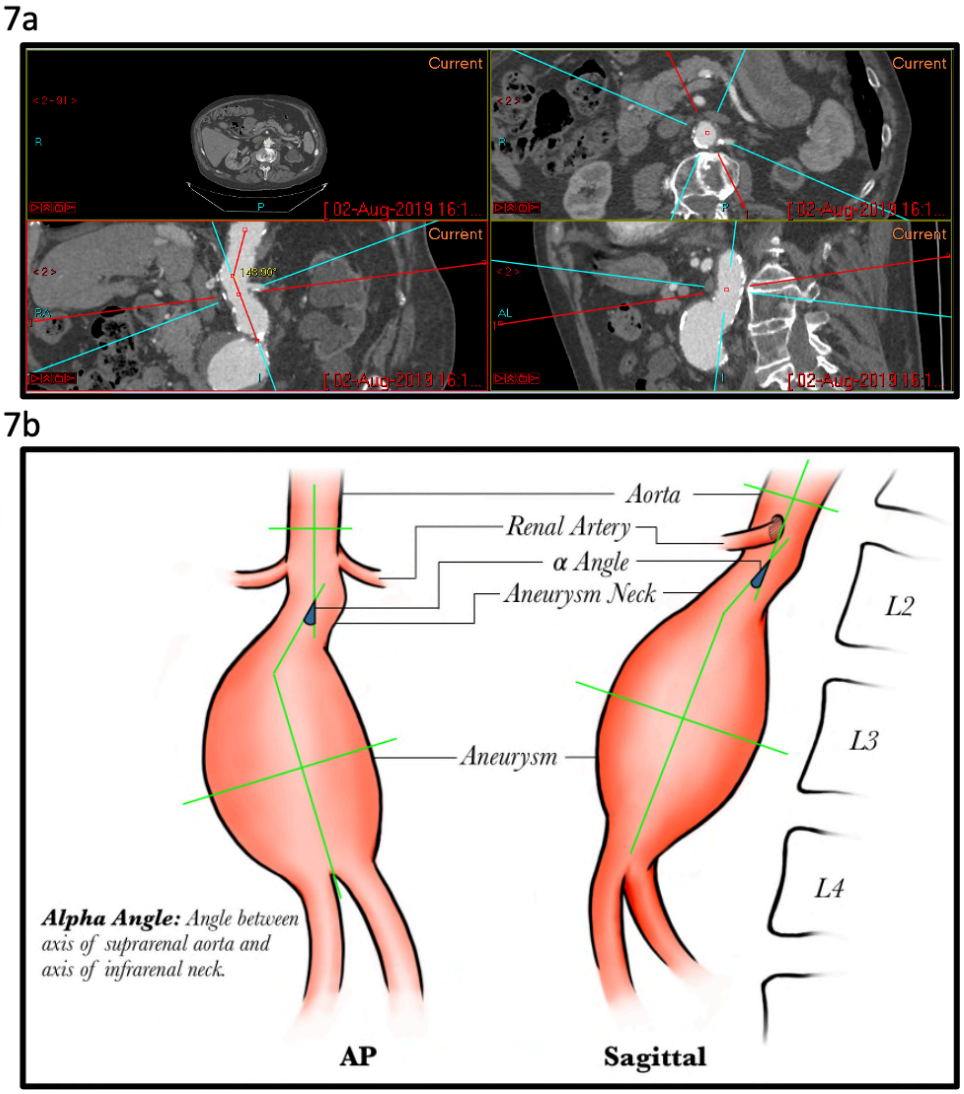


Figure 4-7 a) screenshot of a multiplanar reconstructed orthogonal view of AAA a -angle measurement, b) diagrammatic representation of this measure.

4.5 Validation Exercise

The measurement process for interpretation of the aortic neck is the most important and unique part of the cohort study, as it accurately leads to the inclusion of a population of interest with minimal heterogeneity. For the results of any subsequent comparative analysis to be applicable to the real world, the measurement process must be standardised and reproducible. It was to this aim that, once the protocol had been finalised, a validation exercise was performed to assess the reproducibility of following the measurement process.

An internal validation study was performed on a subset of 70 CT Angiogram scans, randomly selected from a pool of the first 500 CT scans received in the Corelab as part of study set-up. 3 assessors of varying seniority (medical student, junior vascular trainee and senior vascular trainee) undertook independent and blinded assessment of the CT scans using the Corelab Protocol described above in this chapter.

Seven measurements undergoing validity testing included maximal aneurysm diameter, total neck length, beta angle and neck diameters at 4 points along a 15mm length. Assessment of calcification and thrombus is based on subjective visual assessment of the images, as opposed to a software tool that would provide a quantitative result, and so no validation was attempted for these metrics. Additionally, the results of the two trainees (of a seniority level reasonably expected to perform the Corelab analysis) underwent analysis to investigate potential discrepancies of patient grouping or inclusion into the study as a result of the raw measurements. Groupings were into the anatomical subgroups specified in the study design, namely Group 1: 0-4mm neck length, Group 2: 5-9mm neck length, Group 3: ≥10mm neck length but with other adverse morphological characteristics, with the addition of Group 4 representing non-complex or standard necks.

Comparisons between Rater 1 vs Rater 2, Rater 3 vs Rater 1 and Rater 3 vs Rater 2 were performed in order to calculate and summarise the inter-rater variability for each measure. A two-way mixed effects model (each measurement done by the same set of raters, who are the only possible evaluators) was used to estimate the intra-class correlations (ICC) along with 95% confidence intervals for all 7 different measurements.

Furthermore, Bland-Altman plots were generated to demonstrate the results. Bland-Altman plots are traditionally used to plot agreement between two different measurements. The process was

therefore modified to accommodate three measurements per domain. In order to generate the scatter plots, for each of the 7 domains domain, the mean across the three observers was calculated for each scan (x-axis). Then, the difference from the mean was calculated for each measurement for all three observers and combined (y-axis). This enabled a scatter plot to be generated of the mean value vs the difference from the mean. If a measurement was available for each scan, one would expect to have 210 different circles on the scatter plot. However, if the observers assigned exactly the same value to an item, then some of the circles will be drawn on top of each other, resulting in a lower number of circles spotted on the plot.

All statistical analysis was performed using STATAv15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) An alpha level of 5% was assumed.

Inter-rater variability for the 3 raters across the 7 different measurement domains is demonstrated in Table 4-2. Intra-class correlation is demonstrated in Table 4-3. A high degree of reliability was found between all measurements in all 7 domains across all 3 raters (ICC >90% for all 7 measures; $p<0.001$ for all). There was minimal inter-rater variability for all 7 domains as shown in the Bland-Altman plots (Figures 4-8 to 4-14).

For the grouping validation exercise of the 2 trainee measurements, a kappa statistic was calculated in order to examine inter-rater reliability. The distribution of grouping numbers for the two raters is shown in Table 4-4. There was a perfect inter-rater agreement [kappa statistic (k) =1.00, se=0.0881], suggesting that any discrepancies in measurement did not translate to discrepancies in subsequent inclusion or grouping for analysis.

Table 4-2 Inter-rater variability for all measurements, across 3 raters measuring 70 scans.

Statistic	Total neck length (units)	Neck angle	Aneurysm diameter (units)	Diameter 0 (units)	Diameter 5 (units)	Diameter 10 (units)	Diameter 15 (units)
n	210	190	210	190	184	180	164
Mean	1.03	-0.38	0.56	0.03	0.05	0.10	-0.11
SD	6.65	10.14	2.47	1.10	1.27	1.18	2.43
Min	-18.0	-51.0	-4.0	-3.0	-6.0	-4.0	-19.0
Max	31.0	19.0	15.0	5.0	5.0	4.0	3.0

Table 4-3 Intra-class Correlation (ICC) for the 3 measurements across each of the 7 domains.

Statistic	Total neck length (units)	Neck angle	Aneurysm diameter (units)	Diameter 0 (units)	Diameter 5 (units)	Diameter 10 (units)	Diameter 15 (units)
ICC	0.972	0.952	0.983	0.976	0.971	0.974	0.909
95% CI	0.959 – 0.982	0.927 – 0.969	0.974 – 0.989	0.964 – 0.985	0.956 – 0.982	0.960 – 0.983	0.857 – 0.945
F (df1, df2)	F(69, 138)=36.76	F(62, 124)=20.60	F(69, 138)=62.32	F(62, 124)=41.22	F(60, 120)=34.36	F(59, 118)=38.09	F(52, 104)=10.89
p-value	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*

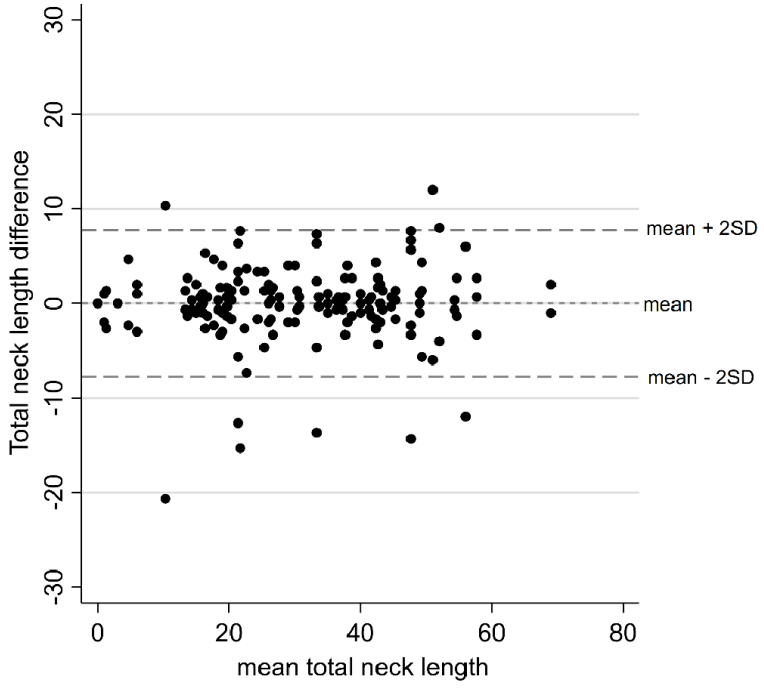


Figure 4-8 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of neck length (mm). (x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

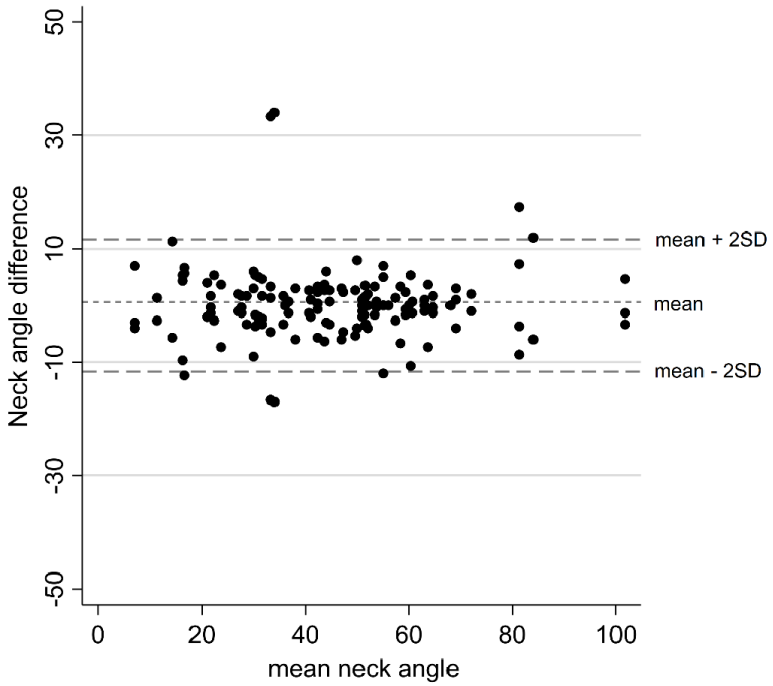


Figure 4-9 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of β-angle (degrees). (x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

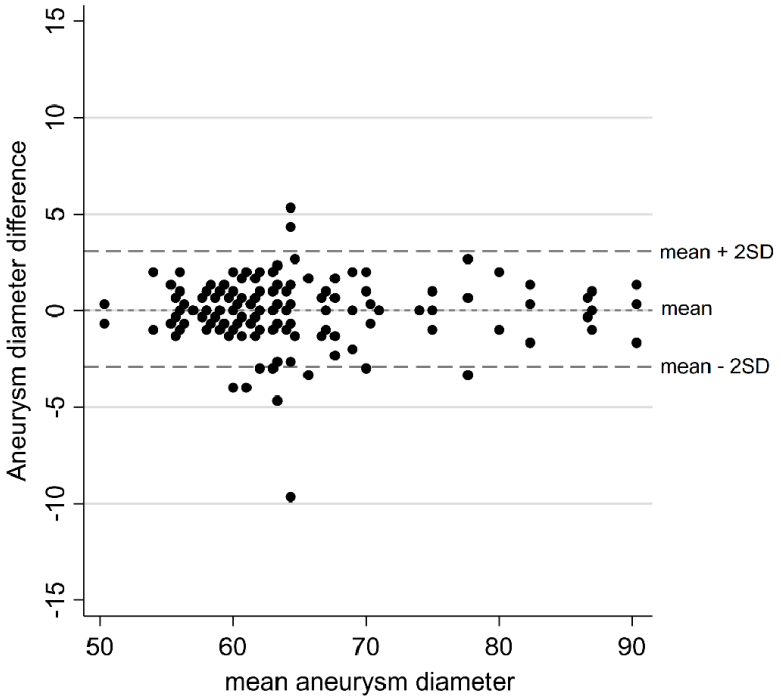


Figure 4-10 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of AAA diameter (mm). (x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

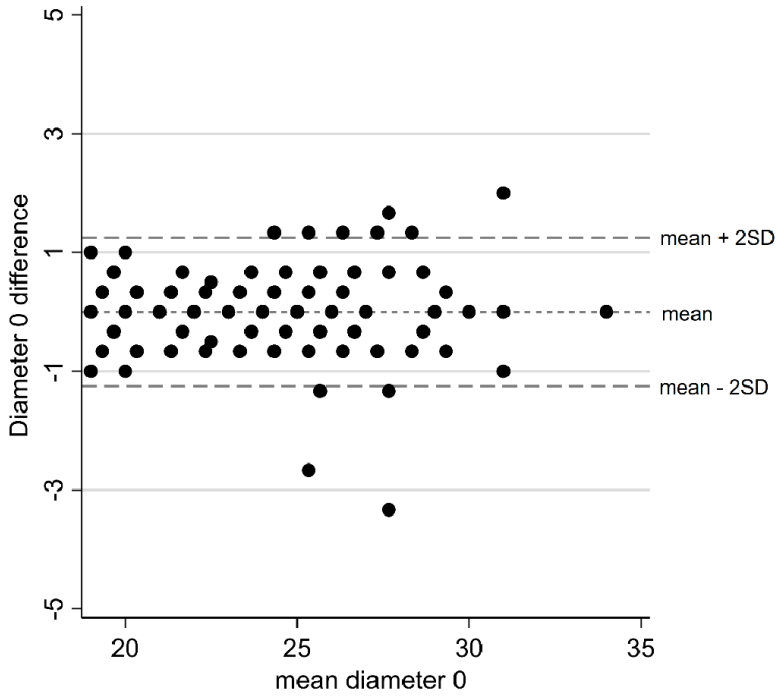


Figure 4-11 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of neck diameter at the level of the lower most renal artery (mm).
(x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

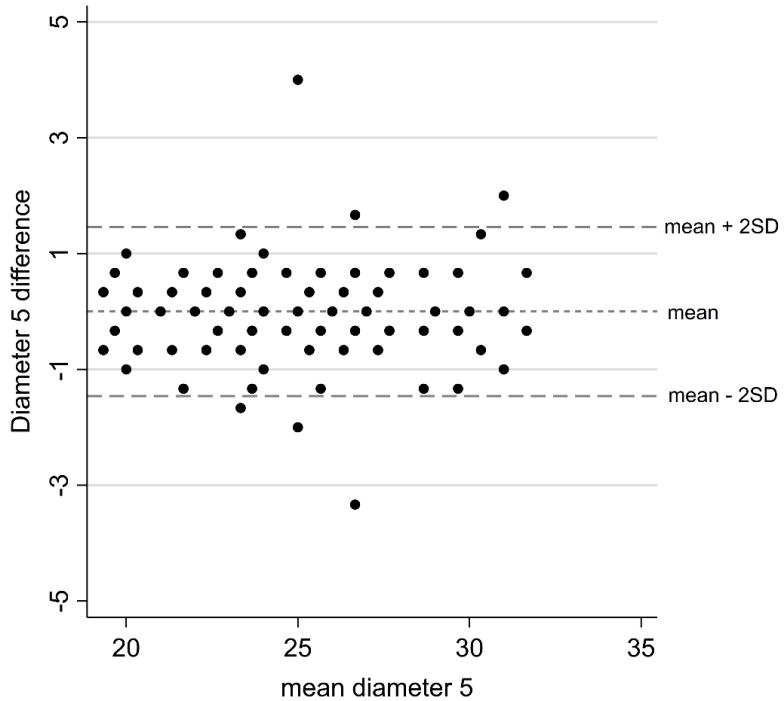


Figure 4-12 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of neck diameter 5mm below the level of the lower most renal artery (mm).

(x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

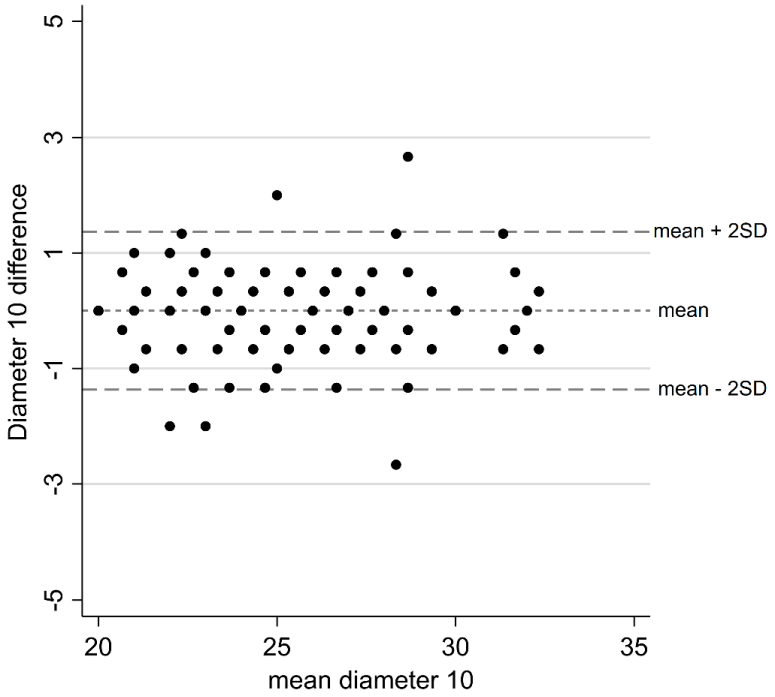


Figure 4-13 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of neck diameter 10mm below the level of the lower most renal artery (mm).
(x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

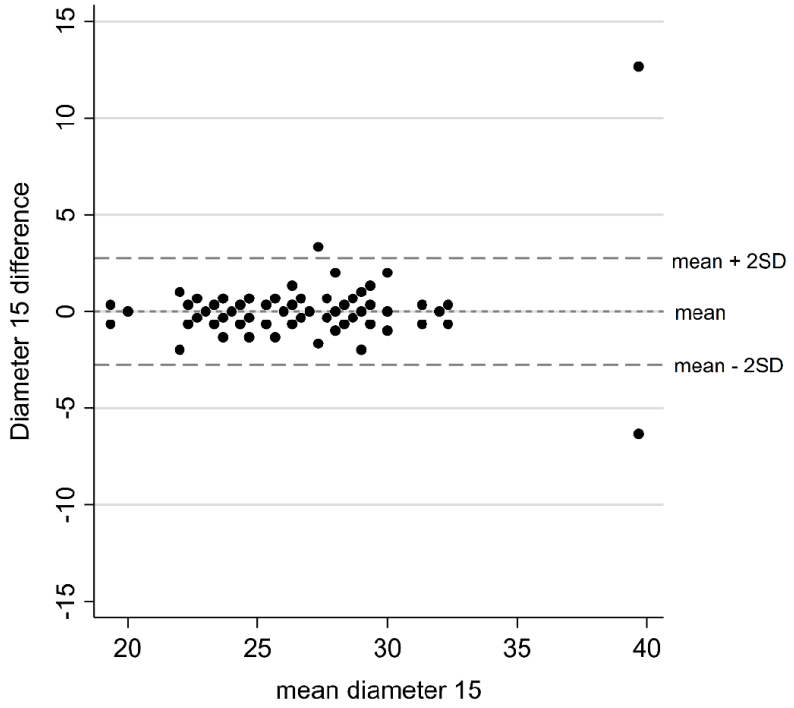


Figure 4-14 Bland Altman Plot comparing the measurements of 3 blinded raters for the domain of neck diameter 15mm below the level of the lower most renal artery (mm).
(x-axis: mean value across the three observers, y-axis: the difference from the mean for all three observers' measurements)

Table 4-4 Distribution of 70 scans allocated to one of four anatomical subgroups by two independent and blinded raters. (Group 1: neck length 0-4mm; Group 2: neck length 5-9mm; Group 3: neck length ≥10mm but with other adverse features; Group 4: standard neck)

		Rater 1				
		Group 1	**Group 2**	**Group 3**	**Group 4**	**Total**
Rater 2	**Group 1**	8	0	0	0	8
	Group 2	0	2	0	0	2
	Group 3	0	0	27	0	27
	Group 4	0	0	0	33	33
	Total	8	2	27	33	70

4.6 Discussion

The proposed cohort comparison study of different techniques used to repair juxtarenal and complex-neck AAAs employed a cohort study design with adjustment for patient risk and stratification by anatomical complexity, the two main factors determining outcomes. Crucially, in order to reduce the subjectivity in reporting anatomical complexity, the study incorporated a Corelab to objectively determine inclusion of cases and subsequent subgrouping, by analysis of CT scans of all patients who have undergone aneurysm repair in England between 2017 and 2019.

Generating definitions for various neck anatomical parameters is difficult. Stemming from the pre-endovascular era, there is a persistence in usage of descriptive but non-quantitative terminology such as the words "juxtarenal", "pararenal" and "suprarenal", when attempting to distinguish complex aneurysms from non-complex aneurysms. The advent of endovascular repair provided an opportunity to assign neck complexity based on anatomical limits as specified in "instructions for use" (IFU) documents of stent-grafts. Anatomical criteria outside of IFU form a range of features requiring stratification. In the absence of an established and robust basis for this in clinical use, we opted for the pragmatic solution of expert clinical consensus. This

provided us with three subgroups of anatomical complexity, each of which is not only easily reproducible in routine clinical practice, but also has distinct relevance to each of the different repair techniques. Specifically, Group 1 patients have anatomy that is off-IFU for all "off-the-shelf" endovascular devices. Group 2 patients have anatomy that is also off-IFU for standard EVAR without adjuncts. However, they may be on-label for alternative endovascular techniques, and in the context of open repair should largely be suitable for infrarenal clamping and not higher. Group 3 patients should also be suitable for open surgery with infrarenal clamping but are still off-label for standard EVAR (on alternative criteria to those in Group 2).

Considering the potential value placed on Corelab analysis, validation of measurement process and its reproducibility are essential. The validation test we conducted demonstrated excellent interobserver consistency with regards to aneurysm morphological assessment, specific to aneurysm diameter, neck length, neck angulation and neck diameter at various positions on the infrarenal aorta. This will provide the basis of addressing heterogeneity within the entire included cohort of aneurysms by permitting stratification, primarily by neck length but also considering other morphological features of neck complexity.

Proving that the measurements are accurate between different raters is useful in being able to ensure the external validity of any future results, i.e. that those in other institutions may apply the findings of this future study to their local cohorts should they follow the standardised measurement and grouping processes.

Corelab assessment has been studied previously in only a few publications in the literature. This validation exercise is unique to have focussed so extensively on the aortic neck across different measures, enabling its applicability to cohorts of complex aneurysms.

Although the context of this Corelab is related to the cohort study for complex AAAs, the processes detailed in this protocol are of relevance to any clinical research field in which there is an interest in objective stratification of image interpretation in order to improve the quality of imaging data analysis.

5 Results Of A National Cohort Comparison Study Of Different Treatments For Juxtarenal And Complex-Neck Abdominal Aortic Aneurysms: Clinical Outcomes In The Perioperative Period And At 3.5 Years Of Follow-up

5.1 Identification Of Patients With A Juxtarenal And Complex-Neck AAA

Some 8994 patients were coded as having undergone a repair of AAA (all anatomical variations and treatment methods included) in England between 1st November 2017 and 31st October 2019, as identified from the Hospital Episodes Statistics *Admitted Patient Care* (HES-APC) dataset. These operations were performed across 64 hospitals in England as listed in the National Vascular Registry (Appendix 2). Acquisition of the last pre-operative CT angiogram from hospitals in England was successful for 8706/8994 (96.8%) patients. Some 8612/8706 (98.9%) scans were of sufficient quality to enable full morphological assessment of infrarenal neck anatomy, as per the pre-designed Corelab protocol provided in Chapter 4 of this thesis.

Of the 8612 cases that underwent analysis in the Corelab, 5855 were excluded from the study for various reasons: 3045 cases were standard infrarenal aneurysms with morphology that would permit on-label endovascular aneurysm repair; 256 cases were of iliac aneurysms with or without concomitant subthreshold AAA; 597 cases had a proximal extent to the aneurysm in either the thoracic or the visceral segment of the abdominal aorta and so were classified as either thoracic aneurysms, thoracoabdominal aneurysms or visceral aortic aneurysms; 526 cases had evidence of previous repair (either open or endovascular) to the infrarenal segment of the aorta and so the identifying code was assumed to be a reintervention; 218 cases were of saccular morphology and/or with a maximal aneurysm diameter of <55mm; 382 cases had appearances consistent with emergency presentations, namely evidence of retroperitoneal haematoma around the aneurysm to suggest rupture or obvious inflammation around the aneurysm to suggest infected or inflammatory pathology; 150 cases seemed to be incorrectly coded as an aneurysm repair when in fact the pathology on imaging was seen to be non-aneurysm related (examples included aortic dissection and stenotic/occlusive disease within a normal diameter aorta). 18 cases were excluded because, despite adequate imaging being identified and retrieved, the identifying code for repair type was unclear. The last group of cases, 663 in total, that were excluded in the Corelab analysis were informally termed necks of "ambiguous" complexity. These were cases where the anatomical profile to the infrarenal neck was on-label for certain stent-grafts but off-label for others.

Ultimately, this led to the Corelab identification of 2757 juxtarenal and complex-neck AAAs, which were unsuitable for repair with standard EVAR, as defined by IFU-based criteria. The process above is summarised in Figure 5-1.

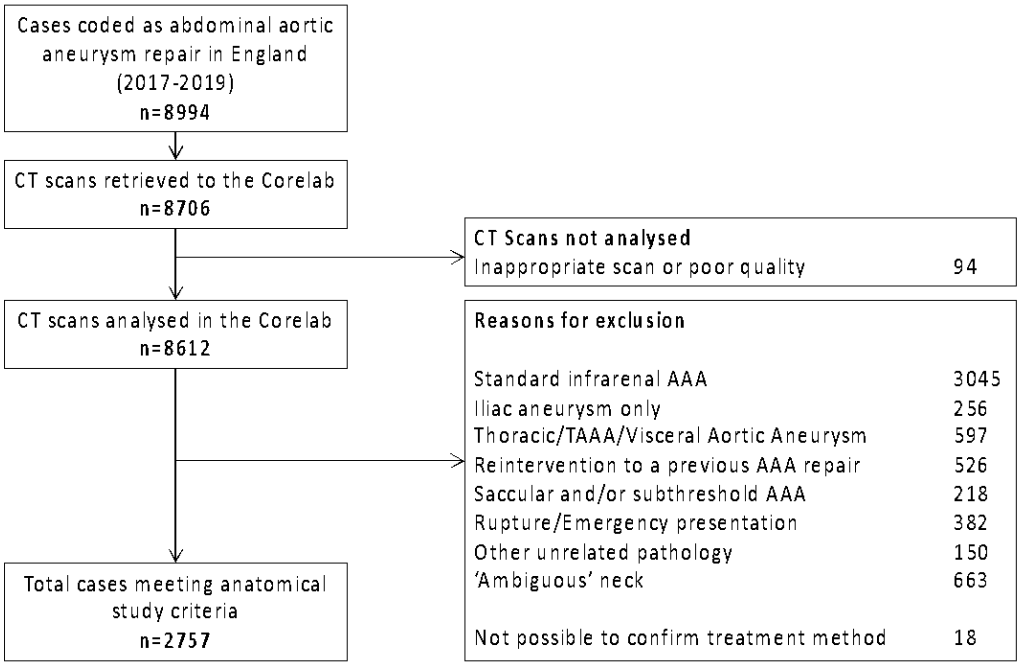


Figure 5-1 Flow chart showing the numbers of cases involved during screening and Corelab analysis, leading to the identification of 2757 juxtarenal and complex-neck aneurysms.

5.2 Dataset Matching, Treatment Allocation, Subgrouping & Patient Characteristics

Of the 2757 patients meeting anatomical inclusion criteria, 2209 (80.1%) patients (originally identified from the HES-APC dataset) were matched with entries in the National Vascular Registry (NVR). Therefore, the remaining 548 patients were excluded from subsequent analysis due to the absence of baseline health information, which is a necessary set of data for both the groupings based on physiological risk and the propensity-based statistics employed in this cohort study.

The British Aneurysm Repair (BAR) score was calculated for each patient individually. The BAR score permitting dichotomisation into the highest risk quartile and the standard risk remainder

(lowest three quartiles) was 0.0888043. The BAR was adapted to ignore operation type, so that the operative technique field (open vs EVAR) was selected to be open repair for all patients.

Some 2209 patients comprised the final cohort of juxtarenal and complex-neck aneurysms that proceeded to comparative analysis. The distribution of the included 2209 patients across the three final treatment groups and anatomical/physiological risk subgroups is shown in Table 5-1 below. Treatments offered to these patients included open surgery with a variety of clamps levels (n=940), fenestrated EVAR (FEVAR) (n=403), off-label standard EVAR (n=770), and EVAR with adjuncts (either chimney EVAR or EVAR with endoluminal screws) (n=96). The numbers of patients receiving EVAR with adjuncts was too small to permit separate analysis and so a decision was made to pool them with the off-label standard EVAR group.

Open Surgery and FEVAR comprised the majority of repairs for juxtarenal and short-necked aneurysms (neck length groups 0-4mm and 5-9mm), with 838/1002 (83.6%) repairs. EVAR with or without adjuncts was hardly used in necks 0-4mm in length (37/596 repairs, 6.2%) but in short necked aneurysms (5-9mm in length) they comprised 31% (127/406) of all repairs which rose to 52.5% (52/99) for the subset of highest physiological risk (Table 5-1).

Open surgery was used fairly equally across the 3 anatomical subgroups: of all open repairs, 327/940 (35%) were in necks 0-4mm long, 206/940 (22%) were in necks 5-9mm long and 405/940 (42%) were in necks ≥10mm long. EVAR with or without adjuncts was used primarily in the treatment of aneurysms with long neck but other adverse features (701/866 EVARS, 81%). Nearly one quarter of all FEVAR cases (97/403, 24.1%), a technology developed primarily for juxtarenal aneurysms, were for cases with neck length ≥10mm but other adverse neck features.

Table 5-1 Operation by anatomical classification and risk group (n=2209, before propensity-based exclusion).

			Subgroup[1] (Anatomical Classification and Risk Group)[2]					
		All (n=2209)	≤4mm neck (n=596)		5-9mm neck (n=406)		≥10mm neck (n=1203)	
			Standard (n=464)	High (n=132)	Standard (n=307)	High (n=99)	Standard (n=875)	High (n=328)
Procedure Type	EVAR +/- adjuncts	866 (39.2%)	23 (2.7%),(5.0%)	14 (1.6%),(10.6%)	75 (8.7%),(24.4%)	52 (6.0%),(52.5%)	447 (51.7%),(51.1%)	254 (29.4%),(77.4%)
	FEVAR	403 (18.2%)	174 (43.3%),(37.5%)	58 (14.4%),(43.9%)	55 (13.7%),(17.9%)	18 (4.5%),(18.2%)	78 (19.4%),(8.9%)	19 (4.7%),(5.8%)
	Open Repair	940 (42.6%)	267 (28.5%),(57.5%)	60 (6.4%),(45.5%)	177 (18.9%),(57.7%)	29 (3.1%),(29.3%)	350 (37.3%),(40.0%)	55 (5.9%),(16.8%)

**Standard risk = Adapted British Aneurysm Risk ($BAR_{adapted}$) score <0.0888043; High risk = $BAR_{adapted}$ ≥0.0888043. Adapted BAR is a measure of risk that ignores operation type and is the BAR score that would be calculated if it is assumed there was open repair.*

[1]Due to missing data 1 participant in the EVAR +/- adjuncts group, 1 participant in the FEVAR group and 2 participants in the Open Repair group could not be assigned subgroups.

[2]Where 2 percentages are provided, subgroup percentages are (proportion of row), (proportion of column). For example, 267 open repairs were conducted for patients of standard risk and neck length 0-4mm. This comprises 28.5% of all open repairs, and 57.5% of patients in that anatomical/physiological risk subgroup.

By definition, the top quartile of individuals stratified by BAR score represented the subgroup with the lowest physiological fitness. This equated to 559/2209 cases. Within just this group of patients, 17% had FEVAR (95/559), 57.2% had EVAR +/- adjuncts (320/559) and 25.8% had open repair (144/449). When comparing the relative use of these to the entire population (18% FEVAR, 39% EVAR +/- adjuncts and 43% open repair), it seems a higher proportion of high-risk individuals had off-label EVAR at the expense of open surgery, whereas the proportion having FEVAR was similar.

The use of different aortic cross-clamp levels, as recorded in the NVR, across different anatomical subgroups is shown in Table 5-2. Use of infrarenal aortic cross clamping (relative to other levels) increased as the neck length of the anatomical subgroups increased: 53% for 0-4mm necks, 76% for 5-9mm necks and 90% for ≥10mm necks. Conversely, suprarenal clamps decreased as a proportion across increasing neck length subgroups: 44% for 0-4mm necks, 22% for 5-9mm necks and 10% for ≥10mm necks. Aortic cross clamping above the level of the SMA or coeliac artery was only ever utilised for 0-4mm necks, although in a minority of cases (11/329 cases, 3.4%).

Table 5-2 Aortic cross-clamp level used across different anatomical subgroups.

Clamp Level	All Open Repairs (n=940)	Anatomical Classification*		
		0-4mm neck (n=329)	5-9mm neck (n=206)	≥10mm neck (n=405)
Infrarenal clamp	698 (74.4%)	174 (53.0%)	159 (77.6%)	365 (90.1%)
Suprarenal clamp	229 (24.4%)	143 (43.6%)	46 (22.4%)	40 (9.9%)
Supramesenteric or supracoeliac clamp	11 (1.2%)	11 (3.4%)	0 (0.0%)	0 (0.0%)

Clamp level was unrecorded in NVR for 2 patients: 1 each in 0-4mm and 5-9mm neck length groups)
**Denominators for percentages are column totals.*

The distribution across operative and anatomical groups for the 548 patients excluded due to failed matching between HES and NVR is shown in Table 5-3; there was no suggestion of bias with regards to the distribution of cases across subgroups when comparing excluded (Table 5-3) and included (Table 5-1) numbers.

Table 5-3 Treatment group and Anatomical group for those not matching HES with NVR entries and therefore, excluded from analysis (n=548).

	0-4mm neck (n=131)	**5-9mm neck** (n=116)	**≥10mm neck** (n=301)
Open Repair (n=230)	81 (61.8%)	56 (48.3%)	93 (30.9%)
EVAR (n=234)	12 (9.2%)	39 (33.6%)	183 (60.8%)
FEVAR (n=84)	38 (29.0%)	21 (18.1%)	25 (8.3%)

%s expressed as a proportion of the anatomical group.

The breakdown of EVAR and EVAR +/- adjuncts across the 6 anatomical/physiological risk subgroups is shown in Table 5-4. EVAR with adjuncts were disproportionately used in 0-4mm neck aneurysms: EVAR with adjuncts comprised 11.1% (96/866 procedures) of all EVAR procedures overall but 38% (14/37) of all EVAR procedures undertaken for 0-4mm necks.

Table 5-4 Frequency of EVAR alone and EVAR with adjuncts across subgroups.

	Overall (n=866)[1]	**0-4mm neck (n=37)**		**5-9mm neck (n=127)**		**≥10mm neck (n=701)**	
		Standard (n=23)	**High (n=14)**	**Standard (n=75)**	**High (n=52)**	**Standard (n=447)**	**High (n=254)**
EVAR alone	770 (88.9%)	15 (65.2%)	8 (57.1%)	53 (70.7%)	45 (86.5%)	414 (92.6%)	234 (92.1%)
EVAR + adjuncts	96 (11.1%)	8 (34.8%)	6 (42.9%)	22 (29.3%)	7 (13.5%)	33 (7.4%)	20 (7.9%)

%s expressed as a proportion of the anatomical/risk subgroup.
[1]Due to missing data 1 participant in the EVAR alone group could not be assigned a subgroup.

The baseline demographics and health information of the 2209 patients successfully matched between HES and NVR is provided in Table 5-5. The demographics are presented across the three treatment groups and for the study population as a whole. Patients undergoing open surgery (median age 71.9) were younger than those undergoing EVAR or FEVAR (77.9 and 75.9 respectively). Gender split was similar across all three groups (approximately 89% male). BMI was similar across all three groups (median BMI was approximately 27 for all three groups).

Table 5-5 Baseline Characteristics of patients included in the analysis (n=2209).

		Open Repair (N=940)	**EVAR** (N=866)	**FEVAR** (N=403)	**All** (N=2209)
AAA Diameter (mm)	Median (IQR)	61 (58, 70)	61 (58, 68)	62 (59, 67)	61 (58, 68)
Neck Length (mm)	Median (IQR)	8 (0, 17)	20 (12, 31)	3 (0, 9)	11 (3, 22)
Age (years)	Median (IQR)	71.9 (67.3,77.2)	77.9 (72.7,82.6)	75.9 (71.2,80.1)	75.0 (69.8,80.1)
	Missing	0	0	0	0
Sex, n (%)	Female	103 (11.0%)	118 (13.6%)	44 (10.9%)	265 (12.0%)
	Male	837 (89.0%)	748 (86.4%)	359 (89.1%)	1944 (88.0%)
	Missing	0	0	0	0
Weight (kg)	Median (IQR)	82.0 (73.0,90.0)	81.0 (72.0,90.0)	82.0 (72.0,92.0)	81.0 (72.0,90.0)
	Missing	20	38	2	60
Height (cm)	Median (IQR)	175.0 (168.0,179.0)	173.0 (168.0,178.0)	174.0 (168.0,178.0)	174.0 (168.0,179.0)
	Missing	23	42	2	67
BMI (kg/m^2)	Median (IQR)	26.8 (24.5,29.8)	27.0 (24.4,29.9)	27.0 (24.3,30.3)	26.9 (24.5,30.0)
	Missing	23	42	2	67
ASA*, n (%)	1 - Normal	9 (1.0%)	10 (1.2%)	5 (1.2%)	24 (1.1%)
	2 - Mild disease	236 (25.1%)	128 (14.8%)	60 (14.9%)	424 (19.2%)
	3 - Severe, not life threatening	655 (69.7%)	642 (74.1%)	310 (76.9%)	1607 (72.7%)
	4 - Severe, life-threatening	40 (4.3%)	82 (9.5%)	28 (6.9%)	150 (6.8%)
	5 - Moribund patient	0 (0.0%)	4 (0.5%)	0 (0.0%)	4 (0.2%)
	Missing	0	0	0	0
Haemoglobin (g/dL)	Median (IQR)	14.2 (13.1,15.5)	13.8 (12.5,15.2)	13.9 (12.5,15.1)	14.0 (12.8,15.3)
	Missing	0	0	1	1
White cell count ($x10^9/L$)	Median (IQR)	7.7 (6.4,9.4)	7.7 (6.4,9.3)	8.0 (6.6,9.6)	7.8 (6.4,9.4)
	Missing	1	0	1	2
Serum sodium (mmol/L)	Median (IQR)	140.0 (138.0,141.0)	139.0 (137.0,141.0)	140.0 (138.0,142.0)	140.0 (137.0,141.0)

		Open Repair (N=940)	EVAR (N=866)	FEVAR (N=403)	All (N=2209)
	Missing	0	0	0	0
Serum potassium (mmol/L)	Median (IQR)	4.4 (4.1,4.7)	4.4 (4.2,4.7)	4.4 (4.2,4.7)	4.4 (4.2,4.7)
	Missing	0	0	0	0
Serum creatinine (mmol/L)	Median (IQR)	86.0 (75.0,101.0)	91.0 (76.0,111.0)	91.0 (79.0,108.0)	89.0 (76.0,106.0)
	Missing	0	0	0	0
Serum albumin (mmol/L)	Median (IQR)	40.0 (36.0,43.0)	40.0 (36.0,43.0)	39.0 (35.0,42.0)	40.0 (36.0,43.0)
	Missing	296	262	185	743
Abnormal ECG, n (%)	Abnormal	218 (23.4%)	293 (34.4%)	116 (29.0%)	627 (28.7%)
	Normal	714 (76.6%)	559 (65.6%)	284 (71.0%)	1557 (71.3%)
	Missing	8	14	3	25
Comorbidities	None	103 (11.0%)	55 (6.4%)	18 (4.5%)	176 (8.0%)
	Chronic Heart Failure	49 (5.2%)	101 (11.7%)	46 (11.4%)	196 (8.9%)
	Chronic Lung Disease	226 (24.0%)	311 (35.9%)	159 (39.5%)	696 (31.5%)
	Chronic Renal Disease	154 (16.4%)	198 (22.9%)	75 (18.6%)	427 (19.3%)
	Diabetes	131 (13.9%)	179 (20.7%)	78 (19.4%)	388 (17.6%)
	Hypertension	740 (78.7%)	706 (81.5%)	338 (83.9%)	1784 (80.8%)
	Ischemic Heart Disease	342 (36.4%)	420 (48.5%)	196 (48.6%)	958 (43.4%)
	Stroke	55 (5.9%)	83 (9.6%)	19 (4.7%)	157 (7.1%)

In terms of baseline physiological fitness, the majority of cases were performed in individuals with an ASA score of 3 regardless of method of repair; this was in nearly 70% of Open Repairs, 74% of EVARs and 76% of FEVARs. However, one quarter of all Open Repairs were performed in individuals with an ASA score of 2, as opposed to in 14% of EVARs and FEVARs. Nearly 10% of all EVARs were performed in individuals with an ASA score of 4, as opposed to in 4% of Open Repairs and in 6.9% of all FEVARs. As shown in Table 5-5, chronic heart failure, chronic lung disease, chronic renal disease, diabetes mellitus and ischaemic heart disease were all less prevalent in the population undergoing Open Surgery as compared to EVAR or FEVAR.

5.3 Results of Propensity Modelling

Propensity modelling was utilised initially to identify patients who had a reasonable chance of undergoing more than one treatment option and therefore would enable a valid comparative analysis.

In the first stage, the probability of receiving each of the three interventions was modelled using multinomial multivariable regression as there were more than two treatment options. An optimal model was derived: First, a model was fitted with the following baseline variables: age, sex, diabetes, chronic lung disease, BMI, creatinine>120 μmol, cardiac disease (history of ischaemic heart disease, heart failure or both), abnormal ECG, abnormal white cell count (<3.0 or >11.0 x 10^9/l), abnormal sodium level (<135 or >145 x mmol/l), AAA maximal diameter (cm), ASA fitness grade and length of infrarenal aortic neck (≤4mm, 5-9mm, ≥10mm). A backward stepwise selection method was employed, with entry and exit p-values of 0.05. The final propensity score model with selected variables is shown in Table 5-6. This model estimates the probability of a patient receiving each intervention depending on the baseline measures. Some 67 patients were excluded from the initial pool of 2209, due to missing covariate data (specifically for the BMI variable), leaving 2142 patients in the model.

In the second stage, a regional of common support was identified; this refers to exclusion of outlier patients based on propensity score. These are patients who had an overwhelming probability to only receive one treatment approach and therefore were not suitable for analyses comparing efficacy. This is demonstrated graphically in Figure 5-2.

Table 5-6 The Propensity Score Model.

	EVAR vs Open Repair				FEVAR vs Open Repair			
	Est	SE	Z	P	Est	SE	Z	P
(Intercept)	-8.65	0.98	78.5	<.0001	-3.68	1.04	12.53	0.0004
Age(Years)	0.13	0.01	197.33	<.0001	0.09	0.01	77.49	<.0001
Creatinine	-0.41	0.17	6.02	0.0141	0.13	0.2	0.42	0.5185
Cardiac Disease (Binary)	-0.46	0.12	15.12	0.0001	-0.44	0.13	11.1	0.0009
AAA Diameter	-0.02	0.01	10.35	0.0013	-0.03	0.01	22.05	<.0001
ASA 2 Vs 1	-1.04	0.6	3	0.0835	-1.19	0.61	3.75	0.0528
ASA 3 Vs 1	-0.68	0.59	1.34	0.247	-0.86	0.6	2.02	0.1551
ASA 4 Vs 1	0.11	0.64	0.03	0.8567	-0.42	0.66	0.4	0.5283
Neck length (mm)	0.07	0	217.67	<.0001	-0.07	0.01	69.41	<.0001
Chronic Lung Disease (Binary)	-0.75	0.13	34.69	<.0001	-0.76	0.14	30.47	<.0001
BMI	0.02	0.01	10.48	0.0012	0.01	0.01	3.24	0.0719

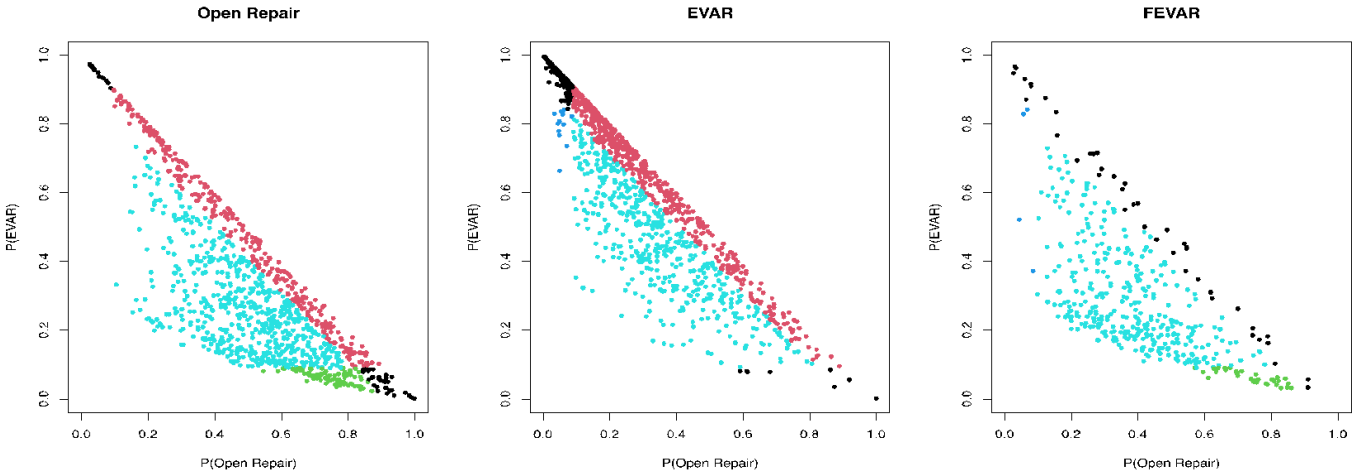


Figure 5-2 Graphical Representation of Univariate Regions of Common Support, each colour representing one of four strata.

Finally, 4 strata were obtained, based on propensity score regions of common support, with a 90% threshold:

Stratum 1:

Patients estimated to be likely (according to propensity score ≥10%) in receipt of any of the three interventions.

Stratum 2:

Patients estimated to have a ≥10% chance of receiving an EVAR and a ≥10% chance of receiving FEVAR, who did not have an Open Repair, and are not in the other strata.

Stratum 3:

Patients estimated to have a ≥10% chance of receiving an Open Repair and a ≥10% chance of receiving a FEVAR, who did not receive an EVAR, and are not in the other strata.

Stratum 4:

Patients estimated to have a ≥10% chance of receiving an Open Repair and a ≥10% chance of receiving an EVAR, who did not receive a FEVAR, and are not in the other strata.

226 patients were not assigned a stratum; these were individuals with a propensity score suggesting that they would not have been eligible for more than 1 treatment method on the balance of probabilities, and so they would be unsuitable for inclusion into a valid comparative analysis. They were therefore excluded from further analysis. The results of the propensity modelling have been summarised in Table 5-7. In total 1916 patients were assigned a stratum and therefore underwent comparative effectiveness analysis (Open n=868, FEVAR n=366, EVAR +/- adjuncts n=682). The distribution of 1916 patients who proceeded to comparative analysis, across the six subgroups, is demonstrated in Table 5-8.

Table 5-7 Summary of Propensity Modelling Results.

Patients available for propensity modelling		n=2209
Patients with missing data for covariates		n=67 (Excluded)
Patients with no significant chance of being offered more than one treatment strategy.		n=226 (Excluded)
Covariates identified to be independently associated with the choice of treatment strategy		
	Patient characteristics:	Age, ASA grade and BMI
	Aneurysm characteristics:	AAA Diameter and Aneurysm Neck length
	Comorbidities:	Cardiac Disease, Chronic Lung Disease and Creatinine >120 μmol.
Patients estimated to have a significant chance (≥10%) of being offered more than one treatment strategy. **Only these patients were included in comparative analyses.**		n= 1916
Patients with chance of being offered FEVAR, OSR and Off-label EVAR		n=1111 (58%)
Patients with chance of being offered EVAR and FEVAR		n= 24 (1.3%)
Patients with chance of being offered FEVAR and OSR		n= 229 (12%)
Patients with chance of being offered EVAR and OSR		n= 552 (28.8%)

Table 5-8 Treatment strategy by subgroup for patients undergoing comparative analysis, as included by propensity scoring (n=1916).

		Subgroup (Anatomical Classification and Risk Group*)[2]						
		All (n=1916)	≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
			Standard (n=443)	High (n=125)	Standard (n=281)	High (n=94)	Standard (n=744)	High (n=227)
Procedure Type	**EVAR +/- adjuncts**	682 (35.6%)	14 (2.1%), (3.1%)	12 (1.8%), (9.6%)	69 (10.1%), (24.6%)	49 (7.2%) (52.1%)	373 (54.7%), (50.1%)	164 (24.0%), (72.2%)
	FEVAR	366 (19.1%)	172 (47.0%), (38.8%)	58 (15.8%), (46.4%)	52 (14.2%), (18.5%)	18 (4.9%) (19.1%)	50 (13.7%), (6.7%)	15 (4.1%), (6.6%)
	Open Repair	868 (45.3%)	257 (29.6%), (58.0%)	55 (6.3%), 44.0%)	160 (18.4%), (56.9%)	27 (3.1%), 28.7%)	321 (37.0%), (43.1%)	48 (5.5%), (21.1%)

**Standard risk = Adapted British Aneurysm Risk ($BAR_{adapted}$) score < 0.0889679 (lowest scoring 75% of the cohort); High risk = $BAR_{adapted}$ ≥0.0889679 (highest scoring 25% of the cohort). Adapted BAR is a measure of risk that ignores operation type.*

[1]Due to missing data, 1 participant in the EVAR +/- adjuncts group, 1 participant in the FEVAR group and 2 participants in the Open Repair group could not be assigned subgroups.

[2]Subgroup percentages are row, column.

5.4 Comparative Outcomes Results

5.4.1 Primary outcome measure: Peri-operative mortality

A total of 55 (2.9%) perioperative deaths were observed among the 1916 patients in the propensity score-based analysis. Across the whole population, logistic regression analysis confirmed that the overall risk of peri-operative death was significantly lower with EVAR (1.2%, 8/682; OR=0.24, 97.5% CI=0.09-0.65, p=0.0014) and FEVAR (2.2%, 8/366; OR=0.25, 97.5% CI=0.10-0.64, p=0.0009) than with OSR (4.5%, 39/868). Perioperative mortality rates in patients with a 0-4mm long infrarenal neck after FEVAR and OSR were 2.3%, and 7.4% respectively in standard-risk patients, and 1.7% and 10.9% respectively in high-risk patients. EVAR +/- adjuncts was utilised very rarely in this group of patients (n=26) and so standard risk and high-risk mortality rates of 7.1% and 8.3% respectively were interpreted with caution. For cases with 5-9mm long neck, mortality rates for FEVAR, EVAR and OSR were 0%, 1.4% and 1.9% for standard risk patients; for cases with a neck length of at least 10mm, mortality rates for FEVAR, EVAR and OSR were 2.0%, 0.5% and 2.2% respectively in standard risk patients. Interpretation of mortality rates for the highest risk patients was limited by low numbers across treatment groups (e.g., there were only 15 patients considered "high risk" in the FEVAR group for the neck length ≥10mm group). Details of peri-operative deaths across patient risk groups are shown in Figure 5-3 and Table 5-9.

Sensitivity analyses were performed for the primary outcome measure of perioperative mortality, under a series of additional assumptions:

1) No adjustment for propensity score: This sensitivity analysis removed the propensity scores for Open Repair and EVAR as adjusting covariates from the model.
2) Adjusting with BAR score: This sensitivity analysis included BAR score as an adjusting covariate.
3) Use of an alternative propensity model stratified and adjusted: This sensitivity analysis used an alternative form of the propensity score model (one that includes age, BMI, neck length, diameter and ASA grade only), including stratification factors and propensity score estimates.
4) Use of an alternative propensity model and stratified but NOT adjusted: This sensitivity analysis used the alternative form of propensity model, including stratification factors but not using propensity score estimates as an adjusting covariate.

5) Use of an alternative propensity model stratified and with further adjustment with BAR score: This sensitivity analysis used the alternative form of propensity model, including stratification factors and including BAR score as an adjusting covariate.

The results of these sensitivity analyses suggested no change to the original finding of a perioperative survival benefit for Endovascular techniques over Open Surgery, as shown in Table 5-10.

Figure 5-3 Perioperative outcomes and intensive care utilisation of the overall population in the comparative analysis and by subgroups according to anatomical class and operative risk group.

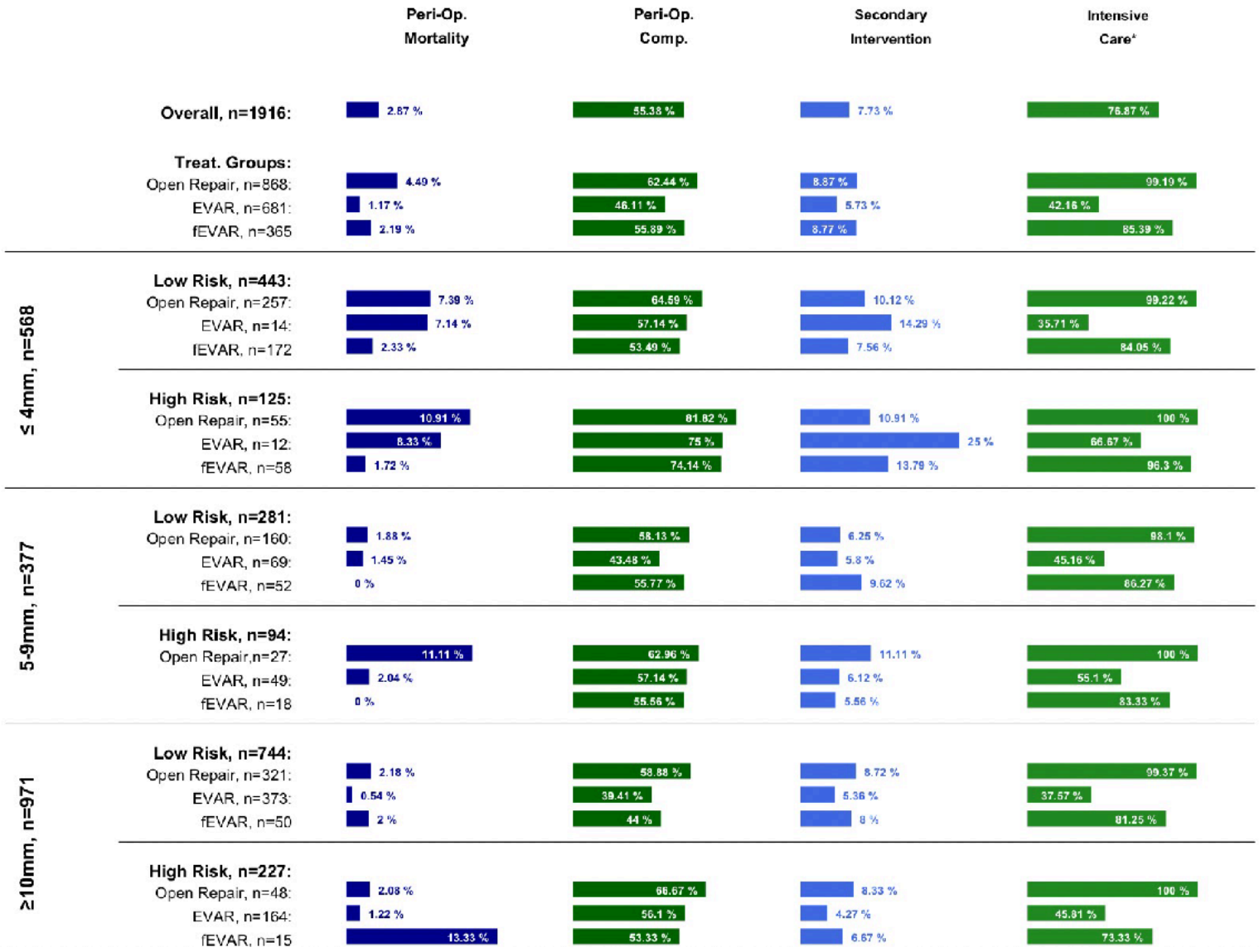


Table 5-9 Primary Outcome Measure Results: Perioperative Mortality Overall and by subgroup (n=1916).

	All (n=1916)	**By Subgroup (Anatomical Classification and Risk Group)[1]**					
		≤4mm neck (n=568)		**5-9mm neck** (n=375)		**≥10mm neck** (n=971)	
		Standard (n=443)	**High** (n=125)	**Standard** (n=281)	**High** (n=94)	**Standard** (n=744)	**High** (n=227)
Overall	55 (2.9%)	24/443 (5.4%)	8/125 (6.4%)	4/281 (1.4%)	4/94 (4.3%)	10/744 (1.3%)	5/227 (2.2%)
Open Repair (n=868)	39 (4.5%)	19/257 (7.4%)	6/55 (10.9%)	3/160 (1.9%)	3/27 (11.1%)	7/321 (2.2%)	1/48 (2.1%)
EVAR (n=682)	8 (1.2%)	1/14 (7.1%)	1/12 (8.3%)	1/69 (1.4%)	1/49 (2.0%)	2/373 (0.5%)	2/164 (1.2%)
FEVAR (n=366)	8 (2.2%)	4/172 (2.3%)	1/58 (1.7%)	0/52 (0.0%)	0/18 (0.0%)	1/50 (2.0%)	2/15 (13.3%)

[1]2 patients could not be assigned a subgroup due to missing data.
Denominators for percentages are subgroup totals.

Table 5-10 Logistic Regression Results; Sensitivity Analyses for the primary outcome measure of perioperative mortality rate.

		Est (SE)	*OR (97.5% Confidence Interval)*	*p-Value*
1) No adjusting factors	**EVAR vs Open Repair**	**-1.23 (0.40)**	**0.29 (0.12, 0.72)**	**0.0022**
	FEVAR vs Open Repair	**-0.93 (0.40)**	**0.39 (0.16, 0.96)**	**0.0190**
2) Adjusting with BAR Score	**EVAR vs Open Repair**	**-1.47 (0.45)**	**0.23 (0.08,0.63)**	**0.0011**
	FEVAR vs Open Repair	**-1.37 (0.42)**	**0.26 (0.10,0.65)**	**0.0011**
	Open Repair Prop. Score	-4.8 (1.35)	0.01 (0.00,0.17)	0.0004
	EVAR Prop. Score	-2.75 (1.35)	0.06 (0.00,1.33)	0.0425
	BAR risk score	2.07 (1.1)	7.91 (0.67,93.55)	0.0606
3) Alternative propensity model, stratified and adjusted	**EVAR vs Open Repair**	**-1.15 (0.42)**	**0.32 (0.12,0.81)**	**0.0062**
	FEVAR vs Open Repair	**-1.26 (0.41)**	**0.28 (0.11,0.72)**	**0.0023**
	Open Repair Prop. Score	-5.95 (1.52)	0 (0,0.08)	<.0001
	EVAR Prop. Score	-3.22 (1.49)	0.04 (0,1.12)	0.0302
4) Alternative propensity model, stratified and NOT adjusted	**EVAR vs Open Repair**	**-0.98 (0.37)**	**0.38 (0.16,0.87)**	**0.0088**
	FEVAR vs Open Repair	**-0.83 (0.4)**	**0.43 (0.18,1.06)**	**0.0361**
5) Alternative propensity model, stratified and further adjustment with BAR score	**EVAR vs Open Repair**	**-1.23 (0.43)**	**0.29 (0.11,0.76)**	**0.0040**
	FEVAR vs Open Repair	**-1.24 (0.42)**	**0.29 (0.11,0.73)**	**0.0028**
	Open Repair Prop. Score	-5.35 (1.55)	0 (0,0.15)	0.0006
	EVAR Prop. Score	-3.17 (1.49)	0.04 (0,1.19)	0.0336
	BAR risk score	2.15 (1.04)	8.6 (0.83,89.35)	0.0394

A further sensitivity analysis of perioperative mortality outcomes involved the separation of the EVAR +/- adjuncts group (n=682) into two separate cohorts: EVAR alone (n=598) and EVAR with adjuncts (n=84). Logistic regression analysis suggested maintenance of the perioperative survival benefit for standard EVAR (1.0%) over Open Surgery (4.5%) after removal of the procedures involving adjuncts (OR 0.22, CI 0.07 – 0.65, p=0.0019).

5.4.2 Secondary Outcome Measures – Perioperative Period

Median length of stay in hospital was lower for EVAR (2 days) and FEVAR (4 days) than for Open Surgery (7 days). Higher level care (HDU/ICU) was utilised in 76.8% of all patients. It was used routinely after Open Surgery (99.2%), and to a greater degree than after FEVAR (85.4%, OR=0.08, 95% CI 0.05-0.14, p<0.0001) or after EVAR +/- adjuncts (42.1%, OR=0.01, 95%CI 0.00-0.02, p<0.0001). The median number of days spent in high dependency/intensive care was 3 days for Open Surgery, 2 days for FEVAR and 0 days for EVAR. The degree of ICU utilisation was distributed across the six subgroups as shown in Table 5-11 and Figure 5-3.

A total of 2,442 perioperative complications were recorded in 1,061 (55.4%) patients. The overall incidence was significantly lower after EVAR (46.2%, OR=0.44, 95%CI 0.35-0.57, p<0.0001) and FEVAR (55.7%, OR=0.57, 95%CI 0.43, 0.74, p<0.0001) than after Open Surgery (62.4%).

Across all operation types and anatomical subgroups, complications were more common in high-risk patients versus standard risk patients. Of note, paraplegia/paraparesis occurred at a clinically significant rate after FEVAR (4.4%) and Open Surgery (3.2%) but to a lesser extent after EVAR (1.8%). Myocardial infarction occurred nearly twice as often after FEVAR (2.5%) and Open Surgery (2.1%) as compared to EVAR (1.2%). Pneumonia and Acute Kidney Injury was seen more often after Open Surgery (16.2% and 21.4%) as compared to FEVAR (7.4% and 12.3%) and EVAR (3.7% 6.0%). Dialysis was required almost exclusively after Open Surgery (3.3%) as compared to FEVAR (0.8%) and EVAR (0.9%). Complication rates across the 6 subgroups is shown in Table 5-12, the incidence of specific complications is shown in Table 5-13, with a breakdown of spinal cord ischaemia cases in Table 5-14.

A total of 244 early secondary interventions were observed in 148 (7.7%) patients. Logistic regression analysis showed a lower incidence of perioperative secondary interventions in the patients treated by off-label EVAR (5.7%, OR=0.62, 95%CI 0.39-0.98, p=0.0410) than OSR patients (8.9%). There was no significant difference between secondary intervention rates between FEVAR (8.7%) and OSR patients (OR= 0.76, 95%CI 0.48-1.22, p=0.2569). With regards to the specific types of secondary intervention, open reinterventions to the abdomen or lower limb arterial tree and major amputations were seen more commonly after open surgery, whereas endovascular reintervention to the aorta and visceral arteries was seen almost exclusively after EVAR and FEVAR. Perioperative revision (a reintervention to the primary aneurysm repair site) was seen across all 3 types of repair: EVAR (2 cases), Open Surgery (3 cases) and FEVAR (2 cases). These revisions were a mixture of both open and endovascular approaches. Incidence of secondary interventions (both overall reintervention rate and for specific types of interventions) across the different subgroups is demonstrated in Table 5-15 and Table 5-16.

Table 5-11 Need for intensive care in the perioperative period, overall and by subgroup (n=1847).

Need for intensive care	All (n=1847[2])	By Subgroup (Anatomical Classification and Risk Group*)[1]					
		≤4mm neck (n=552)		5-9mm neck (n=365)		≥10mm neck (n=929)	
		Standard (n=432)	**High** (n=120)	Standard (n=271)	**High** (n=94)	Standard (n=712)	**High** (n=217)
Overall	1419 (76.8%)	395/443 (91.4%)	114/125 (95.0%)	227/281 (83.8%)	69/94 (73.4%)	485/744 (68.1%)	129/227 (59.4%)
Open Repair (n=859)	852 (99.2%)	253/257 (99.2%)	54/55 (100.0%)	155/160 (98.1%)	27/27 (100.0%)	316/321 (99.4%)	47/48 (100.0%)
EVAR (n=639)	269 (42.1%)	5/14 (35.7%)	8/12 (66.7%)	28/69 (45.2%)	27/49 (55.1%)	130/373 (37.6%)	71/164 (45.8%)
FEVAR (n=349)	298 (85.4%)	137/172 (84.0%)	52/58 (96.3%)	44/52 (86.3%)	15/18 (83.3%)	39/50 (81.3%)	11/15 (73.3%)

*[1]1 patient could not be assigned a subgroup due to missing data, [2]69 patients were excluded due to missing data, *Denominators for percentages are subgroup totals.*

Table 5-12 Any perioperative Complication, overall and by subgroup (n=1916).

Any perioperative complication	All (n=1916)	By Subgroup (Anatomical Classification and Risk Group*)[1]					
		≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
		Standard (n=443)	**High** (n=125)	Standard (n=281)	**High** (n=94)	Standard (n=744)	**High** (n=227)
Overall	1061 (55.4%)	266/443 (60.0%)	97/125 (77.6%)	152/281 (54.1%)	55/94 (58.5%)	358/744 (48.1%)	132/227 (58.1%)
Open Repair (n=868)	542 (62.4%)	166/257 (64.6%)	45/55 (81.8%)	93/160 (58.1%)	17/27 (63.0%)	189/321 (58.9%)	32/48 (66.7%)
EVAR (n=682)	315 (46.2%)	8/14 (57.1%)	9/12 (75.0%)	30/69 (43.5%)	28/49 (57.1%)	147/373 (39.4%)	92/164 (56.1%)
FEVAR (n=366)	204 (55.7%)	92/172 (53.5%)	43/58 (74.1%)	29/52 (55.8%)	10/18 (55.6%)	22/50 (44.0%)	8/15 (53.3%)

[1]2 patients could not be assigned a subgroup due to missing data, *Denominators for percentages are subgroup totals.

Table 5-13 Perioperative Complications, overall and by operation type (n=1916).

Perioperative complication	Open Repair (n=864)	EVAR (n=684)	FEVAR (n=363)	Overall (n=1911)
Paraplegia/Paraparesis	28 (3.2%)	12 (1.8%)	16 (4.4%)	56 (2.9%)
Stroke	2 (0.2%)	7 (1.0%)	7 (1.9%)	16 (0.8%)
Transient Ischaemic Attack (TIA)	1 (0.1%)	1 (0.1%)	2 (0.5%)	4 (0.2%)
Myocardial Infarction	18 (2.1%)	8 (1.2%)	9 (2.5%)	35 (1.8%)
Acute heart failure	30 (3.5%)	49 (7.2%)	26 (7.1%)	105 (5.5%)
Atrial Fibrillation/Flutter	128 (14.7%)	113 (16.6%)	62 (17.0%)	303 (15.8%)
Cardiac Arrest	14 (1.6%)	5 (0.7%)	5 (1.4%)	24 (1.3%)
Arrhythmia Other	14 (1.6%)	9 (1.3%)	8 (2.2%)	31 (1.6%)
Other cardiac events (identified through NVR)	11 (1.3%)	4 (0.6%)	2 (0.6%)	17 (0.9%)
Pneumonia	141 (16.2%)	25 (3.7%)	27 (7.4%)	193 (10.1%)
Chest Infection	16 (1.8%)	8 (1.2%)	8 (2.2%)	32 (1.7%)
Respiratory failure	4 (0.5%)	1 (0.1%)	0 (0.0%)	5 (0.3%)
Lung collapse / Atelectasis	38 (4.4%)	7 (1.0%)	16 (4.4%)	61 (3.2%)
Other Respiratory Event (identified through NVR)	26 (3.1%)	10 (1.5%)	2 (0.6%)	38 (2.0%)
Re-bleed	58 (6.7%)	42 (6.2%)	33 (9.0%)	133 (6.9%)
Acute limb ischaemia	96 (11.1%)	50 (7.3%)	13 (3.6%)	159 (8.3%)
Lower limb dissection	100 (11.5%)	55 (8.1%)	33 (9.0%)	188 (9.8%)
Renal artery dissection	5 (0.6%)	1 (0.1%)	5 (1.4%)	11 (0.6%)
Deep vein thrombosis	1 (0.1%)	1 (0.1%)	2 (0.5%)	4 (0.2%)
Other renal events (identified through NVR)	43 (5.1%)	10 (1.5%)	8 (2.2%)	61 (3.2%)
Graft complications (bleed, thrombosis, stenosis) excluding infection	14 (1.6%)	50 (7.3%)	48 (13.2%)	112 (5.9%)
Pseudoaneurysm – iliac/lower limb	100 (11.5%)	55 (8.1%)	33 (9.0%)	188 (9.8%)
Pulmonary embolism	7 (0.8%)	1 (0.1%)	2 (0.5%)	10 (0.5%)
Rupture of artery	1 (0.1%)	2 (0.3%)	1 (0.3%)	4 (0.2%)
Acute kidney injury	186 (21.4%)	41 (6.0%)	45 (12.3%)	272 (14.2%)
Dialysis	29 (3.3%)	6 (0.9%)	3 (0.8%)	38 (2.0%)

Table 5-14 Cases of perioperative spinal cord ischaemia, overall and across the 6 subgroups (n=1916).

Paraplegia/Paraparesis	All (n=1916)	By Subgroup (Anatomical Classification and Risk Group*)[1]					
		≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
		Standard (n=443)	High (n=125)	Standard (n=281)	High (n=94)	Standard (n=744)	High (n=227)
Overall	56 (2.9%)	14/443 (3.2%)	7/125 (5.6%)	11/281 (3.9%)	2/94 (2.1%)	18/744 (2.4%)	4/227 (1.8%)
Open Repair (n=868)	28 (3.2%)	8/257 (3.1%)	5/55 (9.1%)	5/160 (3.1%)	1/27 (3.7%)	6/321 (1.9%)	3/48 (6.3%)
EVAR (n=682)	12 (1.8%)	0/14 (0.0%)	0/12 (0.0%)	4/69 (5.8%)	0/49 (0.0%)	8/373 (2.1%)	0/164 (0.0%)
FEVAR (n=366)	16 (4.4%)	6/172 (3.5%)	2/58 (3.4%)	2/52 (3.8%)	1/18 (5.6%)	4/50 (8.0%)	1/15 (6.7%)

*[1]2 patients could not be assigned a subgroup due to missing data, *Denominators for percentages are subgroup totals.*

Table 5-15 Any perioperative secondary intervention, overall and by subgroup (n=1916).

Any perioperative secondary intervention	All (n=1916)	By Subgroup (Anatomical Classification and Risk Group*)[1]					
		≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
		Standard (n=443)	High (n=125)	Standard (n=281)	High (n=94)	Standard (n=744)	High (n=227)
Overall	148 (7.7%)	41/443 (9.3%)	17/125 (13.6%)	19/281 (6.8%)	7/94 (7.4%)	52/744 (7.0%)	12/227 (5.3%)
Open Repair (n=868)	77 (8.9%)	26/257 (10.1%)	6/55 (10.9%)	10/160 (6.3%)	3/27 (11.1%)	28/321 (8.7%)	4/48 (8.3%)
EVAR (n=682)	39 (5.7%)	2/14 (14.3%)	3/12 (25.0%)	4/69 (5.8%)	3/49 (6.1%)	20/373 (5.4%)	7/164 (4.3%)
FEVAR (n=366)	32 (8.7%)	13/172 (7.6%)	8/58 (13.8%)	5/52 (9.6%)	1/18 (5.6%)	4/50 (8.0%)	1/15 (6.7%)

*[1]2 patients could not be assigned a subgroup due to missing data, *Denominators for percentages are subgroup totals.*

Table 5-16 Perioperative secondary interventions, by subgroup (n=1916).

	Open Repair (n=868)			EVAR (n=682)			FEVAR (n=366)		
	≤4mm neck (n=312)	5-9mm neck (n=187)	≥10mm neck (n=369)	≤4mm neck (n=26)	5-9mm neck (n=118)	≥10mm neck (n=537)	≤4mm neck (n=230)	5-9mm neck (n=70)	≥10mm neck (n=65)
Any re-intervention	**54 [32(10.3%)]**	**24 [13(7%)]**	**45 [32(8.7%)]**	**9 [5(19.2%)]**	**8 [7(5.9%)]**	**33 [27(5%)]**	**29 [21(9.1%)]**	**7 [6(8.6%)]**	**6 [5(7.7%)]**
Adhesiolysis	1 [1(0.3%)]	0 [0(0%)]	2 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Bowel Resection +/- Stoma	12 [10(3.2%)]	2 [2(1.1%)]	9 [8(2.2%)]	1 [1(3.8%)]	1 [1(0.8%)]	2 [2(0.4%)]	2 [2(0.9%)]	0 [0(0%)]	0 [0(0%)]
Bypass - Visceral artery	1 [1(0.3%)]	2 [2(1.1%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	2 [2(0.4%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Bypass - infrainguinal	1 [1(0.3%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Bypass - suprainguinal	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
CFA/groin reintervention	2 [2(0.6%)]	2 [2(1.1%)]	1 [1(0.3%)]	0 [0(0%)]	1 [1(0.8%)]	4 [4(0.7%)]	3 [3(1.3%)]	1 [1(1.4%)]	1 [1(1.5%)]
Embolectomy	5 [5(1.6%)]	4 [4(2.1%)]	7 [7(1.9%)]	1 [1(3.8%)]	0 [0(0%)]	2 [2(0.4%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Endovascular Reintervention - Iliofemoral/Lower Limb	3 [3(1%)]	1 [1(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	3 [3(0.6%)]	2 [2(0.9%)]	1 [1(1.4%)]	0 [0(0%)]
Endovascular Reintervention - Other	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	2 [2(7.7%)]	0 [0(0%)]	3 [3(0.6%)]	9 [7(3%)]	2 [2(2.9%)]	1 [1(1.5%)]
Endovascular Reintervention - Upper Limb	4 [4(1.3%)]	3 [3(1.6%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Endovascular Reintervention - Visceral Artery/Aorta	10 [9(2.9%)]	2 [2(1.1%)]	5 [5(1.4%)]	0 [0(0%)]	3 [3(2.5%)]	7 [7(1.3%)]	1 [1(0.4%)]	2 [2(2.9%)]	2 [2(3.1%)]
Fasciotomy	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
GI Endoscopy	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	1 [1(3.8%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Hernia	0 [0(0%)]	1 [1(0.5%)]	2 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Image guided drainage of collection	4 [3(1%)]	3 [3(1.6%)]	7 [7(1.9%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(1.4%)]	0 [0(0%)]
Laparotomy - Bleeding	2 [1(0.3%)]	1 [1(0.5%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Laparotomy - Unspecified	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]

	Open Repair (n=868)			EVAR (n=682)			FEVAR (n=366)		
	≤4mm neck (n=312)	**5-9mm neck (n=187)**	**≥10mm neck (n=369)**	**≤4mm neck (n=26)**	**5-9mm neck (n=118)**	**≥10mm neck (n=537)**	**≤4mm neck (n=230)**	**5-9mm neck (n=70)**	**≥10mm neck (n=65)**
Major Amputation	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Minor Amputation	2 [2(0.6%)]	1 [1(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Nephrostomy/Ureteric Stent/Other renal	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	1 [1(0.8%)]	2 [2(0.4%)]	2 [2(0.9%)]	0 [0(0%)]	0 [0(0%)]
Other organ resection (spleen, gallbladder, kidney)	1 [1(0.3%)]	0 [0(0%)]	1 [1(0.3%)]	1 [1(3.8%)]	1 [1(0.8%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Revision - Endovascular	1 [1(0.3%)]	1 [1(0.5%)]	1 [1(0.3%)]	1 [1(3.8%)]	0 [0(0%)]	0 [0(0%)]	2 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Revision - Open	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	1 [1(1.5%)]
Thoracic/Cardiac/Coronary Intervention	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	1 [1(1.5%)]
Unknown	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(3.8%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Upper limb artery repair	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Visceral artery repair - open	2 [2(0.6%)]	1 [1(0.5%)]	0 [0(0%)]	1 [1(3.8%)]	1 [1(0.8%)]	1 [1(0.2%)]	3 [3(1.3%)]	0 [0(0%)]	0 [0(0%)]
Wound Reinterventions and debridements	1 [1(0.3%)]	0 [0(0%)]	2 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]

5.4.3 Secondary Outcome Measures – 3.5 Years Follow-Up Period

Mid-term outcomes presented in this subsection relate to the 1916 patients included in the propensity score analysis. Minimum follow-up was 2.5 years and maximum follow-up was 4.5 years, with a median of 3.5 years.

Late all-cause mortality refers to any deaths that occur after the perioperative time period. A total of 341 (17.8%) late deaths were observed. Across the 6 subgroups, late all-cause mortality ranged from 13.3% (≥10mm neck, standard risk, 99/744 patients), through to 30.4% (0-4mm neck, high risk, 38/125 patients). For the population as a whole, late all-cause mortality rate was 24.0% after EVAR +/- adjuncts (164 deaths/682 patients), 25.4% after FEVAR (93 deaths/366 patients) and 9.7% after Open Surgery (84 deaths/868 patients). The adjusted risk of late death was significantly greater after EVAR (HR 2.18, 95% CI 1.61-2.95, p<0.001) and FEVAR (HR 2.01, 95% CI 1.46-2.77, p<0.001) than after OSR (Figure 5-4). Late mortality rates by treatment type and subgroup are summarised in Table 5-17.

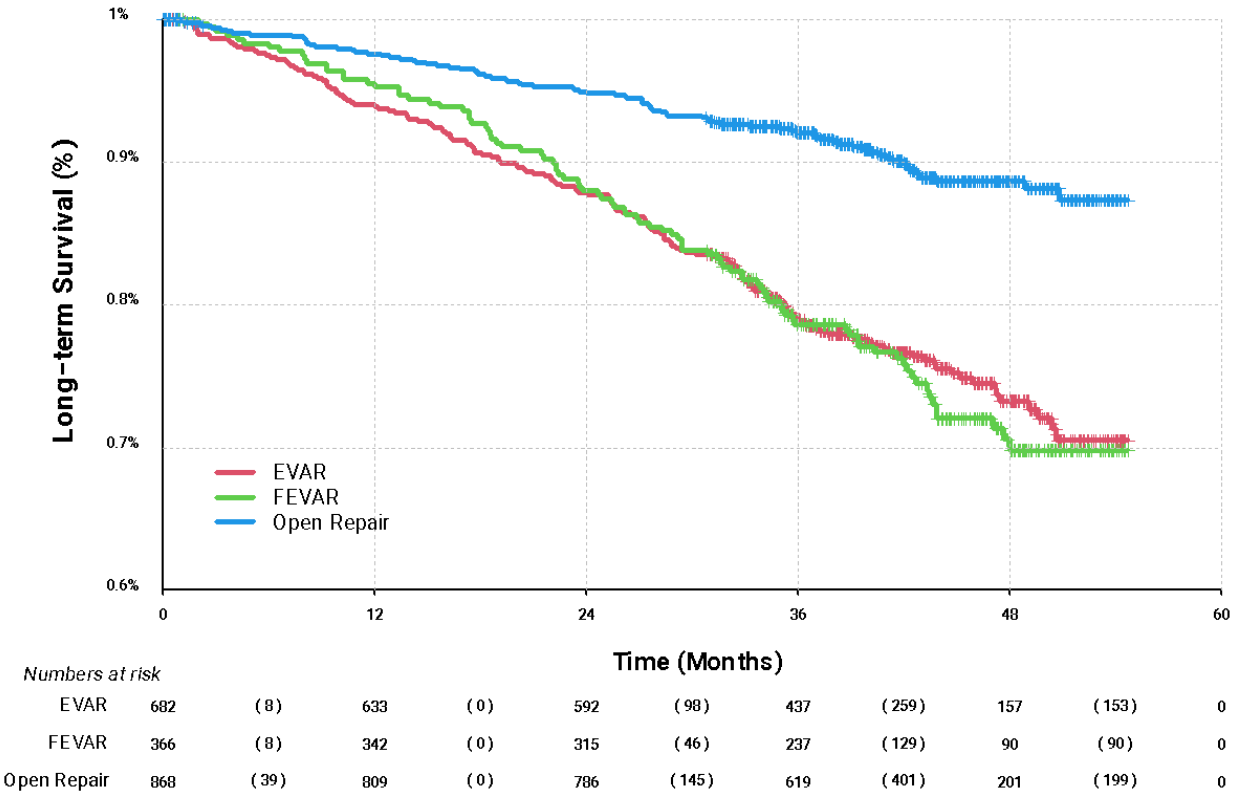


Figure 5-4 Kaplan-Meier Graph of freedom from late all-cause mortality (excluding those who died perioperatively).

However, this late survival advantage in favour of Open Surgery was not observed for the true juxtarenal aneurysm group (0-4mm neck length group): For standard risk patients in this group, late all-cause mortality after EVAR (HR 2.4, 95%CI 0.82-6.98, p=0.109) and FEVAR (HR 1.64, 95%CI 0.991-2.71, p=0.054) was equivalent to Open Surgery. A similar result was seen when comparing EVAR (HR 2.02, 95%CI 0.62-6.55, p=0.241) and FEVAR (HR 2.14, 95%CI 0.95-4.80, P=0.066) to Open Surgery for high-risk patients in this anatomical group. The drivers of the late survival advantage in favour of Open Surgery for the wider population were the standard-risk patients in the short neck (5-9mm length) and complex neck (≥10mm length) subgroups. In the former, EVAR (HR 3.55, 95%CI 1.58-7.97), p=0.002) and FEVAR (HR 2.83, 95%CI 1.21-6.64, p=0.017) patients suffered approximately 3x the late mortality as Open Repair patients. In the latter, an even larger late all-cause mortality difference was seen between Open Surgery patients and both EVAR (HR 3.52, 95%CI 1.97-6.29, p<0.001) and FEVAR (HR 4.18, 95%CI 1.80-9.67, p=0.001) patients. In the highest risk patients (across all 3 anatomical subgroups), there was equivalent long-term survival between open surgery and both EVAR and FEVAR.

Overall mortality rates are calculated by combination of perioperative and late deaths. The total number of these deaths among the 1,916 patients, including early and late mortality, was 396 (20.7%). Across the 6 subgroups, overall mortality ranged from 14.7% (≥10mm neck, standard risk, 109/744 patients), through to 36.8% (0-4mm neck, high risk, 46/125 patients). For the population as a whole, overall mortality rate was 25.2% after EVAR +/- adjuncts (172 deaths/682 patients), 27.6% after FEVAR (101 deaths/366 patients) and 14.2% after Open Surgery (123 deaths/868 patients). Patterns within specific subgroups generally mirrored that of late all-cause mortality. For the population as a whole, the risk of overall mortality was significantly greater after EVAR (HR 1.58, 95% CI 1.21-2.08, p=0.001) and FEVAR (HR 1.4, 95% CI 1.05-1.87, p=0.02) than after OSR (Figure 5-5), mirroring the result of late mortality. Overall mortality rates by treatment type and subgroup are summarised in Table 5-18.

This result from this analysis of overall mortality did not hold the assumption of proportional hazards due to a reversal of treatment effect direction during the follow-up period (Figure 5-5). Specifically, there is a perioperative survival benefit for endovascular techniques but a later disadvantage. This "crossover" of direction occurred at 10.3 months for EVAR vs Open Surgery and 12.1 months for FEVAR vs Open Surgery. Statistically, non-proportional hazards were

confirmed with an assessment of Schoenfeld residuals against the rank of time giving a p-value of <0.001.

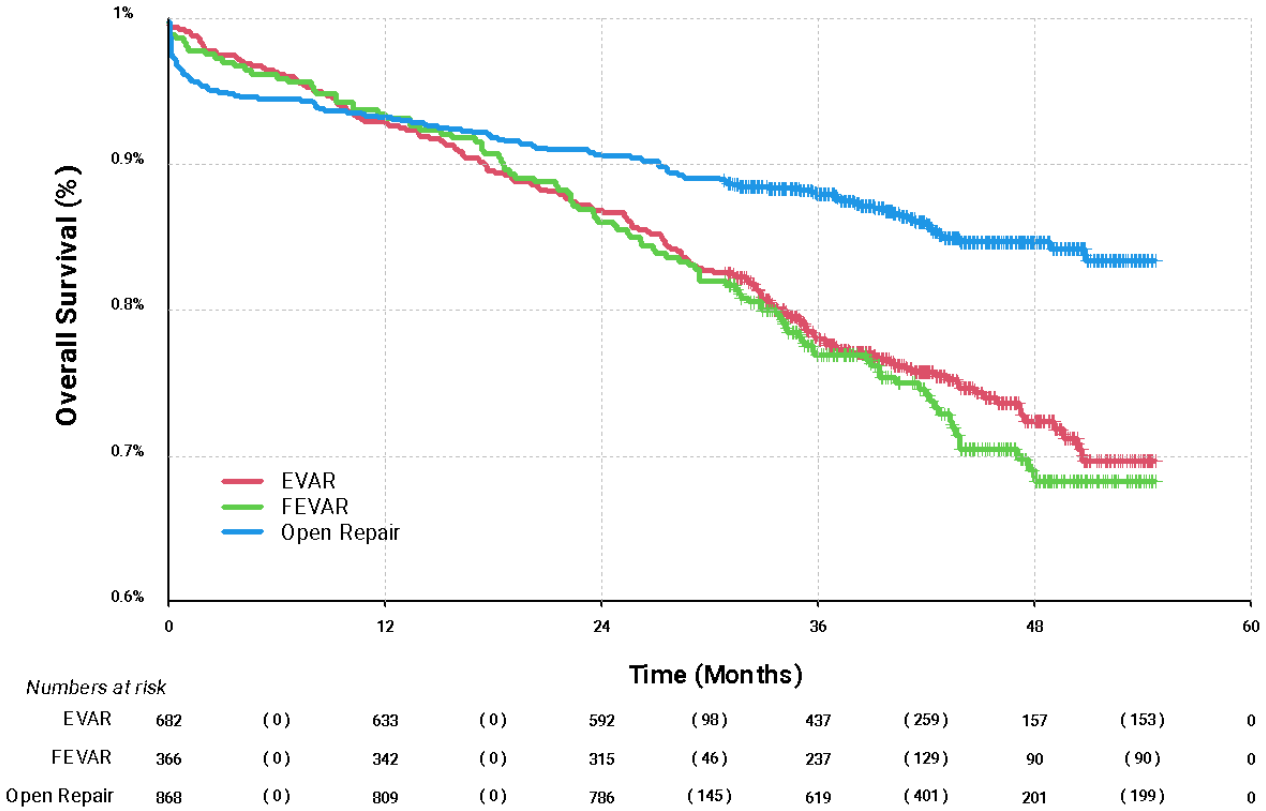


Figure 5-5 Kaplan-Meier graph of overall survival (including the perioperative period).

Similar to the results of late all-cause mortality, the overall survival benefit with Open Surgery over Endovascular techniques was not seen in the 0-4mm neck length group. For these patients, overall survival between EVAR vs Open surgery and FEVAR vs Open Surgery was equivalent at 3.5 years of follow-up. Further Kaplan-Meier survival curves are presented for all 6 subgroups in Figure 5-6 through to Figure 5-11.

A breakdown of statistical comparative analysis for both overall and late all-cause mortality, and for the time to loss of early survival benefit is presented for all patients and across all subgroups in Table 5-19 and Table 5-20.

Table 5-17 Late (excluding peri-operative deaths) all-cause mortality rates, overall and by subgroup for the analysis cohort (n=1916).

Late all-cause mortality (excluding peri-operative deaths)	All (n=1916)	By Subgroup (Anatomical Classification and Risk Group*)					
		≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
		Standard (n=443)	**High** (n=125)	Standard (n=281)	**High** (n=94)	Standard (n=744)	**High** (n=227)
Overall	341 (17.8%)	71/443 (16.0%)	38/125 (30.4%)	40/281 (14.2%)	26/94 (27.7%)	99/744 (13.3%)	66/227 (29.1%)
Open Repair (n=868)	84 (9.7%)	29/257 (11.3%)	10/55 (18.2%)	12/160 (7.5%)	7/27 (25.9%)	16/321 (5.0%)	10/48 (20.8%)
EVAR (n=682)	164 (24.0%)	4/14 (28.6%)	6/12 (50.0%)	17/69 (24.6%)	12/49 (24.5%)	71/373 (19.0%)	53/164 (32.3%)
FEVAR (n=366)	93 (25.4%)	38/172 (22.1%)	22/58 (37.9%)	11/52 (21.2%)	7/18 (38.9%)	12/50 (24.0%)	3/15 (20.0%)

*[1]2 patients could not be assigned a subgroup due to missing data. *Denominators for percentages are subgroup totals.*

Table 5-18 Overall (Combined early and late) mortality rates, overall and by subgroup for the analysis cohort (n=1916).

All mortality	All (n=1916)	By Subgroup (Anatomical Classification and Risk Group*)[1]					
		≤4mm neck (n=568)		5-9mm neck (n=375)		≥10mm neck (n=971)	
		Standard (n=443)	**High** (n=125)	Standard (n=281)	**High** (n=94)	Standard (n=744)	**High** (n=227)
Overall	396 (20.7%)	95/443 (21.4%)	46/125 (36.8%)	44/281 (15.7%)	30/94 (31.9%)	109/744 (14.7%)	71/227 (31.3%)
Open Repair (n=868)	123 (14.2%)	48/257 (18.7%)	16/55 (29.1%)	15/160 (9.4%)	10/27 (37.0%)	23/321 (7.2%)	11/48 (22.9%)
EVAR (n=682)	172 (25.2%)	5/14 (35.7%)	7/12 (58.3%)	18/69 (26.1%)	13/49 (26.5%)	73/373 (19.6%)	55/164 (33.5%)
FEVAR (n=366)	101 (27.6%)	42/172 (24.4%)	23/58 (39.7%)	11/52 (21.2%)	7/18 (38.9%)	13/50 (26.0%)	5/15 (33.3%)

*[1]2 patients could not be assigned a subgroup due to missing data. *Denominators for percentages are subgroup totals.*

Table 5-19 Summary table of comparative effectiveness between Open and Endovascular techniques, in terms of overall and late all-cause mortality rates across the population as a whole, across the 3 anatomical subgroups and the 2 populations of varying physiological risk.

		Overall Mortality		Late Mortality	
		HR (95% CI)	Pval	HR (95% CI)	Pval
Full Population		1.58 (1.206, 2.075)	0.001	2.18 (1.608, 2.95)	<0.001
		1.4 (1.053, 1.865)	0.02	2.01 (1.463, 2.772)	<0.001
0-4mm neck	EVAR Vs Open Repair	1.65 (0.843, 3.228)	0.144	2.38 (1.118, 5.07)	0.025
	FEVAR Vs Open Repair	1.08 (0.744, 1.561)	0.692	1.73 (1.127, 2.662)	0.012
5-9mm neck	EVAR Vs Open Repair	1.62 (0.891, 2.938)	0.114	2.11 (1.104, 4.036)	0.024
	FEVAR Vs Open Repair	1.98 (1.038, 3.764)	0.038	2.63 (1.329, 5.224)	0.006
≥10mm neck	EVAR Vs Open Repair	2.09 (1.392, 3.15)	<0.001	2.69 (1.706, 4.239)	<0.001
	FEVAR Vs Open Repair	2.16 (1.161, 4.019)	0.015	2.35 (1.182, 4.656)	0.015
Standard Risk	EVAR Vs Open Repair	1.95 (1.392, 2.74)	<0.001	2.74 (1.878, 4.006)	<0.001
	FEVAR Vs Open Repair	1.51 (1.066, 2.128)	0.02	2.26 (1.533, 3.337)	<0.001
High Risk	EVAR Vs Open Repair	1.02 (0.648, 1.597)	0.941	1.36 (0.821, 2.24)	0.234
	FEVAR Vs Open Repair	1.24 (0.75, 2.057)	0.4	1.66 (0.947, 2.898)	0.077

Table 5-20 Summary table of comparative effectiveness between Open and Endovascular techniques, in terms of overall and late all-cause mortality rates, across the population as a whole and across 6 subgroups.

			Overall Mortality			Late Mortality	
			Full follow-up		Time to loss of early survival benefit (months)*	HR (95% CI)	Pval
			HR (95% CI)	Pval			
Full Population			1.58 (1.206, 2.075)	0.001	10.3	2.18 (1.608, 2.95)	<0.001
			1.4 (1.053, 1.865)	0.02	12.1	2.01 (1.463, 2.772)	<0.001
0-4mm neck	Standard Risk	EVAR Vs Open Repair	1.62 (0.632, 4.147)	0.316	1.3	2.4 (0.822, 6.984)	0.109
		FEVAR Vs Open Repair	1.05 (0.681, 1.622)	0.822	33.8	1.64 (0.991, 2.715)	0.054
	High Risk	EVAR Vs Open Repair	1.46 (0.515, 4.168)	0.474	0.6	2.02 (0.624, 6.547)	0.241
		FEVAR Vs Open Repair	1.26 (0.62, 2.548)	0.526	27.1	2.14 (0.952, 4.805)	0.066
5-9mm neck	Standard Risk	EVAR Vs Open Repair	3.06 (1.429, 6.553)	0.004	4.6	3.55 (1.585, 7.967)	0.002
		FEVAR Vs Open Repair	2.24 (0.989, 5.064)	0.053	3.8	2.83 (1.208, 6.639)	0.017
	High Risk	EVAR Vs Open Repair	0.65 (0.276, 1.553)	0.336	NA	0.91 (0.337, 2.456)	0.852
		FEVAR Vs Open Repair	1.43 (0.504, 4.05)	0.502	10.3	1.95 (0.626, 6.093)	0.249
≥10mm neck	Standard Risk	EVAR Vs Open Repair	2.45 (1.484, 4.038)	<0.001	14	3.52 (1.973, 6.291)	<0.001
		FEVAR Vs Open Repair	3.23 (1.495, 6.971)	0.003	1	4.18 (1.802, 9.676)	0.001
	High Risk	EVAR Vs Open Repair	1.27 (0.625, 2.582)	0.508	2.8	1.37 (0.652, 2.885)	0.406
		FEVAR Vs Open Repair	1.17 (0.378, 3.613)	0.786	0.5	0.79 (0.202, 3.069)	0.732

**The point in time at which the Kaplan-Meier survival curves for each treatment cross each other*

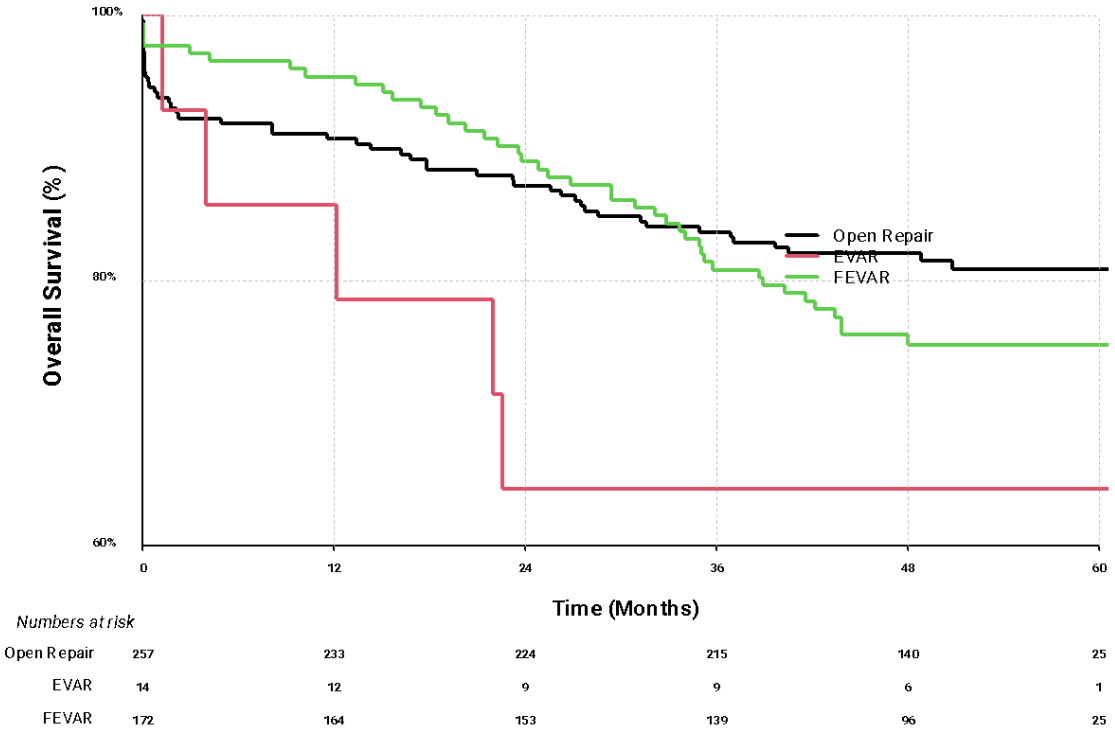


Figure 5-6 Kaplan-Meier graft of overall survival for the patient subgroup with neck length 0-4mm and standard physiological risk.

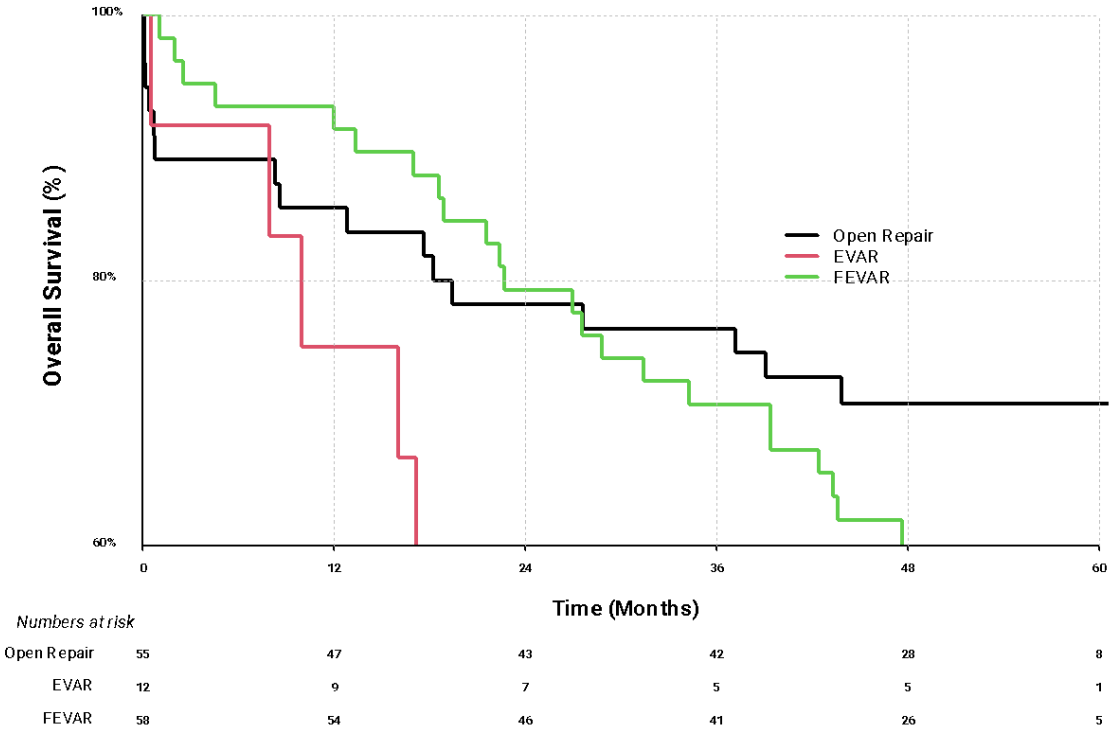


Figure 5-7 Kaplan-Meier graph of overall survival for the patient subgroup with neck length 0-4mm and high physiological risk.

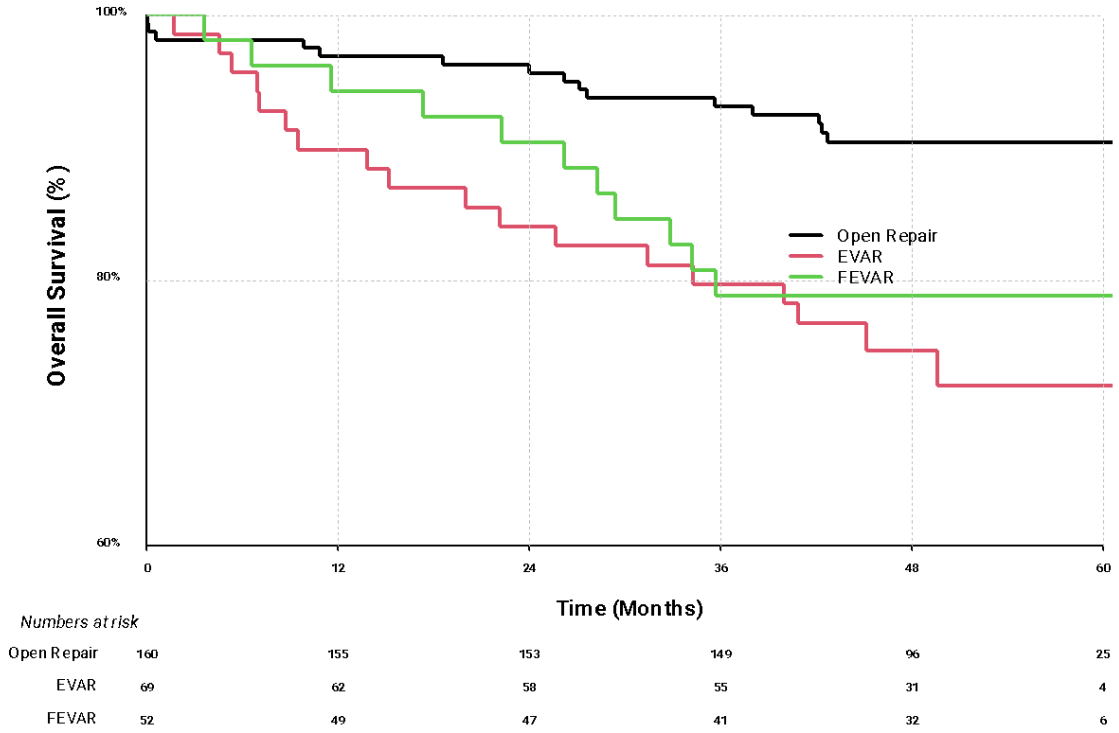


Figure 5-8 Kaplan-Meier graph of overall survival for the patient subgroup with neck length 5-9mm and standard physiological risk.

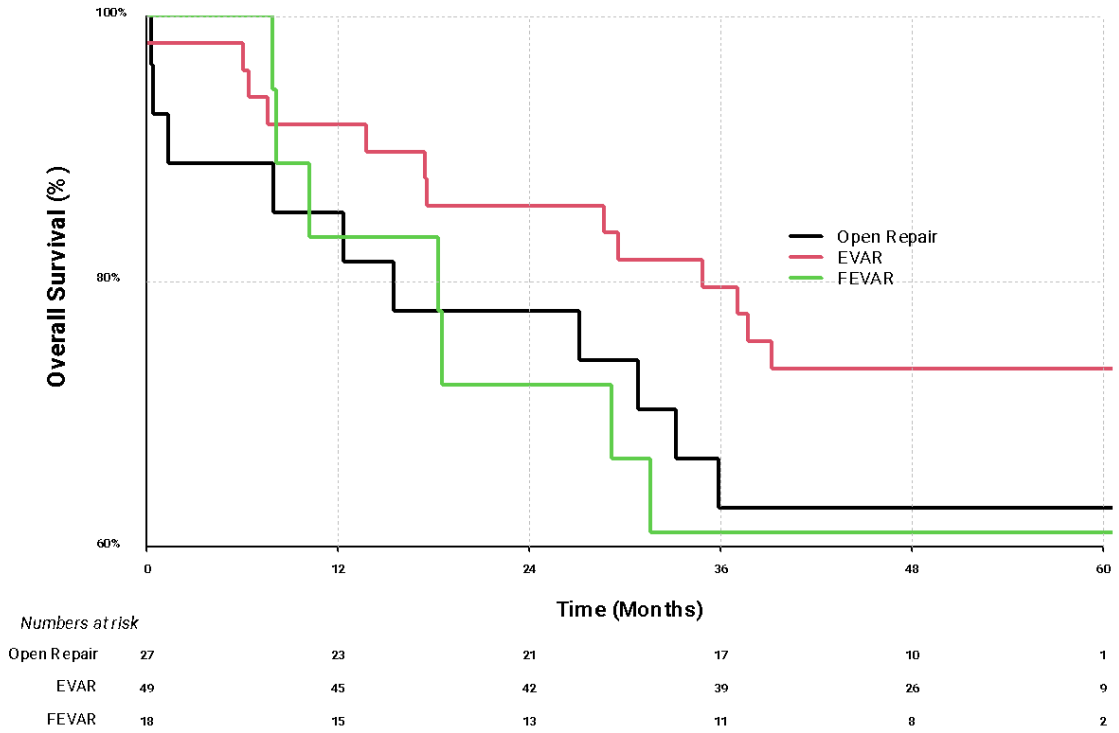


Figure 5-9 Kaplan-Meier graph of overall survival for the patient subgroup with neck length 5-9mm and high physiological risk.

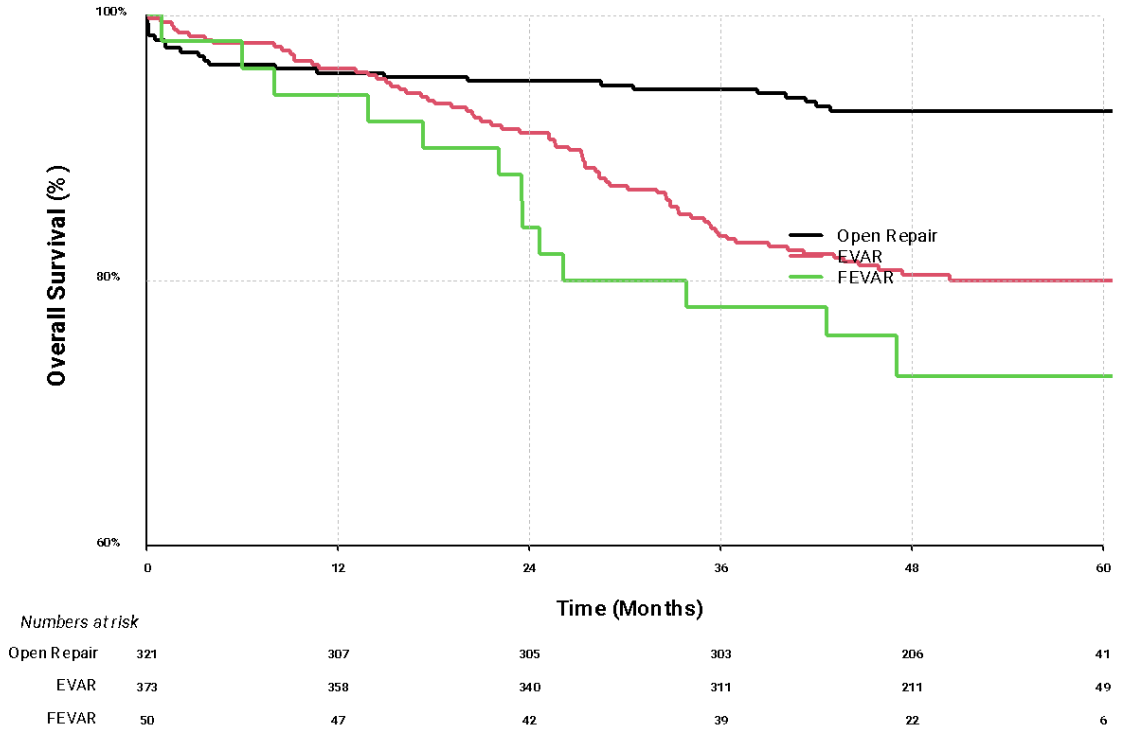


Figure 5-10 Kaplan-Meier graph of overall survival for the patient subgroup with neck length ≥10mm and standard physiological risk.

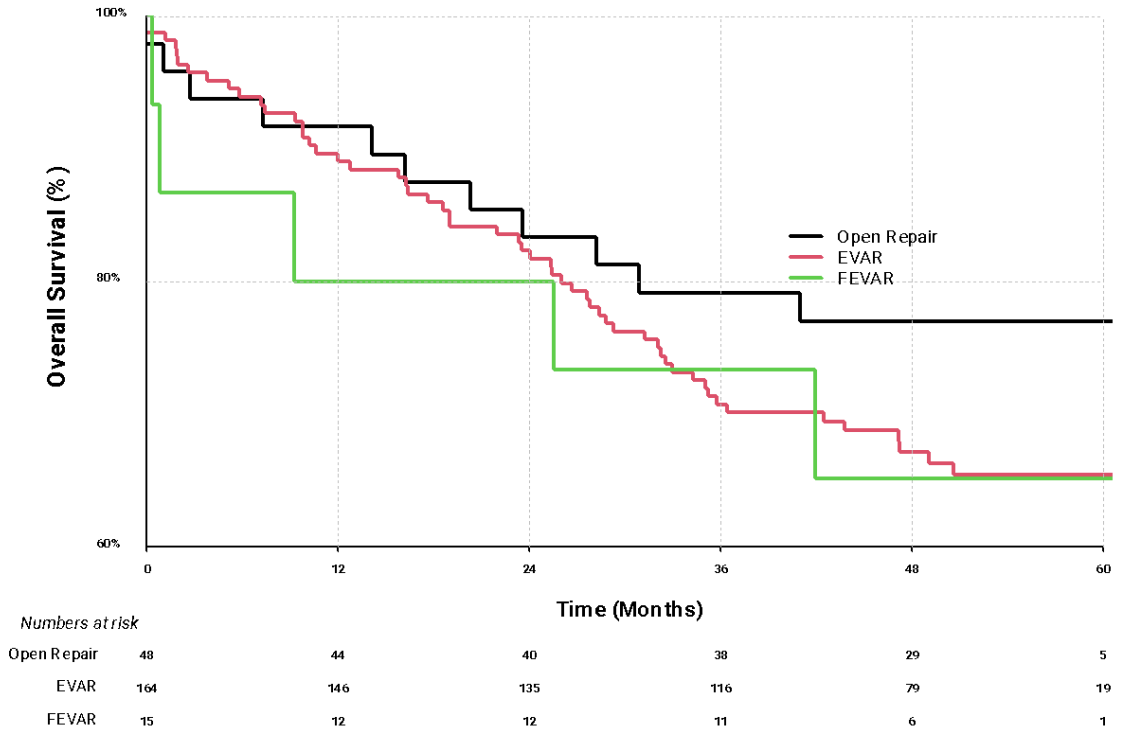


Figure 5-11 Kaplan-Meier graph of overall survival for the patient subgroup with neck length ≥10mm and high physiological risk.

Twenty-six (1.4%) mid-term aneurysm-related deaths were observed. Aneurysm related mortality at 3.5 years was 1% (9/868) after Open Surgery, 1.8% (12/682) after EVAR +/- adjuncts and 1.4% (5/366) after FEVAR. Subgroup mortality rates ranged from 0.9% (≥10mm neck, standard risk, 7/744 patients), through to 1.8% (0-4mm neck, standard risk, 8/443 patients, and ≥10mm neck, high risk, 4/227 patients). The adjusted risk of mid-term aneurysm-related death (after the perioperative period) was similar after EVAR (HR 2.19, 95% CI 0.68-9.37, p=0.13) and FEVAR (HR 0.97, 95% CI 0.26-3.66, p=0.96) as compared to OSR. Despite this, there was a clear disadvantage to using EVAR +/- adjuncts in patients with shortest aortic neck length (0-4mm): for these Group 1 patients, incidence of aneurysm-related mortality was 1.3% after Open Surgery, 1.3% after FEVAR and 11.5% after EVAR +/- adjuncts. Aneurysm-related mortality data by subgroup is summarised in Table 5-20. A Kaplan-Meier plot of freedom from mid-term aneurysm-related mortality is shown in Figure 5-12.

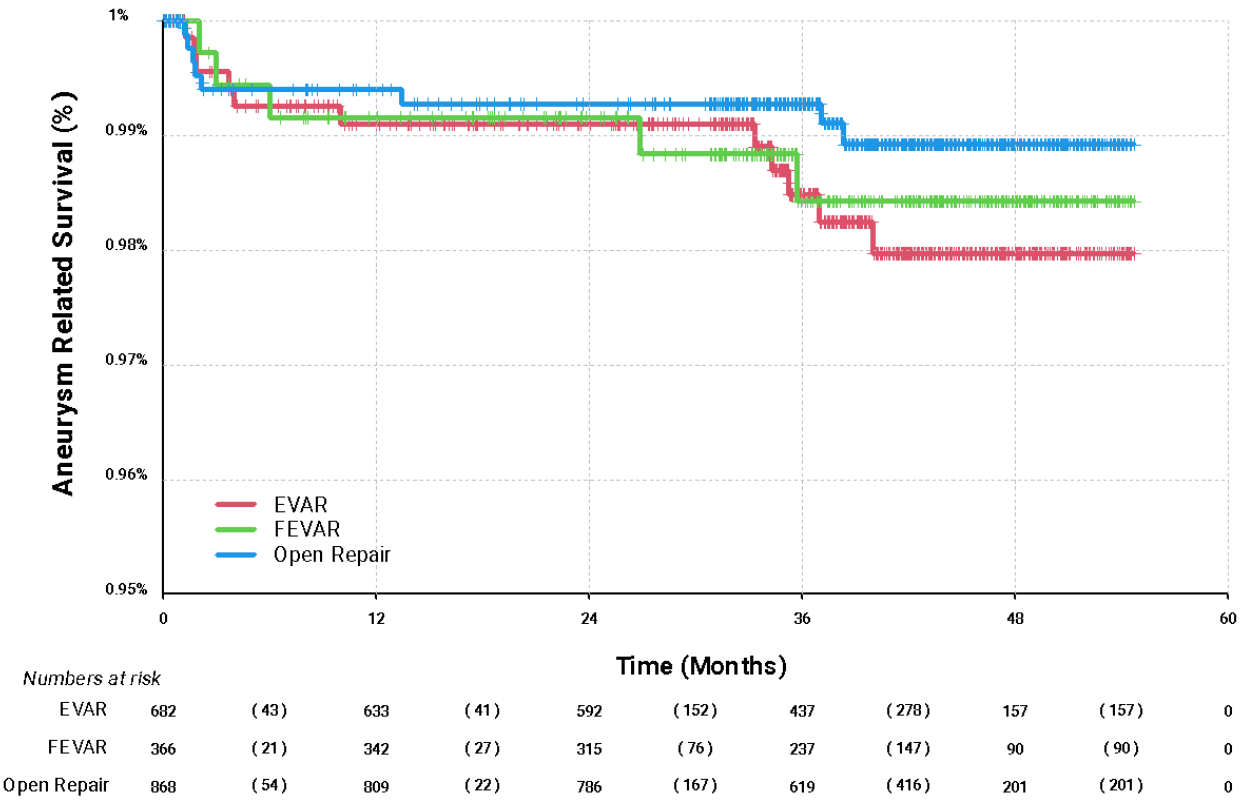


Figure 5-12 Kaplan-Meier graft of Freedom From Late Aneurysm-related mortality (excluding perioperative deaths).

A total of 178 (9.3%) patients underwent secondary interventions related to their AAA repair after the peri-operative period. Distribution of these across the various subgroups are shown in

Table 5-21. Reintervention rates were 3.8% (36 patients) in the Open Surgery group, 9.0% (78 patients) in the EVAR group and 15.6% (64 patients) in the FEVAR group. The adjusted risk of mid-term secondary intervention was significantly greater after EVAR (HR 2.65, 95% CI 1.71-4.10, $p<0.001$) and FEVAR (HR 5.29, 95% CI 3.36-8.33, $p<0.001$) than after Open Surgery (Figure 5-13). Of note, mid-term revision (re-intervention to the treated aortic segment) was performed significantly more often after endovascular procedures. Incidence was 0.4% after Open Surgery (4/940 patients), 1.3% after EVAR +/- adjuncts (11/866 patients) and 1.2% after FEVAR (5/403 patients). Adhesiolysis and Incisional hernia repair were seen exclusively after Open Surgery (0.5% and 2.2% respectively). The majority of secondary interventions were endovascular interventions after EVAR or FEVAR, including Type II Endoleak embolisation procedures, Iliac or lower limb revascularisations or catheter angiograms (Table 5-22).

Table 5-21 Mid-term aneurysm-related mortality, overall and by subgroup for the analysis cohort (n=1916).

Mid-term aneurysm related mortality	**All** (n=1916)	**By Subgroup (Anatomical Classification and Risk Group*)[1]**					
		≤4mm neck (n=568)		**5-9mm neck** (n=375)		**≥10mm neck** (n=971)	
		Standard (n=443)	**High** (n=125)	**Standard** (n=281)	**High** (n=94)	**Standard** (n=744)	**High** (n=227)
Overall	26 (1.4%)	8/443 (1.8%)	2/125 (1.6%)	4/281 (1.4%)	1/94 (1.1%)	7/744 (0.9%)	4/227 (1.8%)
Open Repair (n=868)	9 (1.0%)	4/257 (1.6%)	0/55 (0.0%)	0/160 (0.0%)	1/27 (3.7%)	3/321 (0.9%)	1/48 (2.1%)
EVAR (n=682)	12 (1.8%)	2/14 (14.3%)	1/12 (8.3%)	3/69 (4.3%)	0/49 (0.0%)	3/373 (0.8%)	3/164 (1.8%)
FEVAR (n=366)	5 (1.4%)	2/172 (1.2%)	1/58 (1.7%)	1/52 (1.9%)	0/18 (0.0%)	1/50 (2.0%)	0/15 (0.0%)

*[1]2 patients could not be assigned a subgroup due to missing data, *Denominators for percentages are subgroup totals.*

Table 5-22 Any mid-term secondary intervention, overall and by subgroup for the analysis cohort (n=1916).

Any mid-term secondary intervention	**All** (n=1916)	**By Subgroup (Anatomical Classification and Risk Group*)[1]**					
		≤4mm neck (n=568)		**5-9mm neck** (n=375)		**≥10mm neck** (n=971)	
		Standard (n=443)	**High** (n=125)	**Standard** (n=281)	**High** (n=94)	**Standard** (n=744)	**High** (n=227)
Overall	178 (9.3%)	38/443 (8.6%)	15/125 (12.0%)	23/281 (8.2%)	6/94 (6.4%)	67/744 (9.0%)	28/227 (12.3%)
Open Repair (n=868)	36 (4.1%)	7/257 (2.7%)	3/55 (5.5%)	9/160 (5.6%)	1/27 (3.7%)	15/321 (4.7%)	1/48 (2.1%)
EVAR (n=682)	78 (11.4%)	0/14 (0.0%)	1/12 (8.3%)	4/69 (5.8%)	3/49 (6.1%)	45/373 (12.1%)	25/164 (15.2%)
FEVAR (n=366)	64 (17.5%)	31/172 (18.0%)	11/58 (19.0%)	10/52 (19.2%)	2/18 (11.1%)	7/50 (14.0%)	2/15 (13.3%)

*[1]2 patients could not be assigned a subgroup due to missing data, *Denominators for percentages are subgroup totals.*

Table 5-23 Summary of Mid-term Secondary Interventions across different operation types and subgroups (n=1916).

	Open Repair (n=940)			EVAR (n=866)			FEVAR (n=403)		
	≤4mm neck (n=329)	**5-9mm neck (n=206)**	**≥10mm neck (n=405)**	**≤4mm neck (n=37)**	**5-9mm neck (n=128)**	**≥10mm neck (n=701)**	**≤4mm neck (n=232)**	**5-9mm neck (n=73)**	**≥10mm neck (n=98)**
Any re-intervention	13 [10(3.2%)]	11 [10(5.3%)]	25 [16(4.3%)]	1 [1(3.8%)]	11 [7(5.9%)]	108 [70(13%)]	58 [42(18.3%)]	19 [12(17.1%)]	12 [9(13.8%)]
Adhesiolysis	2 [2(0.6%)]	2 [2(1.1%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Bowel Resection +/- Stoma	2 [2(0.6%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Bypass - Suprainguinal	1 [1(0.3%)]	0 [0(0%)]	3 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	7 [5(0.9%)]	2 [2(0.9%)]	1 [1(1.4%)]	1 [1(1.5%)]
CFA/groin reintervention	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	5 [5(0.9%)]	3 [3(1.3%)]	0 [0(0%)]	1 [1(1.5%)]
Endovascular - Embolisation (other)	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.8%)]	1 [1(0.2%)]	1 [1(0.4%)]	0 [0(0%)]	0 [0(0%)]
Endovascular - Angioplasty of Aorta	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Endovascular - Catheter Angiography	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(3.8%)]	1 [1(0.8%)]	10 [10(1.9%)]	6 [4(1.7%)]	3 [3(4.3%)]	1 [1(1.5%)]
Endovascular - Endoanchors	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.8%)]	5 [5(0.9%)]	0 [0(0%)]	1 [1(1.4%)]	0 [0(0%)]
Endovascular - Iliac stent	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(1.4%)]	0 [0(0%)]
Endovascular - Type II Endoleak Embolisation	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.8%)]	22 [16(3%)]	7 [5(2.2%)]	4 [4(5.7%)]	2 [1(1.5%)]
Endovascular Reintervention - Iliofemoral/Lower Limb	1 [1(0.3%)]	1 [1(0.5%)]	5 [3(0.8%)]	0 [0(0%)]	4 [3(2.5%)]	37 [31(5.8%)]	17 [16(7%)]	3 [3(4.3%)]	3 [3(4.6%)]
Endovascular Reintervention - Upper Limb	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Endovascular Reintervention - Visceral Artery	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	6 [4(0.7%)]	19 [17(7.4%)]	4 [3(4.3%)]	3 [3(4.6%)]
Incisional Hernia Repair	5 [5(1.6%)]	8 [8(4.3%)]	8 [8(2.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Laparotomy - Unspecified	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Major Amputation	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	1 [1(1.5%)]
Revision - Endovascular - Chimney	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]

	Open Repair (n=940)			EVAR (n=866)			FEVAR (n=403)		
	≤4mm neck (n=329)	**5-9mm neck (n=206)**	**≥10mm neck (n=405)**	**≤4mm neck (n=37)**	**5-9mm neck (n=128)**	**≥10mm neck (n=701)**	**≤4mm neck (n=232)**	**5-9mm neck (n=73)**	**≥10mm neck (n=98)**
Revision - Endovascular - Fenestrated Re-lining	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.8%)]	4 [4(0.7%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Revision - Endovascular - Infrarenal Re-lining	0 [0(0%)]	0 [0(0%)]	1 [1(0.3%)]	0 [0(0%)]	2 [2(1.7%)]	1 [1(0.2%)]	2 [2(0.9%)]	1 [1(1.4%)]	0 [0(0%)]
Revision - Endovascular - Proximal Cuff	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Revision - Endovascular Unspecified	1 [1(0.3%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	1 [1(0.2%)]	1 [1(0.4%)]	1 [1(1.4%)]	0 [0(0%)]
Revision - Open	0 [0(0%)]	0 [0(0%)]	2 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	4 [4(0.7%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]
Wound Complications/Debridements	0 [0(0%)]	0 [0(0%)]	4 [2(0.5%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]	0 [0(0%)]

Results are expressed as: number of reinterventions[number of patients (% of column total)].

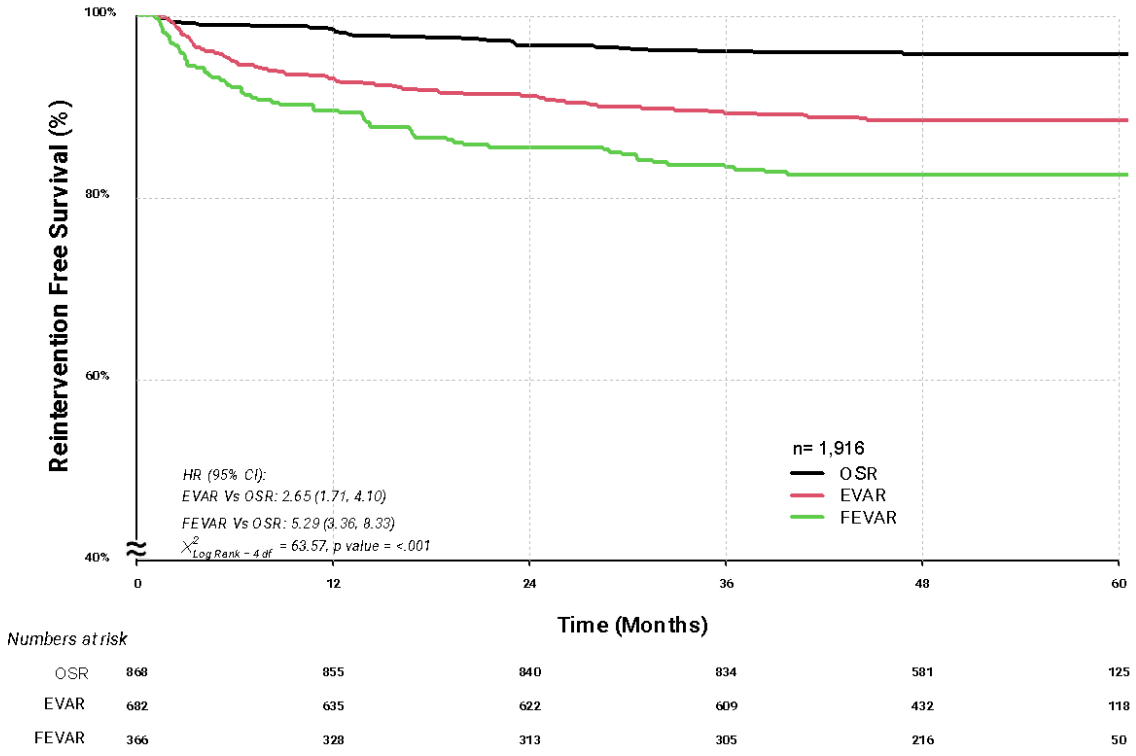


Figure 5-13 Kaplan-Meier graph of mid-term freedom from secondary intervention (excluding perioperatively secondary interventions).

5.5 Interpretation and Discussion of Cohort Study Results

This study of all elective procedures performed to treat juxtarenal, short neck or complex-neck AAA in England over a two-year period provided comparative effectiveness evidence that is highly generalisable. In the whole study population, endovascular strategies were safer than open repair in the perioperative period (lower rates of death, complications, and secondary interventions). This early advantage, however, was rapidly lost and reversed during follow-up, with all-cause mortality following endovascular strategies reaching nearly double that of OSR by 3.5 years of follow-up across the study population, along with higher rates of secondary interventions. This unexpected and stark finding warrants a re-appraisal of the current clinical application of endovascular strategies.

It was unsurprising that endovascular strategies were associated with less perioperative mortality and morbidity across all subgroups. For juxtarenal aneurysms (neck length 0-4mm), perioperative mortality was 7.4% for OSR compared against 2.3% for FEVAR in standard risk patients, a clinically significant difference. The high mortality for OSR may have been associated with a need for suprarenal clamping of the aorta, which was done in nearly half of the open repairs of

aneurysms with neck length 0-4mm, compared with only 14% of procedures for aneurysms with neck length ≥5mm. For those with at least a 5mm long aneurysm neck, in standard risk patients, the differences were smaller than anticipated and failed to reach the 4% absolute risk reduction deemed significant a priori (2.1% for OSR, 1.0% for FEVAR, and 0.7% for off-label EVAR).

The purpose of elective AAA treatment is prevention of premature death, so overall survival is the most important measure of treatment utility. Aneurysm operations are normally offered only to patents with reasonable life expectancy, which in turn is threatened by multiple and competing causes beyond the perioperative period, especially in view of the general age of AAA patients. Overall survival of the whole study population was similar to that described in RCTs comparing open and endovascular surgery for infrarenal AAA - approximately 80% at three years for the whole study population (39).

Across the whole study population all-cause mortality in FEVAR or off-label EVAR patients was 27.6% and 25.2% respectively - nearly double that of 14.2% in OSR patients by 3.5 years. This pattern of early survival advantage from endovascular treatments being lost in the follow-up was also seen in RCTs of standard infrarenal AAA treatment (29). It is striking, however, how early the "catch-up" in mortality occurred in this study, followed by a reversal of the advantage and marked divergence of survival curves.

In patients treated for juxtarenal aneurysms (0-4 mm neck), survival up to three years was similar between FEVAR and OSR. By contrast, initial survival benefits seen in patients with short neck (5-9 mm) or complex neck (≥10mm) aneurysms treated by endovascular means were lost within a matter of months, followed by markedly worse survival in the mid-term.

There are two potential explanations for these findings, both warranting an urgent change of clinical practice and review of commissioning practices. It is possible that that propensity score analysis did not fully compensate for biases in clinical practice such as offering OSR to healthier patients who also have better longevity, and endovascular strategies to less healthy patients who do not have similar life expectancy. Alternatively, endovascular aneurysm treatments lead to poor mid-term survival through potential sequalae such as malignancies (115), inflammatory effects of thrombus (116), and changes in aortic stiffness leading to cardiac failure (117, 118). Whether poor survival was caused by endovascular treatments or simply associated with it, the marked

differences seen do call for a more judicious use of endovascular strategies with better patient selection, even the aim is to achieve survival equivalence with OSR patients.

It should be noted that mid-term failure of aneurysm treatment (i.e. problems with the implant or rupture of the treated AAA) was responsible for only a small proportion of deaths in this study and was not a reason for the differences in the overall survival between treatments. Investigating this further will be the focus of future work.

The overall profile of perioperative complications and early reinterventions was much as previously reported in other studies (37, 59, 106), but the rate of spinal cord ischaemia deserves special mention. Spinal cord ischaemia is a recognised complication of aortic surgery, especially for thoracoabdominal aneurysms, but it is expected to be rare after AAA repair (119). However, paraplegia or paraparesis was noted overall in 2.9%, with the highest rates seen in FEVAR patients at 4.4%. The unexpectedly high incidence of this serious complication suggests that spinal cord protection strategies should perhaps be considered for juxtarenal/complex-neck AAA surgery.

Mid-term secondary intervention rates were significantly higher after endovascular treatments than after OSR. The profile of secondary interventions revealed no surprises; incisional hernia repair and adhesiolysis were seen exclusively in OSR patients, while those treated by endovascular strategies required a range of interventions to manage well-recognised complications such as endoleaks, target vessel threat and stent-graft migration. Ultimately, the inferior overall survival (compared to open surgery) seen within mid-term follow-up and a significantly greater reintervention rate suggest that FEVAR and off-label EVAR are poor choices for patients with short neck (5-9mm) or complex neck AAAs (≥10mm but unsuitable for on-label standard EVAR) compared to OSR.

At the outset we investigated feasibility of an RCT. Heterogeneity of aneurysm neck anatomy in the target population and of the technical complexities of different surgical techniques necessitates adaptive randomisation protocols, making it unlikely that recruitment to an RCT could have been completed within a meaningful duration in the UK. Furthermore, we found little support for an RCT from the physician community due to a bias towards the perioperative safety of endovascular techniques and a reluctance to offer 'Best Medical Therapy' alone versus

endovascular strategies in patients unfit for OSR. Widely recognised uncertainty regarding long-term survival benefit was not enough to change these attitudes towards an RCT.

The propensity analysis took account of an extensive range of patient and anatomical characteristics with a potential to influence treatment decisions or patient outcomes. This approach enabled exclusion of patients who were likely to be suitable for only one type of treatment (e.g. FEVAR, but not OSR) such that patients included in this analysis were only those who might plausibly have been recruited to an RCT comparing different treatments. We cannot claim that unknown confounders would have been balanced as they would be in an RCT, but the empirical evidence produced by this study carries a level of external validity unobtainable by an RCT given that every patient who underwent AAA repair in England was screened for inclusion.

The main surgical strategies considered for patients with juxtarenal aneurysms ought to have been FEVAR or OSR: off-label EVAR should not have been a primary treatment strategy for these patients (from a regulatory perspective) but it was employed frequently. Off-label treatment is an acceptable option in theory (120, 121), but the extent of its use in England was striking - in 7% of all juxtarenal (0-4mm neck); in 32% of all short neck (5-9mm) AAAs; and in 60% of complex-neck AAAs with neck length ≥10mm. Such frequent off-label use of standard EVAR devices is unlikely to be a practice exclusive to England, and these findings should perhaps prompt vascular multidisciplinary teams to re-evaluate their clinical decision making. This is particularly relevant to those that currently consider EVAR +/- adjuncts an acceptable treatment for cases with a neck length 0-4mm: in this subgroup, aneurysm-related mortality at 3.5 years was 11.5%.

Adjunctive endovascular technologies such as chimneys/parallel stent-grafts and endoluminal screws (e.g. Heli-FX EndoAnchor System; Medtronic Vascular, Santa Rosa, CA, USA) are a further consideration (67, 122). Their use was infrequent during the case capture period, such that it was not possible to analyse their effects separately: it was noted to be on-label in some patients and off-label in others. We combined all these patients within the off-label EVAR strategy and conducted sensitivity analyses to ascertain whether the use of adjuncts influenced the results; we found that conclusions did not change.

We stratified the study population according to operative risk (standard-risk and high-risk patients) and aneurysm neck length (0-4 mm, 5-9 mm and ≥10 mm with adverse features

precluding on-label standard EVAR), forming six subgroups. The inclusion of complex-neck aneurysms with neck lengths ≥10mm could potentially be criticised but excluding them would have missed a group of patients in whom FEVAR would be an on-label treatment strategy; nearly a quarter of all FEVAR procedures recorded were performed in such patients.

As expected, higher perioperative mortality rates were observed in high-risk patients compared to standard-risk patients, in every anatomical class, and with all the treatment strategies. Whilst relative safety of endovascular strategies may weigh more heavily in the balance in high-risk patients because of lesser concern regarding durability of treatment due to lower life expectancies, the poor overall mid-term survival observed invites further research on the relative benefits of operation versus no operation. The lack of a 'no surgical intervention' cohort is a limitation of this study.

Ultimately, this is the first instance of analysis of a whole nation's population treated for a complex AAA supported by a validated Corelab. The exceptionally high level of external validity of this study, the large number of patients, and the presence of a Corelab with precisely defined anatomical characteristics, distinguish this study from any previous work. Published reports generally lack clarity and definition of anatomical inclusion criteria, patient selection, and management of internal and external validity. Consequently, systematic reviews and meta-analyses of these reports have replicated these weaknesses (123). The large numbers of patients and the absence of any undefined exclusions makes this "real world" observational study a powerful addition to our knowledge of the outcomes of patients treated for juxtarenal and complex-neck AAA.

6 Discussion On The Treatment Of Juxtarenal And Other Complex-Neck Abdominal Aortic Aneurysms

This thesis explored the use of different strategies for the elective repair of juxtarenal and other "complex-neck" abdominal aortic aneurysms i.e., those with anatomy outside the instructions for use criteria guiding the appropriate use of standard endovascular stent grafts.

This topic represents a large existing gap in the evidence-base for treatment of AAAs mainly because previous major RCTs comparing open surgery with endovascular technology (33, 38) intentionally excluded these patients on the basis that they are considered unsuitable for "standard" endovascular aneurysm repair as per manufacturers' guidance. There is therefore a lack of clear clinical guidance internationally around the repair of such aneurysms and the associated treatment options. It relates to an important group of patients, comprising (as an estimate prior to this work) up to 50% of all AAAs repaired; this would equate to nearly 2000 operations per year in England and Wales (26)

European Society of Vascular Surgery 2019 Guidelines (5), in *Recommendation 95*, rather vaguely state that "in patients with juxtarenal abdominal aortic aneurysm, open repair or complex endovascular repair should be considered based on patient status, anatomy, local routines, team experience and patient preference." *Recommendation 96* states that endovascular repair with fenestrated stent grafts should be considered the preferred treatment option "when feasible". Both recommendations are attributed a Class "IIa" (that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure, but that weight of evidence/opinion is in favour of it) and Level "C" (any evidence is derived from the consensus of opinion of the experts and/or small studies, retrospective studies or registries). NICE (The National Institute for Health and Care Excellence) Guidelines (43) in the United Kingdom suggest offering complex endovascular techniques only if the patient is made aware of the uncertainty around both perioperative and long-term outcomes, and only in the setting of formal infrastructure for audit and research. Clearly, there is a need to add to the poor existing evidence base and provide clinicians with data to inform and justify treatment decisions.

This thesis initially described this very context by way of a systematic review and network meta-analysis comparing the published outcomes of different treatment options for the repair of juxtarenal and other complex-neck abdominal aortic aneurysms. Secondly, it described the methodology behind a national comparative study for various treatment options employed for

the repair of such AAAs; this included the description and validation of a Corelab protocol utilising CT angiograms for the assessment of the infrarenal aortic 'neck', a key anatomical component of complex AAAs that strongly influences decision-making around repair choices. Thirdly, it presented the results of said national study to generate data that may now inform clinicians when faced with the dilemma of repairing complex abdominal aortic aneurysms.

The 8 pre-specified hypotheses were all subsequently addressed through this piece of work and will be addressed in turn.

Hypothesis 1: The existing evidence underpinning the practice of repairing juxtarenal and complex-neck AAAs is of poor quality.

This thesis proved the first hypothesis by way of a systematic review of the literature. By searching for only studies comparing more than one treatment method employed to repair AAAs not anatomically suitable for standard EVAR, the review directly broached the topic of interest. As of the search date – April 2020, no studies employed randomisation to account for confounding. All were retrospective cohort studies, and only 7/24 studies applied some form of statistical methodology to account for confounding secondary to variations in physiological fitness; namely that open surgery is reserved for the fittest patients, whereas the least fit patients are more likely to be offered endovascular techniques. Anatomical confounding was also often poorly accounted for; for example, ChEVAR was only offered if FEVAR was not anatomically possible in certain studies. As a result of these study designs, 4/24 studies and 20/24 studies had a high or moderate risk of bias respectively on assessment using the Newcastle-Ottawa Score.

An additional consideration is the lack of comparative reporting of all possible treatment methods. Specifically, EndoAnchor screws as an adjunct to standard EVAR is a treatment method in its own right and is a licensed technique for short neck aneurysms, yet there was no comparative evidence available in the literature to include it in the systematic review. The literature was also found to be heavily biased to reporting on juxtarenal aneurysms as opposed to those with other adverse features. Specifically, 19/24 studies focussed on juxtarenal (short neck) aneurysms alone. Therefore, outcomes research for complex aneurysm cases that have adverse neck features other than short length are clearly neglected in the literature. The nature of studies that were excluded during the search phase of the systematic review also provide clues as to the poor quality of published work to date. Dozens of excluded studies did not provide any

comparative analysis at all and were case series for an individual technique. 8 studies were excluded because of significant anatomical heterogeneity; examples included the inappropriate pooling of juxtarenal aneurysms with visceral aortic or thoracoabdominal aortic aneurysms, and the pooling of all endovascular techniques into one arm to compare against open repair. These studies fail to acknowledge the individual nature to subtypes of aortic aneurysm and the techniques available to repair them, and so cannot provide meaningful data to guide modern practice.

Overall, at the outset of this piece of work, there was insufficient evidence to strongly recommend one treatment method over another for the repair of juxtarenal or complex-neck aneurysms given the poor quality of published studies.

Hypothesis 2: According to existing evidence, endovascular techniques are safer in the perioperative period compared to open surgery for the repair of juxtarenal and complex-neck AAAs.

This thesis attempted to prove the second hypothesis by way of a network meta-analysis. Although there was acknowledgment of poor-quality studies contributing data to the quantitative analysis, there was a strong signal for perioperative benefit in favour of off-label EVAR (10-fold by Relative Risk) and FEVAR (6-fold by Relative Risk) over Open Surgery (0.5% vs 4.8% and 3.1% vs 4.8% respectively), for the primary outcome measure of mortality. SUCRA scoring (a method that provides probability of the treatments occupying a certain ranking relative to one another), rated EVAR off-IFU and FEVAR as the 1st and 2nd safest treatment options respectively. Of note, there was no difference in mortality between Open Surgery and ChEVAR, suggesting that perhaps not all endovascular techniques are safer in the perioperative period. This finding is likely to be influenced by the fact that ChEVAR is reserved for the more "urgent" cases, offering an off the shelf alternative to FEVAR, and so may be used in the most technically challenging and unwell patients.

Safety also refers to the absence of perioperative complications. In the NMA, perioperative MI was less common after off-IFU EVAR (Relative Risk 0.42) and FEVAR (Relative Risk 0.37) as compared to Open Surgery. Reintervention and Renal Failure were seen equally across all treatment groups, but other significant complication types such as stroke were not analysed due to inconsistent reporting across studies.

Firm conclusions were ultimately unable to be drawn from the network meta-analysis due to bias in studies and inconsistencies in reporting structures, and this was reflected in an overall GRADE rating of "Low" for the majority of comparisons (GRADE being a tool to rate the confidence in estimates generated in a network meta-analysis). However, there was a suggestion from the data that supports Hypothesis 2, with respect to juxtarenal aneurysms specifically (the anatomical profile that dominated the populations in the included studies).

Hypothesis 3: According to existing evidence, endovascular techniques confer equivalent mid-term efficacy to open surgery for the repair of juxtarenal and complex-neck AAAs but are associated with greater re-interventions and cost.

The same network meta-analysis generated data to challenge this hypothesis. The purpose of electively repairing AAAs is to prevent premature death from aneurysm rupture. To that end, there are 2 principal metrics for assessing comparative "efficacy": these are 1) all-cause mortality (i.e., do patients live longer after one type of repair over another?) and 2) aneurysm-related mortality (i.e., do patients die because of complications from their repaired aneurysm more after one type of repair than another?).

In this NMA, 3481 patients' data contributed to the analysis for mid-term mortality. Compared to OSR, EVAR off-IFU was associated with a higher mid-term all-cause mortality (HR 1.78), although FEVAR and OSR had equivalent mid-term all-cause mortality. 2987 patients' data contributed to the analysis for mid-term aneurysm-related mortality. There were equivalent outcomes across all 4 treatment options for this outcome measure.

With regards to mid-term reintervention, it was shown that OSR patients underwent significantly fewer procedures as compared to the patients undergoing FEVAR, but not EVAR or ChEVAR. Only 3 studies proceeded to report on cost and/or cost-effectiveness. The largest of these studies (Michel et al), demonstrated that FEVAR was twice as costly, both perioperatively and in the mid-term. It was also demonstrated to be cost-ineffective (as compared to Open Surgery) with an ICER of €110,216,700 per death averted.

This hypothesis has only been proven in part; namely that EVAR off-IFU was not as effective as Open Repair in the mid-term, but that FEVAR and Open Repair were indeed of equivalent

efficacy. Additionally, there was a paucity of data on cost, but one large study suggested greater costs with FEVAR over Open Repair.

Hypothesis 4: According to existing evidence, fenestrated EVAR provides greater long-term efficacy compared to other endovascular techniques for the repair of juxtarenal and complex-neck AAAs.

Within the same network, as presented for the analysis of Hypothesis 3 above, compared to EVAR off-IFU, FEVAR was associated with a lower mid-term all-cause mortality. FEVAR was associated with an equivalent mid-term all-cause mortality as compared to ChEVAR. As mentioned earlier, there were no differences for aneurysm-related mortality across all treatment techniques. Thus, this hypothesis has not been supported by the results of the network meta-analysis, although the results should be acknowledged within the context of the significant selection bias demonstrated within included studies.

Hypothesis 5: When identifying complex aortic neck morphology on a pre-operative computerised tomographic (CT) scan, utilising a pre-designed measurement protocol can produce acceptable inter-rater consistency and accuracy.

A measurement protocol was devised through expert clinical consensus with the intention of providing a framework through which the infra-renal aortic neck could be assessed for complexity on a CT scan with acceptable reproducibility and accuracy. On a subset of 70 randomly selected CT angiogram scans, 3 individuals of varying experience followed the protocol to produce quantitative measures of aortic morphology namely length, angulation, neck diameter at various intervals on the neck and aneurysm diameter. These were the parameters upon which decision for inclusion into a subsequent study was based.

The results showed excellent inter-rater consistency as well as inter-class correlation for all measures across all 3 raters. Between the 2 most senior individuals undertaking the exercise, there was perfect categorisation of included cases into subgroups, as based on their individual raw data measures. This exercise thus demonstrated that the study measurement protocol could be applied to the remaining scans to produce results with good internal validity.

Hypothesis 6: Capturing all cases of complex neck morphology from a wider population of AAA repairs in England over a 2-year period is feasible using a validated measurement protocol in a "Corelab" setting. Additionally, that there are as many AAAs repaired in England with complex-neck morphology as there as standard cases.

Following the successful validation of the measurement protocol, a study to capture all cases of complex neck morphology from England was commenced. From a wide pool of 8994 AAA repairs conducted in England over a 2-year period (as listed in the Hospital Episodes Statistics – Admitted Patient Care dataset), the CT scans of 8706 (97%) cases were retrieved from treating centres to the study Corelab using existing secure data transfer infrastructure. Some 8612 of these scans (99%) were subsequently analysed in accordance with the study measurement protocol, leading to the inclusion of 2757 cases. These figures demonstrate exceptionally high case capture rates and rates of successful Corelab analysis completion.

The reasons for inclusion and exclusion of cases into the cohort study were provided; 2757 cases were included on the basis that their anatomical profile met *a priori* criteria, namely being unsuitable for repair with standard EVAR devices, as described in the manufacturers' IFU document. Some 3045 patients were excluded on the basis that they could have been repaired within the IFU constraints of commonly used devices. The ratio of complex cases to standard cases was therefore 1:1.1 suggesting that nearly half the population of all AAAs repaired in England are not suitable for repair with standard devices.

Hypothesis 7: When adjusting for A) anatomical variation between different subtypes of neck complexity, and B) confounding from variation in physiological risk between groups undergoing different methods of repair, endovascular techniques confer a perioperative safety benefit over open surgery for the repair of juxtarenal and complex-neck AAAs.

In this national cohort study, 2757 patients were included into a comparative effectiveness analysis. They all shared the commonality of having aneurysms unsuitable for repair with standard EVAR. This was recognised at the outset to be a heterogenous group of patients, in terms of anatomy and physiological fitness. In order to increase validity of any comparisons, they were separated into 6 subgroups: 3 groups of differing neck lengths, each of those split further into 2 groups (those in the highest quartile of physiological risk and those remaining deemed "standard risk").

Furthermore, propensity-based statistics were employed to adjust for selection bias between treatment methods. For the population as a whole, FEVAR (OR 0.25) and EVAR (OR 0.24) were associated with a significantly lower adjusted risk of perioperative death than Open surgery. Absolute differences were more stark in some subgroups than in others: for example, for the highest risk patients within the 0-4mm neck length subgroup, FEVAR and Open Surgery mortality rates were 1.7% and 10.9% respectively. Whereas for the standard risk patients within the ≥10mm neck length group, they were 2.0% and 2.2% respectively. Regarding complication rates in the overall population, FEVAR (OR 0.57) and EVAR (0.44) patients suffered from fewer events than Open surgery patients.

Therefore, one may conclude that endovascular techniques are indeed safer than open surgery for the repair of juxtarenal and complex-neck AAAs, although the degree to which they are safer varies across population subgroups.

Hypothesis 8: When adjusting for A) anatomical variation between different subtypes of neck complexity, and B) confounding from variation in physiological risk between groups undergoing different methods of repair, FEVAR is associated with equivalent mid-term efficacy to open surgery for the repair of juxtarenal and complex-neck AAAs.

FEVAR versus Open surgery was the comparison of interest at the outset of this thesis, given that they are the two principle methods of repair employed globally for cases where EVAR is not recommended by stent graft manufacturers. This study demonstrated inferior mid-term survival in FEVAR patients as compared to Open Surgery patients. A "crossing over" of survival benefit for endovascular techniques in the perioperative period to a disadvantage in the mid-term period occurred within 1 year. In terms of overall survival for the entire study population, at a median follow-up time point of 3.5 years, risk of death was 40% greater after FEVAR as compared to Open Surgery. This was not explained by death from aneurysm-related complications which were equally common between the two treatment methods. Of note, this pattern in the overall survival analysis was not seen for the anatomical subgroup with 0-4mm necks specifically; in this group, for "standard-risk" patients, loss of survival benefit occurred later at close to 3 years, with equivalent survival thereafter. Rate of secondary intervention at the same time point was 5 times higher after FEVAR as compared to Open Surgery.

Therefore, with respect to the hypothesis, FEVAR does not seem to be associated with equivalent mid-term efficacy to open surgery for the majority of non-standard AAAs: it is inferior to open surgery in terms of overall survival and secondary interventions, although survival may be considered equivalent in patients with true juxtarenal aneurysms (0-4mm long necks).

There are some clear interpretations for the results presented in this thesis, but others will require future work for clarification. Firstly, the poor quality of evidence in the existing literature around the repair of aneurysms not suitable for standard EVAR is undeniable. The inherent biases that accompany the comparison of patients undergoing open repair and various endovascular techniques are largely not accounted for in published studies and as such, pooling the results in a meta-analysis is of extremely limited value. Secondly, this thesis has clearly demonstrated how the anatomical assessment of aortic morphology can be effectively standardised with use of a measurement protocol.

The results of the national cohort study itself adds to the existing evidence significantly. However, interpretation of these results requires consideration of the subgroup analyses. It is clear that the overall population results do not paint a complete picture. Results for Group 1 (0-4mm length neck) vary to those seen in Groups 2 (5-9mm length neck) and 3 (≥10mm length neck) suggesting that aneurysm morphologies that are considered unsuitable for standard EVAR are a heterogenous group, by both anatomy and clinical outcomes. Just separating the groups by neck length alone highlighted different results; it follows that separating Group 3 further into groupings for different adverse neck features (conicality, angulation, thrombus load and calcium load) may highlight further differences and clinical implications.

Considering Group 1 alone with a focus on the comparison of interest between open surgery and FEVAR, there is a clear perioperative survival benefit seen with FEVAR over Open Surgery, as well as for the incidence of major complications. This is likely to reflect the dangers associated with clamping the aorta proximal to branches supplying vital visceral organs. During mid-term follow-up, there is no survival difference between the two cohorts in this subgroup; this suggests that FEVAR is likely to be an acceptable treatment option for these patients although cost-effectiveness was not studied in this thesis. Other studies have suggested there is higher cost after FEVAR that may negate this clinical effectiveness benefit. The findings of a significantly

higher mid-term reintervention rate after FEVAR in this new study may contribute to such future conclusions.

Considering Groups 2 and 3, the perioperatively mortality rate after open surgery (largely with infrarenal clamping) in the UK is surprisingly low - approximately 2%. This is half the mortality rate seen after open surgery in the EVAR-1 randomised controlled trial conducted between 1999 through to 2004 - 4.3%. Despite there also being a perioperative mortality benefit to FEVAR in this context, the narrowing of the differential benefit would perhaps suggest that open surgery is more of an acceptable option than previously thought. Add to this, the demonstrated clear survival benefit in the mid-term for Open Surgery over FEVAR, then it becomes increasingly difficult to justify FEVAR as a primary treatment option for this large group of patients.

The interpretation of these results is admittedly clouded by the absence of a clear explanation for the findings. Aneurysm-related mortality explained the long-term drop in survival after endovascular surgery in the RCTs recruiting standard aneurysms. In this study however, there was no difference in aneurysm-related mortality between the different techniques. One can therefore postulate that there is either a mechanism at work that is as yet undiscovered, or that the propensity-based statistics have failed to adjust for differences in baseline physiological fitness between the groups. This will no doubt be the subject of fierce debate between various stakeholders who read this work.

The co-existing evidence base for this study provides varied results. Other studies that investigated the same question were explored in the systematic review and network meta-analysis. But a brief additional focus on the largest included studies reveals 3 database analyses (89, 99, 101).

O'Donnell et al (101), using the VQI database (USA), compared open surgery with complex endovascular aneurysm repair for cases in which endovascular seal or open aortic clamping was performed above the level of the renal artery. Juxtarenal aneurysms were examined as a subgroup of this heterogenous population that would have also included suprarenal aneurysms. Propensity-based comparison (weighted logistic regression and Cox regression) between open surgery (n=1894) and FEVAR (n=678) for juxtarenal cases demonstrated similar mortality rates both perioperatively (3.6% vs 3.5% respectively) and at a median follow-up to 2 years.

Locham et al (99) interrogated the NSQIP (USA) database (n=1191 patients) to compare FEVAR, ChEVAR and Open Surgery for the repair of suprarenal, juxtarenal and pararenal aneurysms. Adjusted multivariate regression analysis demonstrated a 2-to-5-fold increase in perioperative mortality risk after open surgery versus endovascular repair, with no difference between FEVAR and ChEVAR cohorts.

Michel et al (89) reported on the WINDOW Trial, a prospective registry analysis from France that compared registry entrants who had undergone complex endovascular aneurysm repair against a control cohort of open repairs from a separate national dataset. A wider and heterogenous group of included patients (ranging from short-neck AAAs through to subdiaphragmatic TAAAs) allowed subgroup analysis of juxtarenal aneurysms (neck length <10mm). Perioperative mortality in this subgroup was equivalent between open repair and complex EVAR (5.8% vs 4.3% respectively). This equivalence was also seen at 2 years of follow-up (11.4% vs 11.2%) (95).

Additionally of note, the "JAMES" study (124) was published in 2023, following the completion of the systematic search and so was not incorporated into the final network meta-analysis. Capturing cases in the decade between 2010 and 2020, it retrospectively compared open surgery with complex endovascular aneurysm repair for the repair of juxtarenal and pararenal aneurysms. These were defined by a short neck <10mm in length and the necessity for aortic clamping above at least 1 renal artery. It pooled cases from 5 high-volume centres across Europe (Helsinki, Bologna, Amsterdam, Milan and Belgrade) and although it started with a case capture of 834 consecutive patients (n=234 endovascular, n=600 open), propensity score was used in a case matching process, resulting in comparison cohorts of n=145 each. The two groups experienced similar perioperative and overall (up to 7 years follow-up) survival rates.

Divergence of these findings from the results of this thesis' cohort study could be explained by differing anatomical inclusion criteria (with no use of a Corelab for accurate inclusion in any of the described studies), follow-up time point (variable from 2 years up to 7 years across the 4 studies) and the fact that contributors of FEVAR cases into these registries are a select group of high-volume centres of excellence. It should also be noted that none of these large studies included complex-neck AAAs and their populations are likely to have reflected only part of Group 1 in our study (those patients whose anatomy necessitated suprarenal, or more proximal, clamping in open surgery).

There is substantial importance to the work presented in this thesis. The Corelab analysis defined precisely how big an issue the thesis aimed to address: nearly 50% of all AAAs repaired in England are unsuitable for standard infrarenal EVAR on direct analysis of infrarenal aortic neck on the pre-operative CT angiogram. This study therefore provides comparative outcome evidence to guide the treatment of over 1300 patients per year in the UK, where there has been a lack of data with such strong external validity up until now.

Strikingly, off-label EVAR is being used to poor effect in a substantial number of individuals across the country. The manufacturers of these stent grafts advise against using the devices in these anatomical profiles and the data in this study certainly suggests that there is minimal benefit to doing so; there is inferior survival when compared to cohorts undergoing open surgery at very short follow-up time points after intervention. Either there is a mechanistic reason for this poor survival directly attributable to the technology, or they are being placed in patients with very poor life expectancy at the outset. In either case, there needs to be an urgent re-evaluation of practice across the country.

FEVAR has been of interest to researchers and commissioners ever since a fairly recent upturn in its utilisation as a customised treatment for complex AAAs. It was primarily designed as a solution to the short or absent aortic neck, but 25% of all FEVARs in the UK are used in aortic necks of sufficient length for standard EVAR (but in the presence of other adverse neck features). The appropriateness of its use will be in question after this work. It could be argued that it is being inappropriately used in patients with complex-neck aneurysms: there is a survival advantage over open surgery perioperatively but a survival disadvantage in the mid-term (a "crossover" as short as a few months in some subgroups). The fact that the FEVAR cohorts experienced the greatest number of reinterventions also raises concerns for the long-term cost-effectiveness of a technology that is known to be considerably more expensive than its alternatives, although this wasn't the subject of study here. The use of FEVAR for true juxtarenal aneurysms is somewhat more justified in the context of this study with statistical and clinically significant perioperative advantages over open surgery and equivalent survival in the mid-term.

These implications must be considered in the context of strengths and the acknowledged limitations of this thesis. The network meta-analysis that processed pre-existing comparative data on treatments for complex abdominal aortic aneurysms broke new ground by including more

than 2 treatments in a contemporaneous analysis. It demonstrated how any future studies can focus beyond just open repair and fenestrated EVAR. It provided focussed analysis on patients with juxtarenal aneurysms and limited the heterogeneity seen in other studies which pool these cases with thoracoabdominal or suprarenal aortic aneurysms. However, the results of the NMA should be interpreted with caution given that there were no randomised trials in the network and only few studies accounted for selection biases with statistical adjustment. This laid the platform for a more appropriately designed study in the second half of this thesis.

A study design was proposed that accounted for these limitations and the first feature that was considered essential was to address heterogenous anatomical populations within a cohort of cases not suitable for EVAR. This required accurate assessment of the infrarenal aortic neck and so a protocol was devised to enable an accurate and reproducible method of identifying specific morphological characteristics. This was achieved and, coupled with access to the imaging of an entire nation's AAA caseload, provides a significant level of external validity to the findings and will allow the results to be interpreted by all practitioners in the United Kingdom and beyond.

The methods by which selection bias was accounted for may bring scrutiny. We opted to address anatomical bias by creating 3 separate subgroups for analysis. It was felt that the primary anatomical determinant of good outcome is the neck length. Therefore, this was selected to be the discriminatory feature. Physiological confounding is however the most important issue that plagues existing studies: that on the whole, open repair is only offered to the most fit patients. This was adjusted for in a couple of ways. Firstly, the study population was further split from 3 subgroups into 6 by separating each subpopulation into those that make up the highest quartile of risk and the those that comprise the lowest quartile of risk. This was performed using a validated research tool called the BAR score. Furthermore, propensity-based statistics were employed, firstly to exclude those patients that had minimal probability of being offered more than 1 type of repair and secondly, stratification and covariate adjustment (including propensity score as a variable) of the regression analyses was performed. It could be argued that this approach does not provide complete clarity that the compared groups have been equalised in terms of "confounders". An alternative method of case matching by propensity score would allow a more visibly balanced pair of populations being compared. However, this approach would severely reduce the number of cases included in the analysis and also add a significant layer of statistical complexity to a population in which 3 different interventions are being

compared. This was a feature of the recent JAMES study (124) that attracted some criticism (125).

However, there may be some criticism of such an approach. There have been calls by some for randomised controlled trials in this area (97, 106). It may be felt by some that there are strong selection biases at play with recruitment into observational studies that cannot be overcome by propensity-based statistics. Historically, there has been great reluctance to recruit to RCTs in this area, on the basis of a lack of equipoise. The issue of direction in this lack of equipoise is complicated. With the results of this study, it is clear that a RCT would need to focus on a particular anatomical subgroup to provide clinically relevant results. For true juxtarenal aneurysms, there is an undeniable peri-operative benefit to repairing aneurysms with FEVAR with equivalent mid-term outcomes. The long-term durability and survival of these stent grafts and patients respectively cannot be commented on as yet; and so, for now there may be reluctance to randomise a patient to having risky open surgery involving a suprarenal aortic clamp. For Groups 2 and 3, there may logically be a reluctance to recruit in the opposite direction based on this data given the poor overall survival in the endovascular cohorts. Another obstacle to RCT is that of adequate power in such a trial. This cohort study met *a priori* recruitment targets based on power calculation by capturing every single case in the country over 2 years. If an RCT was being considered for a single anatomical subgroup, then the numbers involved would necessitate recruiting a significant, and perhaps unattainable, number of patients over several years, by which time newer techniques may have superseded existing ones in this rapidly evolving arena.

Clearly, despite some novel findings presented in this thesis, many of the answers have simply given rise to further questions. These should be the focus of future research. Although FEVAR has been shown to be clinically more safe than Open Surgery for juxtarenal aneurysms, there will be concern for a significantly higher reintervention rate with the endovascular technology, which in turn may well render it cost-ineffective. This issue stirred much debate in the setting of standard infrarenal aneurysms (126) and it is plausible that the same will be encountered for the repair of complex aneurysms. Data collection in the longer term will need to be addressed as well as cost exercises conducted to this aim.

The cause of death for the population as a whole needs investigating. Why there is such poor survival in the endovascular cohorts is still unclear as it does not seem to be explained by

aneurysm-related mortality. Further work elucidating any mechanisms behind this will be required. In addition to cause of death, factors influencing poor survival will also need to be identified. There is scope for further analysis into specific neck morphological characteristics; despite a vast data collection including several anatomical features to the aortic neck, this study rather crudely created subgroups based on neck length alone. Investigating the exact aneurysm morphologies found in Group 3 in particular may reveal further insights into which adverse neck features have greater influence on outcome than others. By capturing every case in the country, the effect of a volume-outcome relationship may also be investigated. Volume-outcome relationships have been demonstrated in the settings of both standard infrarenal AAA and complex AAA repair (127-129). But the in-depth dataset generated from this study will permit a detailed assessment on whether the volume of certain types of repair affects the outcomes of others. For example, one could query whether a hospital that does not offer FEVAR has worse overall outcomes than one that does. This could help inform discussions around centralisation of complex aneurysm services (125).

Finally, decisions regarding which technology to adopt to repair complex AAAs of different types will need to be made in the context of conservative management; this is particularly appropriate after this study demonstrated that overall survival is poor for many patients undergoing repair. The EVAR-2 RCT (130), comparing EVAR to conservative management in the most unfit patients undergoing repair of standard infrarenal AAAs provided important contextualisation for the EVAR-1 RCT (38) comparing EVAR to Open Surgery for the repair of standard infrarenal AAAs. Similar conclusions may or may not be drawn in the context of complex AAAs.

Up until these additional research questions are investigated however, this thesis has provided contemporaneous and novel data regarding the existing literature, the ability to measure the anatomical profile of complex AAAs accurately and reproducibly, and comparative outcomes of various complex AAA repair techniques across an entire nation's practice over 2 years.

7 Conclusions

This thesis has contributed novel information to the field of repair techniques for juxtarenal and complex-neck AAAs that are objectively unsuitable for standard infrarenal EVAR.

The existing literature has been shown to focus on 4 techniques: Open Surgery, Fenestrated EVAR, off-label standard EVAR and Chimney EVAR. At the time of the review, more novel techniques such as EVAR with endoluminal screws had yet to become established in a published evidence base. The first network meta-analysis ever conducted on this topic suggested a perioperative survival benefit in favour of FEVAR and off-label EVAR as compared to Open Surgery followed by a "catch up" in the mid-term. However, confidence in the findings was low when appraising the network, due to a failure to account for confounding in many included studies.

The remainder of the thesis focussed on conducting a national cohort study that aimed to compensate for many of the methodological deficiencies highlighted in the systematic review and network meta-analysis. An analysis of FEVAR and off-label EVAR (+/- adjuncts) vs Open Surgery was performed after analysing the CTA scans of every AAA repaired in England over 2 years. This "Corelab" was devised with expert input into a clinical consensus exercise and the measurement processes were subsequently validated and shown to be both consistent.

Accuracy of CTA measurement enabled reliable grouping of patients into subgroups based on infrarenal neck length. This, coupled with additional subgrouping based on relative physiological fitness and propensity-based adjustment of comparative outcomes, led to study results with significant external validity. For juxtarenal aneurysms (0-4mm neck), FEVAR was significantly safer than OSR in the perioperative period with equivalent mid-term survival to 3.5 years. Off-label standard EVAR, even with adjuncts, performed poorly in this anatomical class and its use cannot be recommended. For patients with short neck (5-9mm) and complex-neck AAAs (neck length ≥10mm), long-term survival was significantly worse after FEVAR and EVAR than after OSR. This warrants re-appraisal of the current clinical application of endovascular strategies in such patients. For the whole study population endovascular treatment was associated with a nearly two-fold risk of death at 3.5 years, compared with OSR. The poor survival of patients treated by endovascular strategies warrants urgent further research, given that it cannot be explained by aneurysm-related mortality.

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9 Appendices

Appendix 1 - Additional data from Network Meta Analysis

Search Results (April 2020): PubMed

1. (complex OR hostile) AND (comparison OR compared) AND ("aortic aneurysm"[MeSH Terms])
   610

2. (complex OR hostile) AND (outcomes OR comparison) AND neck AND ("aortic aneurysm"[MeSH Terms])
   158

3. (short neck OR juxtarenal OR pararenal OR suprarenal) AND (comparison OR compared) AND outcomes AND ("aortic aneurysm"[MeSH Terms])
   334

4. (calcified OR thrombus OR angulated OR angulation OR conical) AND neck AND outcomes AND (comparison OR compared) AND ("aortic aneurysm"[MeSH Terms])
   125

5. (fenestrated EVAR OR FEVAR OR EVAR OR off-label EVAR OR off-IFU EVAR OR chimney OR endoanchors OR endostaples OR open surgery) AND (comparison OR compared) AND (complex OR hostile) AND outcomes AND ("aortic aneurysm"[MeSH Terms])
   223

6. (complex OR hostile) AND neck AND (comparison OR compared) AND outcomes AND endovascular AND open AND ("aortic aneurysm"[MeSH Terms])
   18

7. (complex OR hostile) AND neck AND (comparison OR compared) AND (cost OR cost-effectiveness OR mortality OR complications) AND ("aortic aneurysm"[MeSH Terms])
   49

Search Results (April 2020): Embase

1. (((complex OR hostile) AND (comparison OR compared)) AND abdominal aortic aneurysm)
   225

2. ((((complex OR hostile) AND (outcomes OR comparison)) AND neck) AND abdominal aortic aneurysm)
   60

3. ((((short neck OR juxtarenal OR pararenal OR suprarenal) AND (comparison OR compared)) AND outcomes) AND abdominal aortic aneurysm)
   69

4. (((((calcified OR thombus OR angulated OR angulation OR conical) AND neck) AND outcomes) AND (comparison OR compared)) AND abdominal aortic aneurysm)
   30

5. (((((fenestrated EVAR OR FEVAR OR EVAR OR off-label EVAR OR off-IFU EVAR OR chimney OR endoanchors OR endostaples OR open surgery) AND (comparison OR compared)) AND (complex OR hostile)) AND outcomes) AND abdominal aortic aneurysm)
   39

6. (((((((complex OR hostile) AND neck) AND (comparison OR compared)) AND outcomes) AND endovascular) AND open) AND abdominal aortic aneurysm)
   8

7. (((((complex OR hostile) AND neck) AND (comparison OR compared)) AND (cost OR cost-effectiveness OR mortality OR complications)) AND abdominal aortic aneurysm)
   28

Search Results (April 2020): Cochrane CENTRAL

1. hostile neck AND compared AND outcomes AND abdominal aortic aneurysm
   1

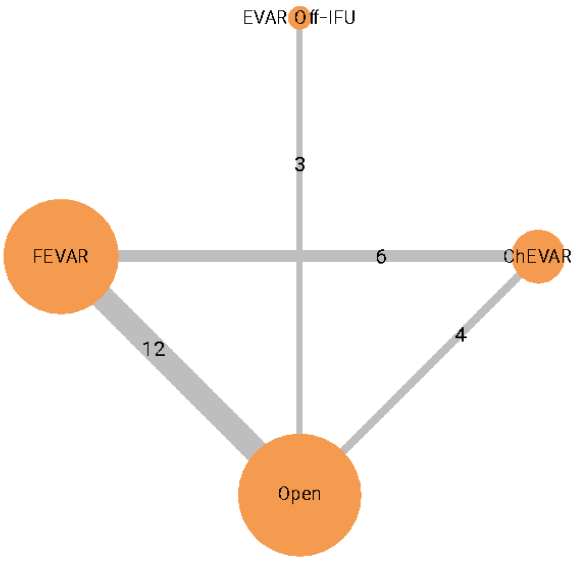
2. juxtarenal AND compared AND outcomes AND abdominal aortic aneurysm
   1

3. endovascular AND open surgery AND complex AND abdominal aortic aneurysm AND compared
   4

Sensitivity Analysis for the primary outcome measure in NMA

3/22 studies were deemed to carry a "High risk" of bias according to analysis using the Newcastle-Ottawa tool (Table 2-3). These 3 studies were removed in a sensitivity analysis for assessment of perioperative mortality (the primary outcome measure). The methodology for performing this sensitivity network meta-analysis was identical to that described in the main text. The results are as follows:

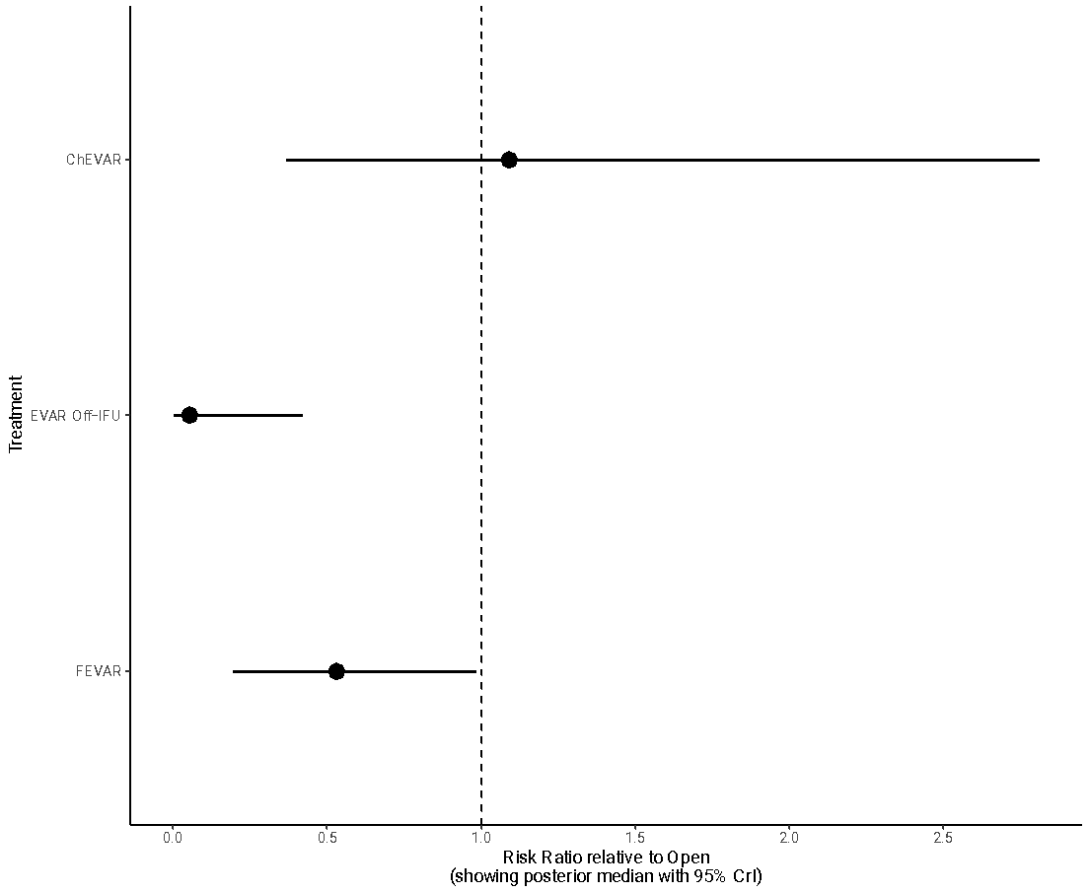
After exclusion of 3 studies at high risk of bias, some 18 studies reported perioperative mortality, defined either as death within 30 days of the aneurysm repair or death during the same admission as the primary procedure. A total of 5951 patients and 4 different modes of complex AAA repair were included in this network meta-analysis. This reflected 16 two-arm studies and 3 three-arm studies, with 209/5951 (3.5%) events (deaths) reported in this network:

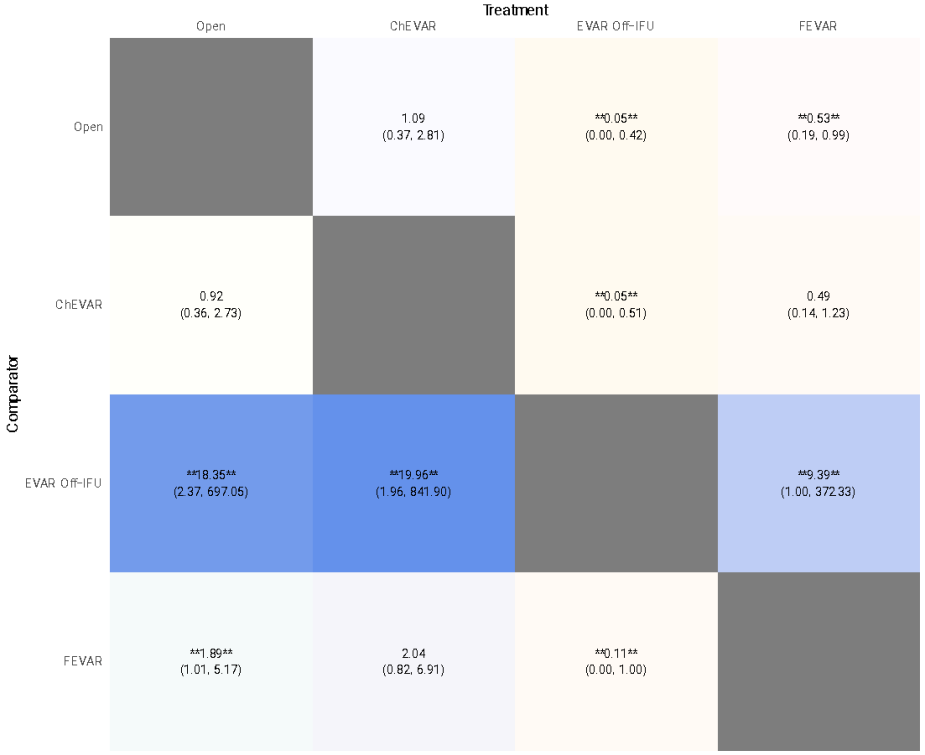


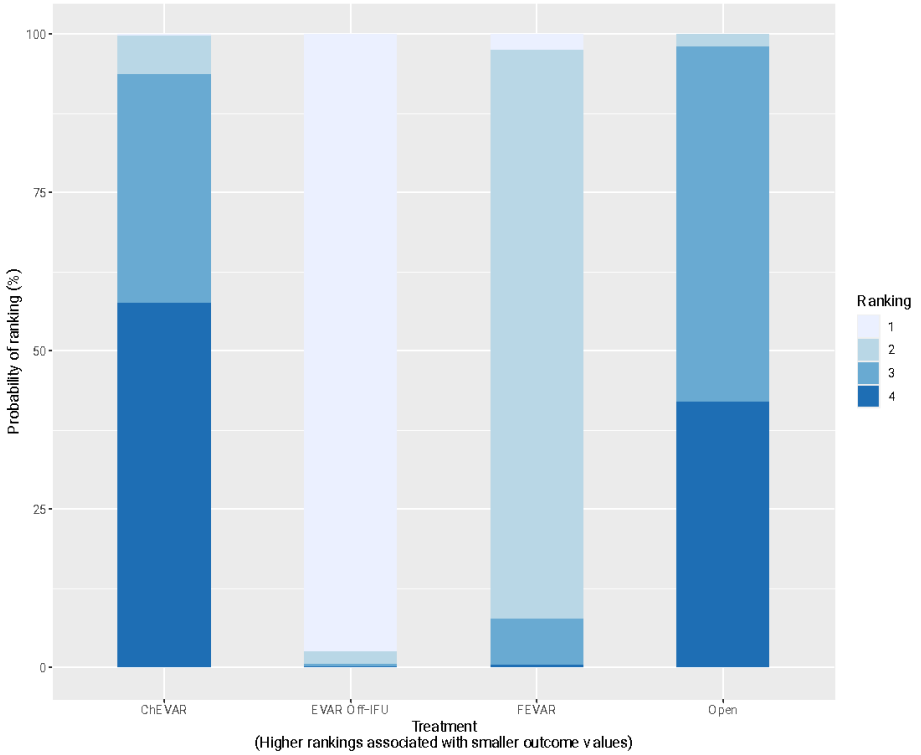
The size of each node corresponds to the number of patients studied for that type of treatment across all study arms. The width of each line corresponds to the number of studies comparing the two interventions directly, and this number is superimposed on the line. FEVAR = fenestrated endovascular aneurysm repair, EVAR Off-IFU = endovascular aneurysm repair off instructions-for-use, ChEVAR = chimney endovascular aneurysm repair.

Unweighted pooled perioperative mortality rates were 3.9% (149 deaths/3873 patients) for Open Surgery, 2.9% (39 deaths/1368 patients) for FEVAR, 4.8% (20 deaths/418 patients) for ChEVAR and 0.3% (1 deaths/292 patients) for EVAR Off-IFU. Results of the NMA show that both EVAR off-IFU (Relative Risk 0.05, 95%CI 0-0.42) and FEVAR (Relative Risk 0.53, 95%CI 0.19-0.99) were associated with lower perioperative mortality compared to OSR. Compared to FEVAR, EVAR off-IFU was associated with lower perioperative mortality (Relative Risk 0.11, 95%CI 0-1. There was no statistically significant difference in perioperative mortality between Open Surgery and ChEVAR (Relative Risk 0.92 95%CI 0.36-2.73).

Comparisons to Open Surgery are shown in a Forest plot and comparisons between all combinations of treatment methods are shown in a NMA heat plot matrix below. Rankogram showed that EVAR off-IFU had the highest probability of being the safest intervention (97% at rank#1). SUCRA scoring rated EVAR off-IFU as the intervention with the highest ranking for perioperative safety, followed by FEVAR as the next safest, followed by OSR. ChEVAR ranked bottom for perioperative safety.


ChEVAR
EVAR Off-IFU
FEVAR
Treatment
0.0
0.5
1.0
1.5
2.0
2.5
Risk Ratio relative to Open
(showing posterior median with 95% CrI)

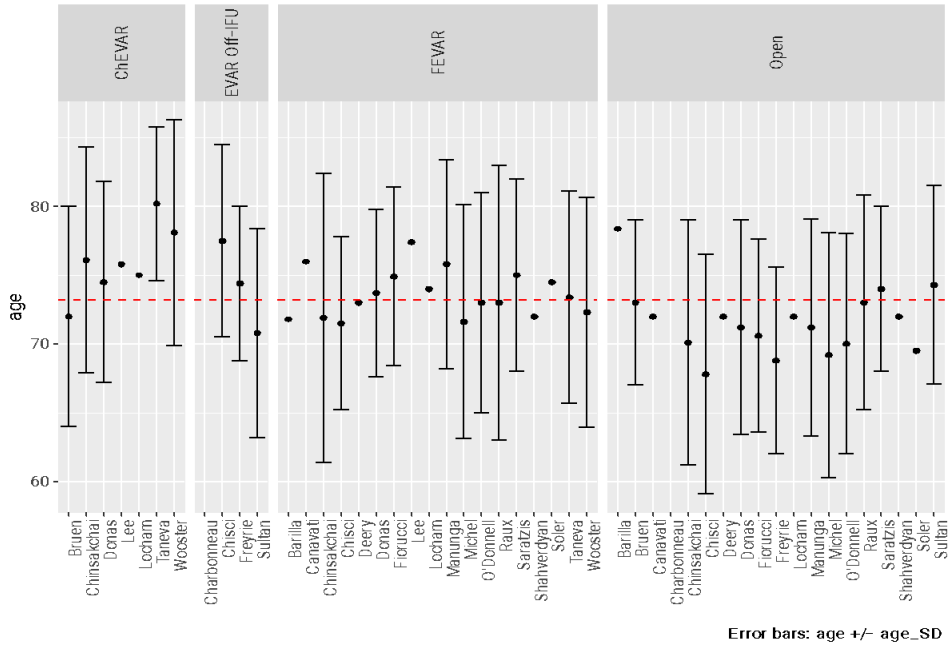

Treatment
Open
ChEVAR
EVAR Off-IFU
FEVAR
Comparator
1.09
(0.37, 2.81)
0.05
(0.00, 0.42)
0.53
(0.19, 0.99)
0.92
(0.36, 2.73)
0.05
(0.00, 0.51)
0.49
(0.14, 1.23)
18.35
(2.37, 697.05)
19.96
(1.96, 841.90)
9.39
(1.00, 372.33)
1.89
(1.01, 5.17)
2.04
(0.82, 6.91)
0.11
(0.00, 1.00)



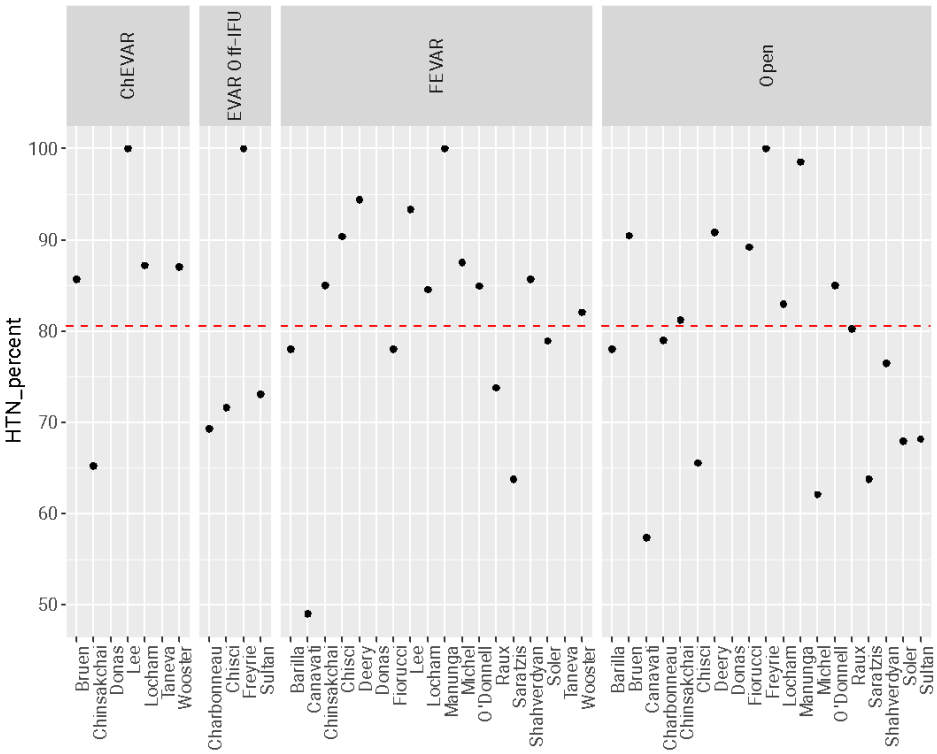
Overall, in a sensitivity analysis removing studies at "High risk" of bias, there was no change to the findings of the NMA for the primary outcome measure.

Patient characteristic plots as part of GRADE assessment for the intransitivity domain in the NMA

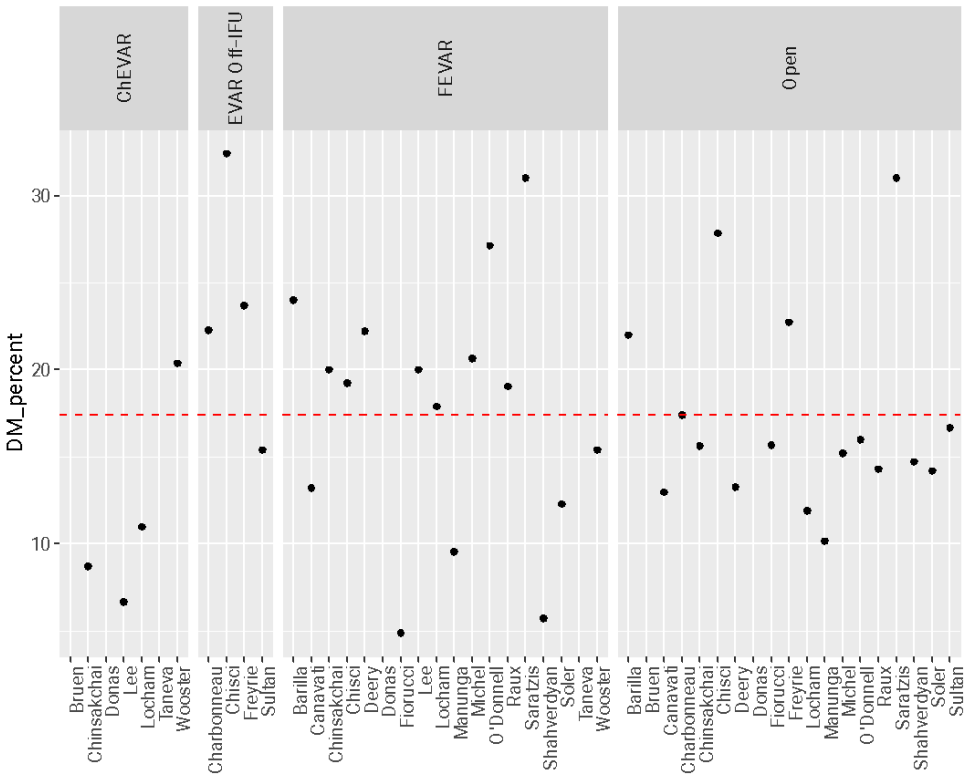
Age



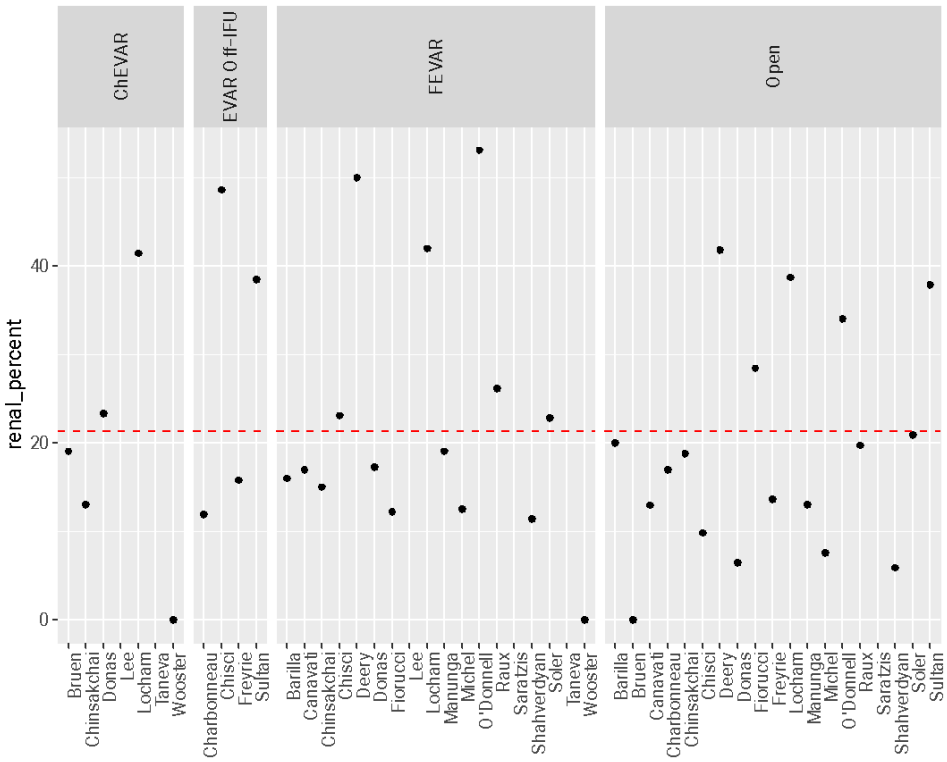
Incidence of Hypertension



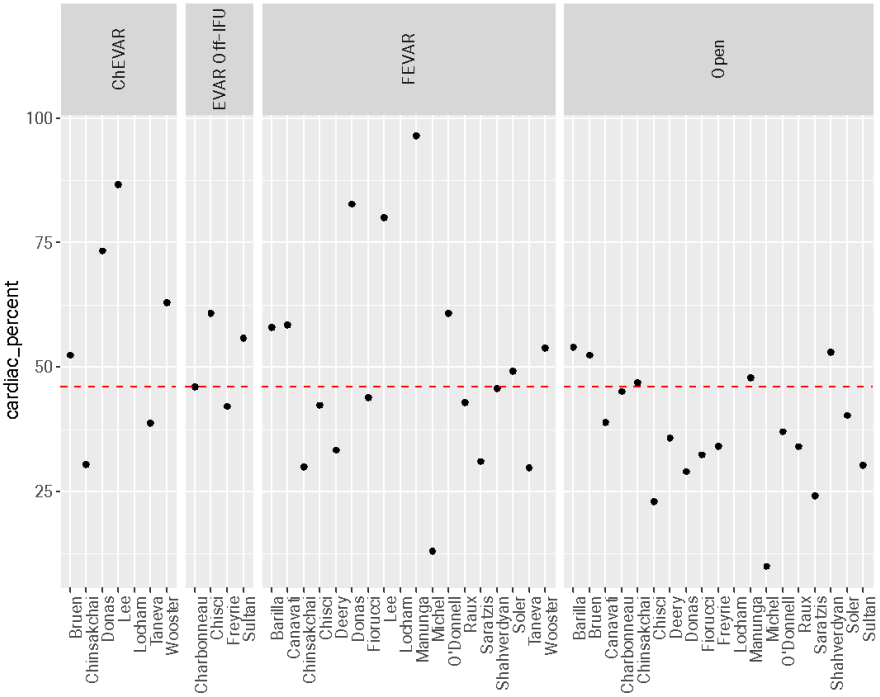
Incidence of Diabetes



Incidence of Chronic kidney disease



Incidence of Ischaemic heart disease



Final GRADE assessment for perioperative mortality comparison between the 4 treatment options in the NMA

Each comparison in the network is graded in turn on a scale of "Very low" -> "Low" -> "Moderate" -> "High" certainty. As per the GRADE guidelines, the starting rating for all comparisons is "Low" due to the non-randomised nature of the included studies:

1. Open vs FEVAR

A) Rating the direct estimate *(RR 1.15 95%CI 0.84-1.58):* Low

Downgrading factors:
Risk of bias: some concern
Heterogeneity: no concern
Indirectness: low concern
Publication bias: no concern

Upgrading factors:
Obvious confounding would relate to physiological risk: open surgery is generally performed in fitter patients. Therefore, to adjust for this would only increase the effect noted (that open surgery has worse perioperative mortality than FEVAR). This therefore upgrades the rating one position for this outcome measure.

B) Rating the indirect estimate: Very Low

The most dominant first order loop is Open -> ChEVAR -> FEVAR:
Open vs ChEVAR rating (direct): Very Low
FEVAR vs ChEVAR rating (direct): Very Low

Transitivity: low concern

C) Rating the network estimate *(RR 1.62 95%CI 1.06-3.10)*: Low

Highest between direct/indirect ratings: Low
Incoherence: No concerns
Imprecision: No concerns

2. Open vs EVAR Off-IFU

A) Rating the direct estimate *(RR 3.84 95%CI 1.08-13.70)*: Moderate

Downgrading factors:
Risk of bias – some concern
Heterogeneity – no concern
Indirectness – low concern
Publication bias – no concern

Upgrading factors:
Obvious confounding would relate to physiological risk: open surgery is generally performed in fitter patients. Therefore, to adjust for this would only increase the effect noted (that open surgery has worse perioperative mortality than EVAR off -IFU). There

is also a very large effect size noted. This therefore upgrades the rating two positions for this outcome measure.

B) Rating the indirect estimate: Very Low

The most dominant first order loop is Open -> FEVAR -> EVAR Off-IFU:
Open vs FEVAR rating (direct): Low
FEVAR vs EVAR Off-IFU rating: Very Low

Transitivity: low concern

C) Rating the network estimate: *(RR 9.97 95%CI 2.47-87.86)*: Moderate

Highest between direct/indirect ratings: Moderate
Incoherence: No concerns
Imprecision: No concerns

3. Open vs ChEVAR

A) Rating the direct estimate *(RR 0.89 95%CI 0.51-1.57)*: Very Low

Downgrading factors:
Risk of bias – some concern
Heterogeneity – no concern
Indirectness – high concern
Publication bias – no concern

Upgrading factors: Nil

B) Rating the indirect estimate: Very Low

The most dominant first order loop is Open -> FEVAR -> ChEVAR:
Open vs FEVAR rating (direct): Low
FEVAR vs ChEVAR rating (direct): Very Low

Transitivity: low concern

C) Rating the network estimate *(RR 0.87 95%CI 0.41-2.02)*: Very Low

Highest between direct/indirect ratings: Very Low
Incoherence: No concerns
Imprecision: Some concerns

4. FEVAR vs ChEVAR

A) Rating the direct estimate *(RR 0.37 95%CI 0.15-0.90)*: Very Low

Downgrading factors:
Risk of bias – some concern
Heterogeneity – no concern
Indirectness – high concern

Publication bias – no concern

Upgrading factors: Nil

B) Rating the indirect estimate: Very Low

The most dominant first order loop is FEVAR -> Open -> ChEVAR:
Open vs FEVAR rating (direct): Low
Open vs ChEVAR rating (direct): Very Low

Transitivity: low concern

C) Rating the network estimate: *(RR 0.54 95%CI 0.22-1.15)*: Very Low

Highest between direct/indirect ratings: Very Low
Incoherence: No concerns
Imprecision: Some concerns

5. FEVAR vs EVAR Off-IFU

A) Rating the direct estimate *(RR 4.27 95%CI 0.46-39.91)*: Low

Downgrading factors:
Risk of bias – some concern
Heterogeneity – no concern
Indirectness – no concern
Publication bias – no concern

Upgrading factors: Nil

B) Rating the indirect estimate: Low

The most dominant first order loop is FEVAR -> Open -> EVAR Off-IFU:
Open vs FEVAR rating (direct): Low
Open vs EVAR Off-IFU rating (direct): Moderate

Transitivity: low concern

C) Rating the network estimate *(RR 6.06 95%CI 1.35-55.05)*: Low

Highest between direct/indirect ratings: Low
Incoherence: No concerns
Imprecision: No concerns

6. EVAR OFF-IFU vs ChEVAR

A) Unable to rate a direct estimate as there are no direct comparisons.

B) Rating the indirect estimate: Very Low

The most dominant first order loop is EVAR Off-IFU -> Open -> ChEVAR:
Open vs ChEVAR rating (direct): Very Low
Open vs EVAR Off-IFU rating (direct): Moderate

Transitivity: low concern

C) Rating the network estimate *(RR 0.09 95%CI 0.01-0.44)*: Very Low

Highest between direct/indirect ratings: Very Low
Incoherence: No concerns
Imprecision: No concerns

Appendix 2 - Additional Information regarding data sources and codes used in cohort study

The table below shows the data fields used in the cohort study and their sources. Fields were populated from multiple sources, including:

1) Hospital Episodes Statistics (HES) database – Admitted patient care (APC) dataset.
2) National Vascular Registry (NVR) database
3) Anatomical neck morphology dataset (Corelab record)

Pre-operative Data

Data Item	NVR Field	HES APC Field	Core Lab Field
Identification			
Patient Identifier	NVR ID	HES Pseudo ID	UKC number
Centre ID	-	SITETRET or PROCODET	-
Basic Demographics			
Age at procedure	Patient:AgeAtSurgery	ADMIAGE	-
Sex	Patient:GenderCode	-	-
Height	Anaesthesia:PatientHeight	-	-
Weight	Anaesthesia:PatientWeight	-	-
Baseline Health Conditions			
Diabetes Mellitus	RiskScores:Comorbidities 1	DIAG_NN: E10-E14	-
Hypertension	RiskScores:Comorbidities 2	DIAG_NN: I10-I13, I15	-
Chronic Lung Disease	RiskScores:Comorbidities 3	DIAG_NN: J41-J45, J47	-
Ischaemic Heart Disease	RiskScores:Comorbidities 4	DIAG_NN: I20, I25	-
Chronic Heart Failure	RiskScores:Comorbidities 5	DIAG_NN: I110, I50	-
Chronic Renal Disease	RiskScores:Comorbidities 6	DIAG_NN: N18, N19	-
Stroke	RiskScores:Comorbidities 7	DIAG_NN: I63, I64	-
Smoking	RiskScores:SmokingStatus	Z720	-
ASA	RiskScores:ASA	-	-
Pre-operative Meds			
Statin	RiskScores:Medication 2	-	-
Antiplatelet	RiskScores:Medication 1	-	-
Beta Blocker	RiskScores:Medication 3	-	-
ACE inhibitor/ARB	RiskScores:Medication 4	-	-

Pre-operative Tests and Anatomy			
Hb	RiskScores:Haemoglobin	-	-
WCC	RiskScores:WhiteCellCount	-	-
Sodium	RiskScores:Sodium	-	-
Potassium	RiskScores:Potassium	-	-
Creatinine	RiskScores:Creatinine	-	-
Albumin	RiskScores:Albumin	-	-
Abnormal ECG	RiskScores:AbnormalECG	-	-
Atrial Fibrillation	-	I48	-
CPET	Anaesthesia: PatientFitnessMeasureCode 1	-	-
Incremental Shuttle Walk	Anaesthesia: PatientFitnessMeasureCode 2	-	-
6-minute Walk	Anaesthesia: PatientFitnessMeasureCode 3	-	-
Dynamic Cardiac Function Test	Anaesthesia: PatientFitnessMeasureCode 4	-	-
Echo +/- Spirometry	Anaesthesia: PatientFitnessMeasureCode 5	-	-
CT scan date	-	HES DID dataset	-
Previous Aortic Surgery	Indications:AaaPrevAorticProcCode 1=Open, 2=EVAR	-	-
Aneurysm Diameter	Indications:AaaSize	-	diam_aneurysm
Neck Length	AAA:NeckLength	-	total_neck_length
Alpha Angle	-	-	neck_angle_alpha
Beta Angle	AAA:NeckAngleCode	-	neck_angle_beta
Neck Diameters	AAA:NeckDiameter	-	diam_n
Excess Thrombus	-	-	thrombus
Excess Calcium	-	-	calcium

Operative Data

Data Item	**NVR Field**	**HES APC Field**	**Core Lab Field**
Date of Admission	NvrEpisode:AdmissionDate	ADMIDATE	-
Date of Operation	NvrEpisode:ProcedureStartDate	OPDATE_NN	-
Operation Start Time	NvrEpisode:ProcedureStartTime	-	-

Operation Type	AAA:RepairTypeCode 1=Open, 2=EVAR, 3=Complex EVAR. IF 3, then to consider AAA:EvarComplexTypeCode 1=FEVAR, 2=BEVAR, OR AAA:Opcs1Code, AAA:Opcs2Code, AAA:Opcs3Code	OPERTN_NN L19* = Open, L266 or O202 = FEVAR, L271, L281 = EVAR, Other L26*, L27*, L28* = non-specific endovascular op	type_of_repair (Open, EVAR alone, EVAR + Screws, EVAR + Chimneys, FEVAR)
Anaesthetic Type	Anaesthesia:AnaestheticTypeCodes	-	-
Clamp Level for OSR	AAA:ClampSiteCode	-	-
Graft configuration for OSR	AAA:GraftTypeCode	-	-
Endo Graft Manufacturer	-	-	graft_manufacturer
EVAR/FEVAR - successful AAA exclusion?	AAA:EvarExcludedCode	-	Completion graft related EL
Endoleak	AAA:ElTypeCode	-	Completion graft related EL, and T2EL
Intraoperative Adjunctive Manoeuvres	AAA:EvarExcludedCode 2	-	Adjunctive interventions

Early Post-operative Data

Data Item	NVR Field	HES APC Field	Core Lab Field
General			
Date of Discharge	NvrEpisode:DischargeDate	DISDATE	-
Death	NvrEpisode:DischargeStatusCode	DISDEST/DISMETH in APC (in-hospital), and HES-ONS Dataset (all deaths)	-
Date of Death	NvrEpisode:DischargeDate (if died)	DISDEST/DISMETH in APC (if died), and HES-ONS Dataset	-
Cause of Death	-	HES-ONS Dataset	-
Length of Stay	Calculate with NvrEpisode:AdmissionDate and NvrEpisode:DischargeDate	Calculate with DISDATE and ADMIDATE, OR EPIDUR	-
Overall crit care days	PostOp:CriticalCareStayDays	DEPDAYS	-
Level 2 care	-	cclev2days (HES CC)	-
Level 3 care	-	cclev3days (HES CC)	-
Early re-admission	FollowUp:Readmission30DaysInd	Additional ADMIDATE	-

Complications		All complications in: DIAG_NN	
Spinal/Neuro			
Paraplegia /Paraparesis	-	G82	-
Stroke	PostOp:CompConditionCodes 3	I63, I64	-
TIA	-	G45	-
Intracranial Bleed	-	I60, I61, I62	-
Cardiac			
Myocardial Infarction	PostOp:CompConditionCodes 1	I21	-
Acute heart failure	PostOp:CompConditionCodes 1	I50	-
Atrial Fibrillation /Flutter	PostOp:CompConditionCodes 1	I48	-
Cardiac Arrest	PostOp:CompConditionCodes 1	I46	-
Arrythmia Other	-	I47,I49	-
Respiratory			
Pneumonia	PostOp:CompConditionCodes 2	J13, J14, J15, J16, J17, J18, J690	-
Chest Infection	PostOp:CompConditionCodes 2	J22	-
COPD exacerbation/Acute Bronchitis	PostOp:CompConditionCodes 2	J20	-
Respiratory Failure	-	J960	-
Lung collapse /Atelectasis	-	J981	-
Haemorrhage			
Re-bleed	PostOp:CompConditionCodes 5	T810	-
Vascular			
Acute limb ischaemia	PostOp:CompConditionCodes 6	I74	-
Lower Limb Dissection	-	I723, I724	-
Renal Artery Dissection		I722	
Deep vein thrombosis	-	I801, I802	-
Graft complications (bleed, thrombosis, stenosis) EXCLUDING INFECTION	-	T823, T828	-
Pseudoaneurysm - iliac/lower limb	-	I723, I724	-
Pulmonary Embolism	-	I26	-
Rupture of Artery	-	I772	-

Renal			
Acute Kidney Injury	PostOp:CompConditionCodes 4	N17	-
Dialysis	PostOp:CompConditionCodes 4	Z49	-
Gastrointestinal			
Bowel ischaemia	-	K550	-
GI bleeding	-	K250, K260, K270, K280, K922	-
Ileus	-	K560	-
Mechanical bowel obstruction	-	K913	-
Bowel perforation	-	K631	-
Abdominal Compartment Syndrome	-	R198	-
Wound/Infections			
Wound dehiscence	-	T813	-
Surgical Site Infection	-	T814	-
Graft infection	-	T827, T857	-
Complications in OPCS-4 (in APC OPERTN_NN)			
Haemodialysis	-	X403	-
Haemofiltration	-	X404	-
Periotenal Dialysis	-	X402	-
RBC Transfustion	-	X332	-
Other product Transfusion	-	X333, X34	-
Re-interventions		**From "OPERTN_NN" in APC**	
Open			
"Return to theatre"	PostOp:CompReturnTheatreInd	-	-
Re-entering the abdomen	-	T301, T302, T303	-
Washout of abdominal cavity	-	T463	-
Exploration of groin	-	T317	-
Open Repair/Recon of iliac artery	-	L48, L49, L52, L53	-
Open Repair/Recon of femoral/popliteal artery	-	L56, L57, L60, L62	-
Open Repair/bypass/recon to	-	L41, L42, L45, L46	-

abdominal visceral vessels			
Open AAA repair (conversion, if primary procedure is endo)	-	L18, L19, L651	-
Open Bypass of Aorta	-	L16, L20, L21	-
Open Lower Limb bypass	-	L50, L51, L58, L59	-
Open Ligation of artery	-	L423, L463, L703	-
Open Visceral vessel embolectomy (inc aorta)	-	L253, L421, L461	-
Open Iliac/Lower limb embolectomy	-	L532, L622, L701	-
Fasciotomy of Lower Limb	-	T553, T554, T555, T556	
Amputation of leg	-	X09	-
Amputation of Foot/Toe	-	X10, X11	-
Bowel resection	-	G69, H04, H05, H06, H07, H08, H09, H10, H11, H33	-
Stoma Formation	-	G74, H14, H15	-
Adhesiolysis	-	T412, T413, T415	-
Open I&D of seroma	-	T964	-
Open I&D of abdominal collection	-	T341, T342, T343	-
Endovascular/IR			
Angioplasty to visceral artery	-	L431, L471	-
Thrombectomy of visceral artery	-	L432	-
Embolisation of visceral artery	-	L433, L472	-
Stenting of visceral artery	-	L435, L474	-
Angioplasty of Aorta/Iliac artery	-	L261, L262, L541	-
Thrombectomy of Aorta/Iliac artery	-	L263, L542	-
Stenting of Aorta/Iliac artery	-	L265, L266, L267, L27, L28, L544	-
Angioplasty of Femoral/Popliteal artery	-	L631	-
Thrombectomy of Femoral/Popliteal artery	-	L632	-
Embolisation of Femoral/Popliteal artery	-	L633	-

Stenting of Femoral/Popliteal artery	-	L635	-
Generic Endo codes for any treated artery	-	L71	-
Coil embolisation	-	O01, O02, O03	-
Liquid polymer embolisation	-	O04	-
IR Drainage of abdominal collection	-	T45	-
Arteriography of artery (various)	-	L434, L473, L543, L634, L721	-

Late post-operative Data

Data Item	NVR Field	HES APC Field	Core Lab Field
General			
Death	NvrEpisode:DischargeStatusCode	DISDEST/DISMETH in APC (in-hospital), and HES-ONS Dataset (all deaths)	-
Date of Death	NvrEpisode:DischargeDate (if died)	DISDEST/DISMETH in APC (if died), and HES-ONS Dataset	-
Cause of Death	-	HES-ONS Dataset	-
Stent-graft complications			
Graft-related Endoleak	-	-	From F/U CT scans/reports
Type 2 Endoleak	-	-	From F/U CT scans/reports
Target vessel loss of patency	-	-	From F/U CT scans/reports
Stent kink	-	-	From F/U CT scans/reports
Stent occlusion	-	-	From F/U CT scans/reports

Possible Re-interventions (to be screened for later inclusion)		**From "OPERTN_NN" in APC**	
Open			
Washout of abdominal cavity	-	T463	-
Exploration of groin	-	T317	-
Open Repair/Recon of iliac artery	-	L48, L49, L52, L53	-
Open Repair/Recon of femoral/popliteal artery	-	L56, L57, L60, L62	-
Open Repair/bypass/recon to abdominal visceral vessels	-	L41, L42, L45, L46	-
Open AAA repair (conversion, if primary procedure is endo)	-	L18, L19, L651	-
Open Bypass of Aorta	-	L16, L20, L21	-
Open Lower Limb bypass	-	L50, L51, L58, L59	-
Open Ligation of artery	-	L423, L463, L703	-
Open Visceral vessel embolectomy (inc aorta)	-	L253, L421, L461	-
Open Iliac/Lower limb embolectomy	-	L532, L622, L701	-
Fasciotomy of Lower Limb	-	T553, T554, T555, T556	
Amputation of leg	-	X09	-
Amputation of Foot/Toe	-	X10, X11	-
Bowel resection	-	G69, H04, H05, H06, H07, H08, H09, H10, H11, H33	-
Stoma Formation	-	G74, H14, H15	-
Adhesiolysis	-	T412, T413, T415	-
Open I&D of seroma	-	T964	-
Open I&D of abdominal collection	-	T341, T342, T343	-
Incisional Hernia Repair	-	T25, T26	
Endovascular/IR			
Angioplasty to visceral artery	-	L431, L471	-
Thrombectomy of visceral artery	-	L432	-
Embolisation of visceral artery	-	L433, L472	-
Stenting of visceral artery	-	L435, L474	-

Transluminal Operation on visceral branch of aorta	-	L478	
Aortography	-	L264	
Angioplasty of Aorta/Iliac artery	-	L261, L262, L541	-
Thrombectomy of Aorta/Iliac artery	-	L263, L542	-
Stenting of Aorta/Iliac artery	-	L265, L266, L267, L268, L27, L28, L544	-
Angioplasty of Femoral/Popliteal artery	-	L631	-
Thrombectomy of Femoral/Popliteal artery	-	L632	-
Embolisation of Femoral/Popliteal artery	-	L633	-
Stenting of Femoral/Popliteal artery	-	L635	-
Generic Endo codes for any treated artery	-	L71	-
Coil embolisation	-	O01, O02, O03	-
Liquid polymer embolisation	-	O04	-
IR Drainage of abdominal collection	-	T45	-
Arteriography of artery (various)	-	L434, L473, L543, L634, L721	-
Generic			
Revision of prosthesis of Aorta	-	L22	-
Attention to prosthesis in organ	-	Y03	-
Attention to graft of organ	-	Y274	-
Removal of other repair material from organ	-	Y264	-
Other attention to repair of organ	-	Y265	-
Revision of reconstruction of artery	-	L65	-
Revision operations	-	Y71	-

The following codes were used to capture all elective abdominal aortic aneurysm repairs in England between Nov 2017 and Oct 2019, sourced from the Hospital Episode Statistics – Admitted Patient Care (HES-APC) dataset, *field name: opertn_nn*

Op code	**Code Translation**
L192	Replacement of aneurysmal segment of thoracic aorta by anastomosis of aorta to aorta NEC
L193	Replacement of aneurysmal segment of suprarenal abdominal aorta by anastomosis of aorta to aorta NEC

L194	Replacement of aneurysmal segment of infrarenal abdominal aorta by anastomosis of aorta to aorta NEC
L195	Replacement of aneurysmal segment of abdominal aorta by anastomosis of aorta to aorta NEC
L196	Replacement of aneurysmal bifurcation of aorta by anastomosis of aorta to iliac artery NEC
L198	Other specified other replacement of aneurysmal segment of aorta
L199	Unspecified other replacement of aneurysmal segment of aorta
L261	Percutaneous transluminal balloon angioplasty of aorta
L263	Percutaneous transluminal embolectomy of bifurcation of aorta
L264	Aortography
L265	Percutaneous transluminal insertion of stent into aorta
L266	Transluminal aortic stent graft with fenestration
L267	Transluminal aortic branched stent graft NEC
L268	Other specified transluminal operations on aorta
L269	Unspecified transluminal operations on aorta
L271	Endovascular insertion of stent graft for infrarenal abdominal aortic aneurysm
L272	Endovascular insertion of stent graft for suprarenal aortic aneurysm
L273	Endovascular insertion of stent graft for thoracic aortic aneurysm
L274	Endovascular insertion of stent graft for aortic dissection in any position
L275	Endovascular insertion of stent graft for aortic aneurysm of bifurcation NEC
L276	Endovascular insertion of stent graft for aorto-uniiliac aneurysm
L278	Other specified transluminal insertion of stent graft for aneurysmal segment of aorta
L279	Unspecified transluminal insertion of stent graft for aneurysmal segment of aorta
L281	Endovascular insertion of stent for infrarenal abdominal aortic aneurysm
L282	Endovascular insertion of stent for suprarenal aortic aneurysm
L285	Endovascular insertion of stent for aortic aneurysm of bifurcation NEC
L286	Endovascular insertion of stent for aorto-uniiliac aneurysm
L288	Other specified transluminal operations on aneurysmal segment of aorta
L289	Unspecified transluminal operations on aneurysmal segment of aorta
O202	Endovascular placement of one fenestrated stent graft

The following codes were used to identify type, site and date of pre-operative CT-scan imaging, for acquisition into the Corelab, as sourced from Hospital Episode Statistics – Diagnostic Imaging Dataset (HES-DID), *field names: scandesc, scandate, provcode, provname, sitecode, sitename*

Imaging Code	**Translation**
CABPEC	CT Abdomen and pelvis with contrast
CABDOC	CT Abdomen with contrast
CART	CT Angiogram
CAABDO	CT Angiogram abdomen
CAAAG	CT Angiogram aorta
CAREA	CT Angiogram renal and abdominal
CABAO	CT Aorta abdominal
CABAOC	CT Aorta abdominal with contrast
CAOTH	CT Aorta thoracic
CAOTHC	CT Aorta thoracic with contrast

CAOWH	CT Aorta whole
CAOWHC	CT Aorta whole with contrast
CEARP	CT Planning endovascular aneurysm repair
CCHAPC	CT Thorax abdomen pelvis with contrast
CCABDC	CT Thorax and abdomen with contrast

The following hospitals in England conducted aortic surgery during the inclusion period, as reported in the National Vascular Registry, and therefore were the sources of inputted HES data as well as the sources of pre- and intra-operative images (n=64).

NHS Digital Organisation Code	**NHS Hospital Trust Name**
R0A	Manchester University NHS Foundation Trust
R1H	Barts Health NHS Trust
R1K	London North West Healthcare NHS Trust
RA9	Torbay and South Devon NHS Foundation Trust
RAE	Bradford Teaching Hospitals NHS Foundation Trust
RAJ	Southend University Hospital NHS Foundation Trust
RAL	Royal Free London NHS Foundation Trust
RBA	Taunton and Somerset NHS Foundation Trust
RC1	Bedford Hospital NHS Trust
RCB	York Teaching Hospital NHS Foundation Trust
RDD	Basildon and Thurrock University Hospitals NHS Foundation Trust
RDE	East Suffolk and North Essex NHS Foundation Trust
RDU	Frimley Health NHS Foundation Trust
RDZ	Royal Bournemouth + Christchurch Hospitals NHS Foundation Trust
REF	Royal Cornwall Hospitals NHS Trust
RF4	Barking, Havering And Redbridge University Hospitals NHS Trust
RGT	Cambridge University Hospitals NHS Foundation Trust
RH8	Royal Devon and Exeter NHS Foundation Trust
RHM	University Hospital Southampton NHS Foundation Trust
RHQ	Sheffield Teaching Hospitals NHS Foundation Trust
RJ1	Guy's and St Thomas' NHS Foundation Trust
RJ7	St George's University Hospitals NHS Foundation Trust
RJE	University Hospital of North Midlands NHS Trust
RJR	Countess of Chester Hospital NHS Foundation Trust
RJZ	King's College Hospital NHS Foundation Trust
RK9	University Hospitals Plymouth NHS Trust
RKB	University Hospitals Coventry and Warwickshire NHS Trust
RLN	City Hospitals Sunderland NHS Foundation Trust
RM1	Norfolk and Norwich University Hospitals NHS Foundation Trust
RNA	The Dudley Group NHS Foundation Trust
RNL	North Cumbria University Hospitals NHS Trust
RNS	Northampton General Hospital NHS Trust
RP5	Doncaster and Bassetlaw Hospitals NHS Foundation Trust

RPA	Medway NHS Foundation Trust
RQ6	Royal Liverpool and Broadgreen University Hospitals NHS Trust
RQ8	Mid Essex Hospital Services NHS Trust
RQW	Princess Alexandra Hospital NHS Trust
RR1	Heart of England NHS Foundation Trust
RR8	Leeds Teaching Hospitals NHS Trust
RRK	University Hospitals Birmingham NHS Foundation Trust
RT3	Royal Brompton & Harefield NHS Foundation Trust
RTD	Newcastle upon Tyne Hospitals NHS Foundation Trust
RTE	Gloucestershire Hospitals NHS Foundation Trust
RTG	University Hospitals of Derby and Burton NHS Foundation Trust
RTH	Oxford University Hospitals NHS Trust
RTK	Ashford And St Peter's Hospitals NHS Foundation Trust
RTR	South Tees Hospitals NHS Foundation Trust
RVJ	North Bristol NHS Trust
RVV	East Kent Hospitals University NHS Foundation Trust
RW6	Pennine Acute Hospitals NHS Trust
RWA	Hull and East Yorkshire Hospitals NHS Trust
RWD	United Lincolnshire Hospitals NHS Trust
RWE	University Hospitals of Leicester NHS Trust
RWG	West Hertfordshire Hospitals NHS Trust
RWH	East and North Hertfordshire NHS Trust
RWP	Worcestershire Acute Hospitals NHS Trust
RWY	Calderdale and Huddersfield NHS Foundation Trust
RX1	Nottingham University Hospitals NHS Trust
RXH	Brighton and Sussex University Hospitals NHS Trust
RXN	Lancashire Teaching Hospitals NHS Foundation Trust
RXP	County Durham and Darlington NHS Foundation Trust
RXR	East Lancashire Hospitals NHS Trust
RXW	Shrewsbury and Telford Hospital NHS Trust
RYJ	Imperial College Healthcare NHS Trust

10 Publications and Presentations For Work From This Thesis

10.1 Peer-Reviewed Publications

1. Vallabhaneni SR, Patel SR, Campbell B, Boyle JR, Cook A, Crosher A, Holder SM, Jenkins MP, Ormesher DC, Rosala-Hallas A, Jackson RJ.
   Comparison of Open Surgery and Endovascular Techniques for Juxtarenal and Complex Neck Aortic Aneurysms: The UK COMPlex AneurySm Study (UK-COMPASS) - Peri-operative and Midterm Outcomes.
   European Journal of Vascular and Endovascular Surgery 2024 Feb: S1078-5884 (24)00197-7
   DOI: 10.1016/j.ejvs.2024.02.037. PMID: 38428672.

2. Patel SR, Ormesher DC, Griffin R, Jackson RJ, Lip GYH, Vallabhaneni SR; UK-COMPASS Trial.
   Editor's Choice - Comparison of Open, Standard, and Complex Endovascular Aortic Repair Treatments for Juxtarenal/Short Neck Aneurysms: A Systematic Review and Network Meta-Analysis.
   European Journal of Vascular and Endovascular Surgery 2022 May;63(5):696-706.
   DOI: 10.1016/j.ejvs.2021.12.042. PMID: 35221243.

3. Patel SR, Ormesher DC, Smith SR, Wong KHF, Bevis P, Bicknell CD, Boyle JR, Brennan JA, Campbell B, Cook A, Crosher AP, Duarte RV, Flett MM, Gamble C, Jackson RJ, Juszczak MT, Loftus IM, Nordon IM, Patel JV, Platt K, Psarelli EE, Rowlands PC, Smyth JV, Spachos T, Taggart L, Taylor C, Vallabhaneni SR.
   A risk-adjusted and anatomically stratified cohort comparison study of open surgery, endovascular techniques and medical management for juxtarenal aortic aneurysms-the UK COMPlex AneurySm Study (UK-COMPASS): a study protocol.
   BMJ Open. 2021 Nov 30;11(11):e054493.
   DOI: 10.1136/bmjopen-2021-054493. PMID: 34848524

10.2 Podium Presentations

1. UK-COMPASS: Study Design and Early Results
   The Vascular Societies' Annual Scientific Meeting
   December 2022
   Brighton, United Kingdom

2. UK-COMPASS: A Study Overview
   The Vascular Societies' Annual Scientific Meeting
   December 2021
   Manchester, United Kingdom

3. A systematic review and network meta-analysis of outcome comparisons between different treatments for juxtarenal AAA and those with other adverse features
   Charing Cross Aortic Vienna
   October 2021
   Virtual Conference