The impact of trans-renal aortic endograft fixation on renal function and the role of NGAL in the management of abdominal aortic aneurysms

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Preface

Dedicated to my wife Claire, for her support in the preparation of this thesis, and to the memory of my mother.

I would like to extend my gratitude to all clinical staff in the Northern Vascular Centre for their help in completion of this research. Of note, Dr J Rose for his radiological advice and expertise. Messrs MG Wyatt, D Lambert, TA Lees, NAG Jones, MJ Clarke and Prof. G Stansby, for access to their patients. Sister L Wilson and Sister V Wheallans for their assistance in patient follow up. Dr R Peaston for his advice and supervision during use of laboratory facilities.

In particular I would like to express my sincere appreciation and gratitude to Mr. Mike Wyatt for his continued support, patience and guidance throughout this period of research.

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The work within this thesis is original, and performed by myself between 2006-2007, at the Northern Vascular Centre, Freeman Hospital, Newcastle upon Tyne, UK.

Table of contents

List of Figures

List of Tables

List of Graphs

Abbreviations

AAA	Abdominal aortic aneurysm
AP	Antero-posterior
ARF	Acute renal failure
ASA	American Society of Anaesthesiologists
AUI	Aorto-Uni-Iliac
BMI	Body mass index
BUN	Blood urea nitrogen
CC	Cystatin C
CIA	Common iliac artery
cm	Centimetre
CrC	Creatinine clearance (ml/min)
CRF	Chronic renal failure
CT	Computed tomography scan
Da	Dalton
DTPA	Diethylene thiamine penta-acetic acid
EDTA	Ethylene diamine tetra-acetic acid
ELISA	Enzyme linked immune-sorbent assay
EVAR	Endovascular Aneurysm Repair
F	Female

FEVAR	Fenestrated EVAR
GFR	Glomerular filtration rate (ml/min)
HRQL	Health related quality of life assessment
IR	Infra-renal (placement of endograft)
k	Kilo
L	Litre
M	Male
µg	Microgram
mg	Milligram
mm	Millimetre
MMP	Matrix metallo-proteinase
MW	Molecular weight
n	Number
NGAL	Neutrophil Gelatinase Associated Lipocalin
ng	Nano gram
NL	Neutrophil Lipocalin
OR	Open repair of AAA
PETIA	Particle enhanced turbidimetric immunoassay
PTFE	Poly tetra fluoro ethylene
sCr	Serum creatinine (µmol/L)
SD	Standard deviation

SR	Supra-renal (placement of endograft)
t	Time
TIMP	Tissue inhibitor of matrix metallo proteinase
USS	Ultra-sound scan

Abstract

Over the last 20 years endovascular aneurysm repair (EVAR) has advanced dramatically. Early devices incorporated infra-renal fixation (IR), and were prone to delayed mechanical failure. Later devices incorporated bare metal stents that deploy in the supra-renal aorta (SR), improving durability, but potentially affecting long term renal function. This is the subject of continued research.

Cystatin C (CC) is a low molecular weight protein, which has demonstrated great sensitivity at detecting renal dysfunction, despite only modest decreases in glomerular filtration rate (GFR). To date it has not been used to evaluate mid to long term renal function following EVAR.

Neutrophil gelatinase associated lipocalin (NGAL) is a member of the lipocalin family of proteins, and rises considerably following renal insult due to surgery or nephro-toxicity. With increasing numbers of abdominal aortic aneurysm (AAA) repairs, it's important to have a reliable indicator and predictor of potential renal dysfunction following surgery.

Aims

- To assess long term renal function following EVAR, in particular SR-EVAR (Study 1)
- To assess mid to long term renal function following EVAR with Cystatin C (Study 2)
- To evaluate the role of NGAL in the management of AAA's (Study 3)

Results

Study 1 assessed 180 EVAR's performed between 1996 and 2001. Patients were grouped according to proximal fixation level. Renal function was recorded annually by serum creatinine

(sCr μmol/L) and Cockroft-Gault derived creatinine clearance (CrC ml/min). Paired renal data was available for 130 patients (IR: 67; SR: 63) with a mean follow up of 40.5 (range 0-120) months. 7 years post EVAR there was no significant deterioration in renal function within either the IR or SR group, with median sCr and CrC values of 117μmol/L and 56 ml/min, and 138 μmol/L and 41 ml/min respectively (all p=NS, Mann Whitney U-Test).

Study 2 was a two limbed study of 34 patients recruited over 12 months from June 2006. Patients were grouped according to previous AAA repair, either open repair (OR, n=17) or endovascular (EVAR, n=17). Both groups were analogous demographically. At 4 years follow up there was no significant deterioration in renal function within either the EVAR or OR group, with mean sCr, CrC and CC values of 112.75 μmol/L, 55.4 ml/min, 1.06 mg/L, and 112.94 μmol/L, 55.5 ml/min and 1.12 mg/L respectively (all p=NS, Mann Whitney U-Test).

Study 3 was a prospective two limbed study of 44 patients recruited over 12 months from June 2006 and grouped according to AAA repair, either open (OR, n=21) or endovascular (EVAR, n=23). Both groups were analogous demographically. There was a weak but statistically significant correlation between sCr (μmol/L) and NGAL (ng/ml) in the AAA population, with a Pearson correlation co-efficient of +0.24 ($p<0.05$). At both 4 and 24 hours post surgery the OR group had a statistically significantly higher median NGAL level than the EVAR group, 187.5 ng/ml and 140.0 ng/ml vs. 182.0 ng/ml and 137.0 ng/ml respectively (all $p<0.05$, Mann Whitney U-Test). In proven renal dysfunction, NGAL was elevated above the diagnostic cut-off level at 4 hours post procedure, although numbers were too small for statistical significance.

Conclusions

Long term renal function remains unaffected following EVAR, irrespective of proximal fixation type, or biochemical marker of analysis.

Although correlating with renal function in the AAA population, the role of NGAL in predicting potential renal dysfunction in these patients remains unclear, and warrants further research.

Chapter 1. The Abdominal aortic aneurysm (AAA)

1.1 The history of the abdominal aortic aneurysm repair

Simply defined as a 'hemispherical tumour of the vessel, which expands beneath the fingers with each pulsation', the first documentation of arterial aneurysmal disease is from ancient Egypt (est. 1552 B.C.), in some of the earliest known medical texts[1].

It would however take a further 3000 years for the abdominal aortic aneurysm (AAA) to be defined as a distinct entity, by anatomist Andreas Vesalius (1514-1564), who simply described 'a pulsating tumour below the stomach' in a selection of his patients[2]. Although recognised as a pathological feature, which could lead to death, it was not until the early 19th century that surgical AAA management was contemplated.

In 1817 pioneering work by Astley Cooper (1768-1841) lead to the first reported case of abdominal aortic ligation for the treatment of a leaking common iliac artery (CIA) aneurysm[3]. Despite initial surgical success, the patient succumbed on the second post-operative day.

It would take a further hundred years for the first successful AAA repair. In 1925 Rudolph Matas (1860-1957) successfully ligated a syphilitic AAA in a 28 year old woman, with no apparent aneurysm associated complications[4]. Whilst successful, the viability of the patient's extremities was dependent on collateral blood flow, and could not be guaranteed long term. An alternative approach allowing maintenance of normal vascular anatomy was needed.

The great leap in aneurysm surgery came from pioneering surgeon Alexis Carrel (1873-1948). In 1912 he was awarded the Nobel Prize for demonstrating that sections of animal aortas could be successfully replaced by interposition grafts consisting of both arterial and venous homografts[5].

This meant simply that aortic blood flow could be restored through the aorta to the lower limbs following surgery, with continuity of normal arterial anatomy.

It would still take several decades before the first successful account of AAA repair in a human with a vascular homograft. In 1952 French surgeon Charles DuBost (1914-1991)[6] described the repair of a large infra-renal aorto-iliac aneurysm by aneurysm resection, and restoration of vascular continuity by placement of an interposition graft, constructed from a previously harvested section of cadaveric thoracic aorta. The graft was successfully anastomosed from the infra-renal aorta onto the right common iliac artery, with vascular continuity to the left limb maintained by an end-to-side anastomosis of the left common iliac artery to the graft. With no reported complications, the patient made a full recovery.

Despite these initial successes, the availability and size constrains of vascular homografts precluded their widespread use. The modern revolution in AAA repair occurred later in 1952, heralded by Vorhees et al.[7], who successfully demonstrated the use of fabric conduits in lieu of homografts.

With AAA repair progressing rapidly, refinement of technique was required to improve outcomes. The currently employed technique of open AAA repair by aneurysmorrhaphy and intra-luminal fabric graft reconstruction was popularised by Oscar Creech (1916-1967) in 1966 [8]. He advised against resection of the aneurysmal aorta, citing the high risk of concomitant damage to adjacent structures, and instead recommended opening the aneurysm sac, and anastomosis of the interposition graft from within, to the preserved native vessel both proximally and distally.

This technique of open aneurysm repair was to gain worldwide acceptance as the standard treatment for AAA's for the next few decades.

1.2 The Epidemiology of AAA's

It is currently estimated from both population and post-mortem studies that the prevalence of AAA's within England is as high as 13%, with up to 5% of the population over the age of 60 years harbouring an asymptomatic AAA. Within the English population the incidence of AAA's increase sharply following the age of 50 years, finally reaching a peak at 80 years.

With such a high prevalence, it is not surprising that the development of AAA's in the infra-renal aorta is linked to common pre-disposing risk factors. These include increasing age, male sex, ethnicity, smoking, hypercholesterolaemia, hypertension, family history and pre-existing vascular disease[9, 10]. Of these risk factors, both smoking and being male are the most important, and increase the risk of AAA development approximately five fold. Additionally, having a first degree relative with an AAA doubles the risk of aneurysm development[11].

Although a controversial topic, the general consensus is to screen radiologically for AAA's those patients who are male, over the age of 50 years, have affected relatives, and significant risk factors.

1.3 The Natural History and Clinical features of AAA's

The natural history of the AAA is to expand and increase in size over time, leading to eventual risk of rupture. The best predictor of rupture is the antero-posterior (AP) size measurement of AAA's, with a greater size leading to greater risk. Following a meta-analysis of 13 studies Law et al. confirmed this, with annual risk of AAA rupture ranging from 0% for less than 3 cm, to 3.3% for 5-5.9 cm, and up to 24% for 7-7.9 cm[12].

Most surgeons subsequently agreed that as long as the risk of surgery for AAA repair was less than the annual risk of rupture, then patients should undergo surgical treatment.

The UK Small Aneurysm Trial[13] aimed to clarify these issues and guide surgeons on whether small aneurysms (<5.5 cm) should be kept under radiological surveillance, or offered treatment, based on the risk of rupture and surgical risk. The trial found no survival benefit from operating on these small aneurysms (<5.5 cm), and recommended that AAA's should be repaired surgically when the AP size exceeds 5.5 cm, or if symptoms relating to the aneurysm develop. Below 5.5 cm, all AAA's should be kept under regular radiological surveillance. These conclusions were based on the findings that at or above 5.5 cm in size, the annual risk of AAA rupture outweighed the risk of open surgical AAA repair. The only exception to this recommendation was for those AAA's with a rapid expansion rate, which was felt to represent unpredictable aneurysm pathology, and an increased likelihood of rupture. It is generally recommended that if the annual AAA expansion rate is greater than 1 cm, then repair should occur regardless of the AAA size.

One of the difficulties in AAA detection is that most are entirely asymptomatic, and are usually discovered incidentally when performing abdominal examination, or radiological imaging (Ultrasound/Computed Tomography) in search of other pathology. The presence of symptoms usually suggests AAA related complications such as fistulation (to bowel or vena cava), inflammation, infection, embolisation (to distal extremities or viscera), pressure related local effects, or imminent rupture. Any patient, presenting with sudden onset central abdominal and back pain, or unexplained collapse over the age of 50 years old, with or without a diagnosis of AAA, should be considered an AAA rupture, and treated as such until proven otherwise. Other

AAA related presentations, such as acute thrombosis or distal embolisation (causing peripheral ischaemia), or fistulation with the vena cava or duodenum (resulting in large gastrointestinal bleeding or high output cardiac failure), are rarer.

1.4 The Typical Open surgical repair of an AAA

The open surgical repair of an AAA as performed in most vascular centres follows a typical sequence of events, each of which may be changed or altered at local discretion.

Following decision to treat an AAA, all patients give informed consent for the procedure. This highlights the main risks and complications, of open abdominal aortic surgery. These include both general and aneurysm specific complications, such as pneumonia, urinary sepsis, graft sepsis, haemorrhage, myocardial infarction, stroke, distal embolisation and limb loss, 'trash feet', need for further procedures, and death (which occurs in up to 5% of cases).

All open AAA repairs are performed under general anaesthetic, with invasive monitoring of the patient in the form of urinary catheterisation, arterial and venous cannulation and possibly an oesophageal Doppler to assess cardiac output. An epidural may be used to reduce postoperative pain, and broad spectrum antibiotics are given at induction, and during the procedure as necessary to minimise the risk of graft infection.

A trans-abdominal or retroperitoneal approach is used to access the aorta, with the retroperitoneal approach favoured in patients with severe adhesions following previous abdominal surgery, or other factors precluding an anterior abdominal approach (presence of stomas). Trans-abdominal is the preferred abdominal approach, and is achieved either via mid-

line incision or transverse abdominal incision, depending on surgeon preference, and whether there is any aneurysmal involvement of the iliac vessels.

Following abdominal access, the small bowel is usually retracted and held either within or outside the abdominal cavity, to allow exposure of the retro-peritoneum. The peritoneum is then incised at the base of the small bowel mesentery, extending to the aortic bifurcation, allowing exposure of the aorta.

The aortic neck and iliac vessel can then be dissected free to allow the application of clamps, once intravenous heparin (up to 5000 units) has been given. The proximal clamp is typically applied as close to the renal arteries as possible, so as to minimise the amount of residual native infra-renal aorta following repair, and subsequent aneurysmal formation.

The anterior surface of the aneurysm sac can then be incised and any patent lumbar or gonadal vessels over sewn to arrest bleeding. The inferior mesenteric artery (IMA) is usually sacrificed, but can re-implanted later in the operation if there are concerns regarding the remaining colonic blood supply.

The surgeon can now decide on the type of graft to be used (straight tube graft or bifurcated), and the size. The graft is then typically secured proximally with 2-0 or 3-0 mono-filament non absorbable sutures, with small pledgets constructed from excess graft to reinforce any areas of friable aortic wall. The proximal anastomosis is then tested, by allowing blood flow through the anastomosis into the graft, which has a separate clamp applied just distal to the anastomosis.

If an adequate seal is achieved, the distal anastomosis is performed to either aorta or iliac arteries depending on the graft used, and the graft flushed with heparinised saline prior to final closure to remove any air.

The iliac vessel clamps are then released consecutively to avoid catastrophic falls in blood pressure. This occurs because of the rapid volume re-distribution into the large dilated distal ischaemic vascular beds, and the release into the circulation of accumulated vaso-active metabolites from the previously clamped limb.

Assuming that haemostasis is achieved, and that the colon is viable (following IMA ligation), the aneurysm sac is loosely sutured over the graft to protect it from the small bowel, the small bowel is returned to the abdomen, and the abdominal incision closed.

At the end of the procedure the lower limbs are assessed to ensure adequate perfusion, and the patient is transferred to either the intensive care unit (ITU) or high dependency unit (HDU) depending on pre-existing co-morbidities, and how they behaved physiologically during the procedure. Patients are then typically returned to the ward within 48 hours, and discharged from hospital between 7-10 days, depending on the presence of any complications.

Whilst this general approach to AAA repair has and continues to serve patients well, the risks associated with major abdominal surgery and the high 30 day post-operative mortality of up to 5%, have led many to seek less invasive or minimal access approaches to AAA repair.

Chapter 2. Endovascular aortic aneurysm repair (EVAR)

2.1 Introduction

For many years surgeons had sought to reduce the high risk of complications and mortality risk following major abdominal surgery for open AAA repair. With the elderly population on the increase in the United Kingdom and increasing numbers of AAA's detected, the need for an alternative option to major abdominal surgery in those with AAA's is becoming increasingly apparent.

A minimally invasive approach for AAA repair is not a new concept. Intra-luminal wires, both with and without electrical current, had previously been employed to try and promote aortic thrombosis with limited success. Self expanding umbrella filters delivered via intra-luminal trochars had also been trialled, with similar high failure rates[14].

Exclusion of AAA's by retrograde cannulation of the aorta and insertion of an endograft was initially performed on animal models. An artificial AAA was created in dogs by replacing an infra-renal segment of the aorta with a fusiform shaped Dacron® conduit. These artificial AAA's were then excluded from the circulation via a trans-femoral introduction of an endograft, constructed from a knitted Dacron® graft overlapped by one third at both the proximal and distal ends, and sutured to a Palmaz® balloon expandable stent. The fabric covered stent essentially re-lined the aorta, providing a new channel in anatomical continuity for the blood to flow[15].

The first endovascular repairs of abdominal aortic aneurysms (EVAR) in humans were reported in 1990 by Parodi et al.[15] In a manner similar to previous studies, they created endografts from balloon expandable metal stents covered in Dacron® graft fabric (sutured to the stent at both ends). They demonstrated that friction from the radial force of the expandable metal stent against the aortic wall secured the graft to the aorta, maintained an adequate haemostatic seal, and

excluded the aneurysm from the circulation, allowing normal blood flow through the graft. The procedure involved femoral artery exposure and arteriotomy. The home-made endograft was then advanced through the femoral artery via an introducer sheath, under radiological guidance, to sit in the aneurysmal aorta. Once in position, a moulding balloon, already incorporated in the introducer sheath, was inflated (50% saline: 50% non-ionic contrast), and pulled distally through the endograft to deploy the proximal metal stent and secure the proximal endograft in the aorta. The distal stent was then expanded with a second incorporated balloon, securing the distal endograft in the aorta. A completion angiogram confirmed exclusion of the AAA from the circulation, and that there were no leaks around the endograft. Introducers and guide wires were then removed, and the femoral arteriotomy closed as per routine procedure. These home-made endografts were deployed successfully in five patients with large AAA's, with no significant complications reported. The era of EVAR had now truly begun.

Over the last 20 years, EVAR has rapidly evolved from the early home-made experimental endografts to commercially produced devices of the highest quality. They are available in tubular (aorto-aortic), aorto-uni-iliac (AUI) or bifurcated configurations. They may be one piece (uni-piece), or modular (several components requiring construction during deployment), and attach to either the infra-renal (IR), or supra-renal (SR) abdominal aorta (via an uncovered portion of bare metal stent struts). More recent developments have been the creation of individually manufactured endografts with scallops at the leading edge of the graft, or fenestrations corresponding to the visceral arteries, for the treatment of juxta-renal aneurysms, or those with challenging aortic necks. The endograft fabric can consist of polyester (Dacron®) or polytetraflourotethylene (PTFE®), and may be either balloon or self expanding.

Endografts are used primarily to treat AAA's, but are now also manufactured and designed specifically to treat a variety of thoracic diseases (aneurysm, dissection, traumatic transection, penetrating ulcers, pseudo aneurysms, aorto-bronchial fistulae and mycotic aneurysms)[16].

Whilst endograft technology has advanced significantly in the past 20 years, and EVAR has gained recognition and acceptance as an alternative to open AAA repair, there is still a great deal to learn. Concerns regarding long term endograft durability, higher financial costs of EVAR compared to open repair, and the need for continued post deployment surveillance persist today[17].

2.2 The Evolution of EVAR

Tube grafts

The first endografts constructed were a simple tube structure, with aorta to aorta attachment (see Figure 1). They were constructed from Dacron® grafts with a Palmaz® stent attached either proximally, or both proximally and distally. Commonly with this type of graft, an unfavourable distal aortic landing zone for the graft to attach resulted in frequent graft migration, and failure to maintain an adequate distal aortic haemostatic seal post deployment, resulting in continued aneurysm expansion and frequent aneurysm ruptures[18]. Failure to achieve this distal haemostatic seal on completion angiography commonly resulted in conversion of the EVAR to open AAA repair[19].

Several large studies of tube endografts seemed to confirm these findings. In 1998 May et al. reported their 5 year experience of EVAR using different configurations of endografts. They

found no significant difference in the peri-operative mortality between the different graft configurations, however Kaplan-Meier curves demonstrated a success probability of only 50% at 40 months for tube grafts, compared to 80% for the others (aorto-iliac, bifurcated)[20]. In 2002 Faries et al. report their experience of deploying 65 tube endografts from various manufacturers. They found no late aortic ruptures requiring surgery, but proximal attachment failure in 2 patients, and distal site failure in 12, with an average time interval to failure of 12.9 months[21].

Due to universal reports of late complications, and because the proximity of the aortic bifurcation meant that only 5% of AAA's were suitable for exclusion with tube-grafts[19], they are no longer used and considered obsolete.

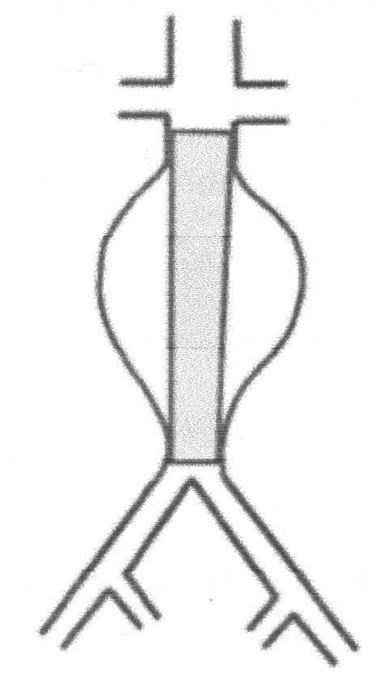


Figure 1: Anatomical representation of an aortic tube graft

AUI grafts

The next milestone in the development of endografts was the introduction of distal endograft fixation in a solitary common iliac artery. There was a general acceptance that common iliac fixation was needed to overcome the problems associated distally with tube grafts, in particular low levels of patients suitability and poor distal aorta quality. An AUI endograft involves a single tubular endograft, attached to both the infra-renal aorta proximally, and the most suitable iliac artery distally (absence of aneurysm, occlusion or tortuosity), referred to as the ipsilateral iliac. The contralateral common iliac is then occluded with an endovascular plug, and a femoral-femoral crossover bypass performed (see Figure 2), to restore blood flow to the contralateral limb. Although this requires a formal surgical placement of a vascular graft, the associated risks seem to be low. Walker et al. published their data on 136 patients following AUI stent-graft insertion, and found on median follow up of 7 months, only 2 graft infections and one graft thrombosis affecting the femoral-femoral graft[22].

Parodi et al. were one of the first centres to document the successful insertion of eight AUI grafts with encouraging early results[23]. Following the report of successful AUI deployment in 8 patients, several other centres reported similar success rates with home-made endografts. Yusuf et al. reported the deployment of modified Gianturco® stent, Dacron® graft and Wallstent® (forming an AUI configuration) in 30 patients, with successful insertion in 25 (83.3%) of the patients and a 30 day overall operative mortality of 2 (6.6%)[24]. Thompson et al. demonstrated similar positive results with their tapered AUI graft constructed from an 8 mm thin-walled expanded PTFE® tube graft pre-dilated proximally to 35 mm, and tapered distally to 15 mm, with the graft sutured proximally to a 5 cm long pre-dilated Palmaz® stent. There was success in

52 (87%) of the 60 patients treated, with aneurysm exclusion in 49 (82%), and a peri-operative mortality of 3%[25, 26].

Larger scale studies using commercially manufactured AUI grafts confirmed all these positive findings. The EVT/Guidant trials[27] compared AUI endografts with bifurcated grafts, tube grafts and open AAA repair. The primary end-points observed were operative morbidity and outcome at 1 year following EVAR. Endograft deployment was achieved in 94.2% of the AUI group, (comparable to the other endovascular techniques), and there was no significant difference in operative mortality between the groups (4.2% AUI, 2.6% bifurcated, 0% tube, 2.7% open repair). The incidence of Type 1 endoleak (proximal aortic seal) at one year were 2.4%, 2.3% and 3.8% for the AUI, bifurcated and tube groups respectively, and there were no reported late aneurysm ruptures or femoral-femoral graft thromboses. They concluded that the AUI endografts were as safe to use as the other configurations.

Currently the most common indication for AUI endograft deployment is the presence of unilateral iliac artery occlusion, preventing aortic access via the blocked limb, and subsequent deployment of a contralateral limb. Due to their relatively rapid deployment, and exclusion of the aneurysm without having to deploy a contralateral limb, many currently advocate their use in the treatment of ruptured aneurysms.

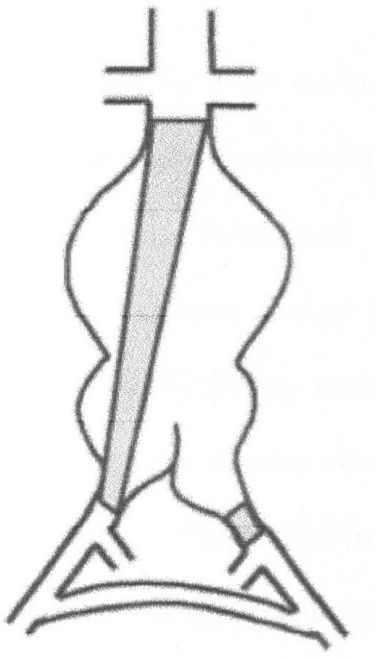


Figure 2: Anatomical representation of an aortic AUI graft, with occluded contra-lateral limb, and femoral-femoral cross-over graft

Bifurcated grafts

Non-modular (Uni-piece)

In current practice, the most commonly used endograft configuration is a bifurcated design. These endografts are an inverted Y shape, allowing proximal fixation in the infra-renal aorta, and distal fixation in each of the common iliac arteries, therefore maintaining anatomical normality, utilising the favourable common iliac arteries as a landing zone, and excluding any concomitant iliac artery aneurysms.

The first documented use of bifurcated endografts was by Chuter et al. in 1994. The home-made devices were made from standard bifurcated Dacron® grafts with Gianturco® stents sutured at

both the proximal and distal extremities. Fifty two procedures were performed over a three year period, during which the device underwent modification, eventually resulting in its professional production (42 home made stent-grafts vs. 10 professionally made). Early results were promising, with 92% successful deployment of the home made devices, and 100% for the professionally made. However long term success was only 64% in the home made group and 90% in the professionally made group. Device failures were attributed to graft thrombosis secondary to kinking and proximal graft migration[28, 29].

The first commercially available bifurcated device was manufactured by Endovascular technologies®, and consisted of an aortic main body, and two identical iliac limbs with self expanding stents attached to each of the landing zones[30]. The Endologix Powerlink® is currently the only commercially available uni-piece bifurcated endograft in production. The US multicentre trial for the Powerlink® stent-graft demonstrated this device to have a comparable outcome with respect to other EVAR devices, and less adverse post-operative events compared to open repair for AAA[31].

In general, uni-piece endografts have drawn criticism for the relative difficulty in deploying the contra-lateral limb, which frequently requires open surgical access, and the inflexibility of the devices due to equal dimensions of the limbs, precluding deployment in patients with different size or complex iliac systems.

Modular design

Modular endografts represent the pinnacle of bifurcated endograft design, and are currently the most commonly used and widely available endograft type. They are in essence a bifurcated endograft with one of the graft limbs detached from the main body of the graft. The principal

difference between other types of endograft is that the main aortic body has both long and short limbs distally. The main body is inserted via the most suitable iliac artery to attach to the aorta, as per other EVAR devices, and once deployed the long limb attaches to the iliac artery on the ipsilateral side. The short limb opens directly into the aneurysm sac, allowing catheterisation from the contralateral iliac artery, and deployment of the contralateral iliac limb, completing the bifurcated graft (see Figure 3). The endograft limbs can be pre-measured to sit correctly within the iliac arteries, or if necessary additional extensions can be placed at the end of deployment. The graft components are self expanding and held together by radial forces. Since different diameter and lengths of iliac limbs can be chosen, modular grafts are infinitely more adaptable than uni-piece endografts, and now form the mainstay of endografts used for EVAR.

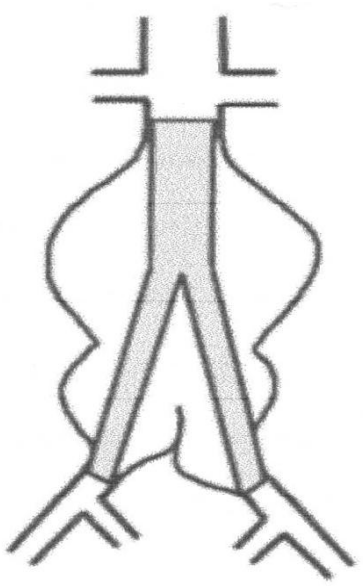


Figure 3: Anatomical representation of an aortic bifurcated graft

The first commercially produced modular endograft was the MinTec Stentor®. This was also the first endograft in which the graft fabric was supported along its entire length by the metal stent (not just at the proximal and distal landing sites), and eventually evolved into the Vanguard® endograft. Unfortunately these early modular devices were prone to late failure, with device migration, graft limb occlusions, stent kinking and limb dislocation all reported. In one of the first large studies to raise concerns regarding these early modular endografts, the Mount Sinai Medical Centre in the USA reported 60 out of 686 modular endograft deployments developed graft fatigue and failure. 43 of these were attributed to metallic stent fractures, and 14 to suture disruption, separating the graft fabric from the metal stent. The two modular endografts most commonly affected were the Vanguard® (16/60, with 9 body separations), and the Talent® endograft (24/60, with 23 metal stent fractures)[32]. Similar results and concerns were raised by other vascular centres. The Northern Vascular Centre, Newcastle, UK, reported similar results with their cohort of 55 Vanguard® endograft deployments. At median follow up of 40 months there were 3 device migrations, 12 occluded limbs and nine type 3 endoleaks. At 48 months, there was a survival rate of 67%, and an endoleak free survival of 81% [33].

The Vanguard® and fellow early endograft Guidant Ancure/EVT® have subsequently been withdrawn due to these reported late failures, and ongoing concerns over their safety. Continuing development of endografts resulted in higher quality stents and design (particularly with respect to the type of proximal fixation), to reduce these worrying complications, and the current generation of modular endografts have excellent long term outcomes and durability. In a review of the EUROSTAR EVAR database in 2005, an analysis of the 6787 patients in the database found the Excluder®, Talent® and Zenith® (all modular endografts), were associated with a

lower risk of migration, kinking, occlusion, and need for secondary intervention compared to the Vanguard® and earlier modular endograft designs[34].

There are currently several commercially available EVAR devices in the UK forming a variety of configurations (see Table 1).

Aortic endografts		
Device name (manufacturer)	**Device configuration**	**Supra-renal component**
Powerlink/XL (Endologix)	Unibody	Optional
Zenith Flex (Cook)	Modular +/- fenestrated	Yes
Talent (Medtronic)	Modular	Yes
Endurant (Medtronic)	Modular	Yes
Anaconda (Vascutek/Terumo)	Modular	No
Excluder (Gore)	Modular	No
Aorfix (Lombard Medical)	Modular	No

Table 1: Commercially available endografts in the UK (as of 2010)

2.3 Supra-renal (SR) versus infra-renal (IR) fixation

Perhaps the most important development in endograft technology, came in response to these reports of early generation endograft late proximal attachment failure[35], and subsequent graft migration[33]. These resulted in failure to exclude the AAA, and reports of delayed rupture following AAA repair. The first generation endografts were deployed just below the renal arteries, and fixation was achieved via either radial forces or barbs or hooks in the endograft metal stent, so called infra-renal (IR) fixation. This IR portion of the aorta is susceptible to continued aneurysmal dilatation following endograft deployment[36], which resulted in these proximal attachment failures. This resulted in several companies taking advantage of the disease free supra-renal (SR) aorta, and the development of endografts with an uncovered bare metal section of proximal stent which crosses the renal arteries, and attaches in the supra-renal aorta via a series of barbs or hooks (see Figure 4 & 5).

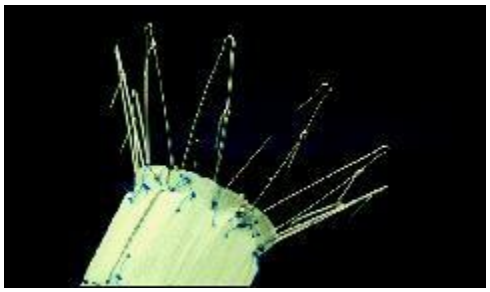


Figure 4: Picture of uncovered trans-renal stent component of an endograft

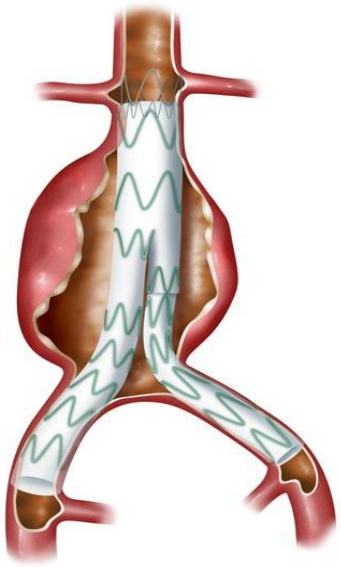


Figure 5: A typical modular bifurcated aortic endograft with trans-renal placement

Although associated with lower rates of proximal attachment failure[34], concern was raised regarding bare metal wires crossing the renal arteries, disrupting blood flow, and affecting renal function.

2.4 Renal function following SR EVAR

The earliest studies assessing renal function following SR EVAR concentrated primarily on the direct disruption to blood flow in the renal arteries by the uncovered bare metal stents.

England et al. demonstrated peripheral or central renal ostia partial coverage in up to 40% of cases unilaterally, and 9% bilaterally[37], raising concern that there could be significant disruption to renal blood flow, especially in those with bilateral coverage. To assess this potential effect, Liffman et al. investigated four different stent wire configurations placed across an arterial orifice. Using complex experimental, numerical and analytical methods, they reported on average only a 1% reduction in blood flow across a 3 mm targeted vessel, suggesting renal safety

in theory[38]. Similar work by Sun et al. using CT virtual intravascular endoscopy to assess the stent strut/ostia relationship, demonstrated no adverse renal complications, and preserved renal patency up to 8.3 months following SR endograft placement[39].

Direct assessment of biochemical renal function following SR EVAR was initially performed on animal (pig) models. Neither Whitbread et al.[40] or Malina et al.[41] could detect any biochemical renal dysfunction (using sCr as a renal marker), altered renal perfusion pressure, organ infarction or micro-embolisation, or radiological evidence of renal dysfunction up to 1 week following SR EVAR.

The earliest assessment of renal function following SR EVAR in the human population was reported by Malina et al. in 1997. Using a homemade SR EVAR endograft in 18 patients, at median follow up of 6 months they found preservation of all renal arteries radiologically, and no elevation in the patients' biochemical renal markers (sCr)[42]. The race to prove long term renal safety following SR EVAR had begun.

Alsac et al. published their series of 277 patients (137 SR EVAR) with a mean follow up of 12.2 months. Both groups showed a decrease in creatinine clearance post procedure (IR 10.9%; SR 9.5%), but the difference between the groups was not statistically significant. They did however demonstrate that in patients with pre-existing renal impairment, the subsequent decrease in creatinine clearance was significantly greater in those patients treated with SR EVAR compared to IR[43].

As more Vascular centres offered EVAR, and patient numbers increased, longer follow up periods were reported. Alric et al. published their series of 315 (SR EVAR) patients with a mean follow up of 30.1 months. 17.2% of the supra-renal group suffered renal impairment (9.5%

persistent) vs. 16.4% for the infra-renal group (8.9% persistent), with no significant differences in dialysis requirements between the groups. Using multi-variate analysis they demonstrate that SR endografts were not significantly associated with renal impairment compared to IR[35].

Due to concern that most studies and series of patients reported were heterogeneous with respect to endograft type used, and the subsequent potential for bias, the Powerlink® Trial investigators report their series of 283 patients (91 SR EVAR) who underwent AAA treatment exclusively with the Endologix Powerlink® endograft during two US FDA trials between over a four year period. The endograft was available in both IR and SR variants. They found no significant difference between groups at any time period for creatinine clearance, renal impairment, renal events, or the need for dialysis, and concluded that SR EVAR was as safe as IR[44]

Despite several positive reports, Bockler et al. published their experience with 663 patients (202 SR EVAR) with a mean follow up of 37 months. They discovered an overall renal infarction rate of 11.9%, with 19% of SR EVAR causing varying degrees of renal infarction vs. 3.7% for the IR EVAR (statistically significant). Although a worrying finding, with concern once again re-ignited over long term SR EVAR safety, they explain that this group comprised the more technically challenging patients, with adverse aneurysmal neck morphology, which could account for this discrepancy[45].

To date, using variable biochemical and radiological methods, several studies have demonstrated the apparent renal safety of SR EVAR in the mid to long term (see Table 2). However, as long term studies are now beginning to demonstrate late endograft failure following EVAR, there is still ongoing concern regarding the long term renal safety of SR EVAR, and continuing research is needed.

Investigators	Year	SR EVAR (n)	IR EVAR (n)	Mean F/U (months)	Biochemical renal assessment used
Malina et al. [42]	1997	18	-	6	sCr
Marin et al. [46]	1998	37	-	10.3	sCr
Kichikawa et al. [47]	2000	18	-	14	sCr
Lobato et al. [48]	2000	35	-	11	sCr
Izzedine at al. [49]	2002	39	-	6	sCr, CrC
Kramer et al. [50]	2002	69	124	12	-
Bove et al. [51]	2003	37	-	29	sCr
Alric et al. [52]	2003	169	146	30	sCr
Cayne et al. [53]	2003	69	61	17	sCr, CrC
Lau et al. [54]	2003	32	57	12	sCr
Surowiec et al. [55]	2004	60	53	23	sCr
Grego et al. [56]	2004	47	-	16	sCr
Mehta et al. [57]	2004	111	385	19	sCr, CrC
Alsac et al. [43]	2005	137	140	12.2	sCr, CrC
Parmer et al. [44]	2006	91	192	30	sCr, CrC

Table 2: Summary of renal studies post SR EVAR

2.5 Patient selection & eligibility for EVAR

Studies have shown that up to 66% of patients with AAA's may be anatomically suitable for EVAR[58], and that this suitability depends on specific morphological characteristics of the aneurysm (see Table 3). These anatomical features include aneurysm neck length and degree of angulation, as well as the absence of thrombus in the aneurysm neck and conical shape. The size, tortuosity and aneurysmal status of the iliac vessels is also important, and all of the above must be considered when selecting patients for EVAR.

The ideal length of AAA neck when considering treatment should be at least 15 mm, allowing sufficient non-aneurysmal proximal aorta to attain an adequate haemostatic seal with the endograft. Stanley et al. reported on their experience of deployment of the Zenith® endograft in 238 patients, over a median follow up of 13.4 months, and found that endoleak rates (failure to maintain a proximal haemostatic seal), in necks less than or equal to 10mm was 57%, and that increased rates of proximal endoleak were significantly associated with both a neck contour change of 3 mm along the neck length, as well as a neck length of less than 20 mm. They concluded that neck contour, length and diameter are the most important factors in preventing endoleaks, and that 15 mm should be the minimum AAA neck length considered safe for EVAR[59]. Similarly, any AAA with a short or heavily calcified neck (a high percentage of aortic neck circumference calcified), are at an increased risk of proximal endoleaks, and EVAR should be used prudently[60].

AAA neck length is not the only consideration when planning patients for EVAR. The angle of the neck of the AAA with the non-aneurysmal aorta can also determine freedom from endoleaks. Sternbergh et al. report their series of 81 patients undergoing EVAR, and the consequences of

varying degrees of neck angulation. They demonstrated the risk of a patient experiencing one or more adverse post-operative events (death, conversion to open repair, and type 1 endoleak), as 70%, 54.5% and 16.6% in patients with severe (> or = 60 degree), moderate (40-59 degrees), and mild (<40 degrees) angulation respectively. They recommend caution in patients with large AAA neck angulations, and recommend an angulation of less than 60 degrees for safe EVAR deployment[61]. For many years considered a restriction to EVAR, necessitating open AAA repair, newer technology endografts, in particular Aorfix® (Lombard Medical), have been specifically designed with flexible metal stent frames, allowing treatment of the most complex AAA necks, with angulation approaching 90 degrees.

In addition to AAA specific factors, the iliac vessels, through which the endograft must travel, must also be carefully assessed prior to EVAR. They should ideally be at least 7 mm in diameter to accommodate the large delivery catheters and sheaths of EVAR, and tortuosity as well as calcification, which account for up to 15% of patient exclusion from EVAR, should be minimal[62]. Whilst important in patient selection for EVAR, adverse iliac vessels are not an absolute contra-indication. The iliac vessels can be either pre-dilated or stented to overcome calibre constraints, and if necessary the use of a brachial to femoral artery guide wire, passed retrogradely from brachial to femoral artery and held under tension, can also aid delivery of the endograft. If all else fails, formal surgical access to the iliac vessels can be achieved to allow safe device delivery.

Selection criteria for endovascular repair
Aortic endografts
Aneurysm diameter > 55 mm or symptomatic
Neck length > 15 mm
Neck angulation < 90 degrees
Iliac vessels > 7 mm diameter
Minimal tortuosity/calcification of iliacs

Table 3: Eligibility criteria for EVAR (as of 2010)

2.6 A typical EVAR procedure

The patient will have been formally assessed and consented in preparation for surgery as if for conventional open AAA repair. Suitable radiological imaging, usually in the form of a CT will be obtained pre-operatively to enable endograft sizing. The EVAR theatre should be capable of combined radiological and surgical procedures, and requires a C-arm for intra-operative radiological imaging.

Once anaesthetised, the patient is prepped and draped, allowing access to both groins as well as the abdomen in case of conversion to open repair. A formal surgical dissection to the common femoral arteries is then performed, to allow the EVAR device catheters and sheaths to be advanced proximally into the AAA under radiological guidance. Once in position, the endograft is deployed. An additional intra-operative measure taken by this centre to minimize renal injury, (particularly infraction), and long term renal dysfunction is the angiographic imaging of the renal arteries following partial stent deployment. Whilst now commonplace, with renal artery marking on the fluoroscopy screen, this was not always traditionally performed. This allows confirmation of the correct device position prior to final deployment, and serves to reduce the incidence of partial or total renal artery occlusion. Following this, the ipsilateral and contralateral limbs are deployed, and balloon moulding is then performed to fully expand the device and ensure a tight haemostatic seal. The catheters and sheaths are then removed, and the arteriotomies closed in a routine fashion.

As per open AAA repair, an inspection of the lower limbs is performed to exclude peripheral ischaemia.

2.7 Complications following EVAR

As a minimally invasive procedure, EVAR avoids the stigmata associated with open AAA repair and major abdominal surgery, with suggested reduced rates of critical care support, myocardial and pulmonary insufficiency, and reduced recovery period. However, despite these positive attributes, EVAR has its own procedure specific range of potential complications, which have to be considered when planning EVAR.

Endoleaks

Defined simply as a 'failure to exclude the aneurysm from the circulation', endoleaks result in continued blood flow into the AAA sac, potential continued AAA sac enlargement, and delayed risk of AAA rupture (see Figure 6). Endoleaks are the most common procedure specific complication to occur following EVAR, and are broadly specified into 5 different types (see Table 4). Type 1 is the failure of the proximal or distal heamostatic seal, usually due to continued aneurysm neck dilatation or endograft migration distally. Type 2 is the result of patent aortic sac branches, usually lumbar arteries, but possibly sacral, gonadal or mesenteric arteries. Type 3 is due to endograft failure directly, with either a fracture in the metal stent structure, modular components disconnecting and separating from each other in vitro, or a tear in the endograft fabric. Type 4 is due to the fabric porosity of the endograft. Whilst continued aneurysm sac expansion typically means an endoleak is present, it can still occur in the absence of radiological confirmation. This is commonly referred to as endotension, or Type 5 endoleak, and is poorly understood. Although the aetiology is not clear, it has been theorised that direct pressure transmission by thrombus or the adjacent aortic lumen, un-detected low flow endoleak, and porosity of the stent-graft to serous fluid are to blame.

The endoleak rate following EVAR varies considerably between studies and depending on the type of endograft used. However in a systematic review of the published data on the safety and efficacy of EVAR conducted in 2005 (61 studies in total), comprising a total of 19804 EVAR patients, endoleak rates were reported as 6.8%, 10.3% and 4.2% for type 1, 2 and 3 respectively. They subsequently concluded that routine post EVAR radiological surveillance is necessary to detect these potentially significant complications[63].

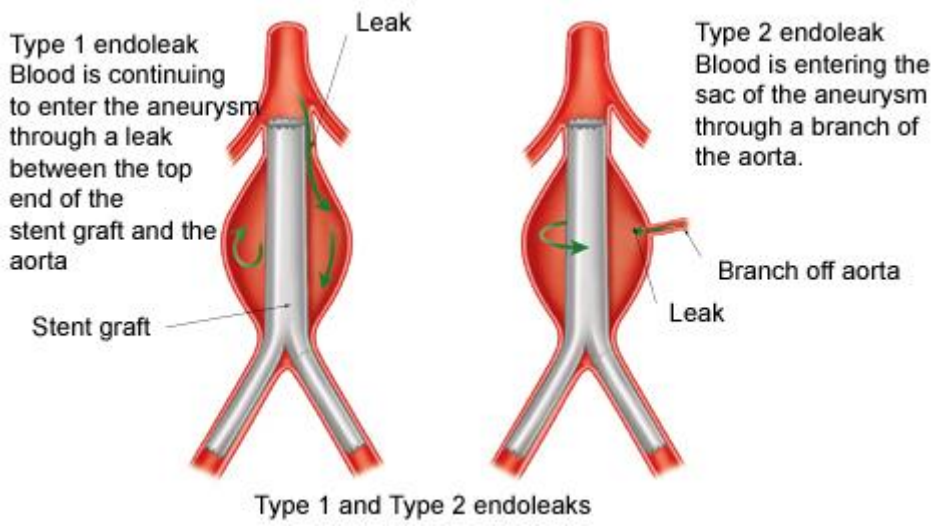


Figure 6: The two most common types of endoleak. Type 1 is typically fixed at the time of surgery with an expandable aortic cuff stent. Type 2 usually resolve conservatively, but can be treated surgically or radiologically

Endoleak type	Endoleak subtype	Source of leak
1	Proximal Distal Iliac Occluder	Endograft attachment site
2	Single vessel Multiple vessel (>2 vessels)	Collateral vessel (ie. lumbars)
3	Junctional leak Suture hole Mid endograft hole	Graft failure
4	Endograft porosity	Endograft wall
5	Endotension	Low flow endoleak Aortic lumen Thrombus Endograft porosity to serous fluid

Table 4: Classification of endoleaks

Device migration and durability

The primary aim of supra-renal endograft fixation is the reduction of device migration and subsequent haemostatic failure of the proximal seal zone by utilising the non-aneurysmal supra renal aorta. Several early studies demonstrated a decreased incidence of device migration and proximal endoleak when comparing supra-renal with infra-renal deployed endografts, but were limited by their short follow up periods and relatively small patient numbers[46, 64]. The findings of these preliminary reports have subsequently been confirmed by several larger scale studies.

The Zenith® Multicentre Trial[65] was a large study reporting on 351 patients having undergone treatment with a supra-renal Cook Zenith® endograft, and followed for up to 24 months. Risk of endograft migration >5mm at 12 months was 2.3%, (although this was higher when the endograft was oversized by >30%), and incidence of proximal type 1 endoleak at 12 and 24 months were also acceptably low. However, despite promising results, with no infra-renal deployed endografts from the enrolled centres, for direct comparison with the Zenith® endograft, it was not possible to comment completely on the superiority of the supra-renal configuration.

To overcome these drawbacks, Tonnessen et al. reported in 2005 their direct comparison of the mid to long term device migration rates between one make of infra-renal (Medtronic AneuRx®), and one make of supra-renal (Cook Zenith®) endograft, implanted in their centre over a seven year period. Minimum follow up was 12 months, with a mean follow up of 39 and 30.8 months for the infra-renal and supra-renal endografts respectively. Analysis demonstrated freedom from migration of 96.1%, 89.5%, 78.0% and 72.0% at 1, 2, 3 and 4 years respectively for the infra-renal group, (85.7% of the patients with migration requiring further intervention). The corresponding values for the supra-renal group were 100%, 97.6%, 97.6% and 97.6%, at 1, 2, 3

and 4 years respectively. The difference between the migration rates was statistically significant, and highlighted the durability benefits of supra-renal fixation for endografts[66].

These studies highlighted that device migration is a time dependent phenomenon, with a reduced risk of endograft migration when using supra-renal fixation. Since there is risk of migration many years following deployment, it is currently necessary to monitor patients with radiological imaging annually, and indefinitely.

Rarer EVAR complications

Whilst the most common complications following EVAR are endoleaks and device migration, there are a host of recognised, but rare potential complications. As can occur with open aneurysm repair, any manipulation of the aneurysm sac carries a potential risk of distal micro-embolisation affecting the lower limbs requiring embolectomy, or resulting in 'trash foot'[67, 68]. Left colonic ischaemia has also been reported following embolisation of the inferior mesenteric artery[69].

Although rare, a case of peripherally seeded mycotic aneurysms following chronic endograft infection has been reported[70].

Insertion of large calibre catheters, guide wires, and the endograft delivery instruments have resulted in delivery vessel injury (rupture and dissection), and delayed pseudo-aneurysm formation has been reported.

2.8 Current status of EVAR (and future directions)

The EVAR 1 trial[17, 71] compared open vs. endovascular repair of AAA in a multi-centre randomised controlled trial. The end-points were mortality (aneurysm related and overall), durability, cost and health related quality of life (HRQL). In total 1082 patients were randomised. The 30 day mortality for EVAR was 1.7% vs. 4.7% for open repair, and although overall mortality between the groups was equivocal by 4 years, the aneurysm related mortality was still lower for EVAR (4% vs. 7%). The HRQL was equivocal between the two groups within 6 months, although the cost for the EVAR group was significantly higher over the 4 years. This was predominantly due to the cost of the stent-grafts, and it is hoped that as endografts develop and EVAR gains greater acceptance, that costs reduce.

Unfortunately the results were not as exciting for those patients deemed surgically unfit. The EVAR 2 trial[72] compared EVAR vs. best medical treatment in those patients deemed unfit for open surgery. Ultimately following per-protocol analysis there was no benefit in favour of EVAR.

A recent EVAR 1 trial update demonstrated at long term follow up, a continuing aneurysm related mortality advantage of 3% over open AAA repair, but no significant difference in all cause mortality or HRQL. Similarly, the EVAR 2 participants demonstrated no long term improved mortality. They concluded that with the higher costs of EVAR, and similar long term mortality to open AAA repair, that patient choice should dictate treatment method in the medically fit, and that greater consideration should be given to medical optimisation pre-procedure for the medically unfit[73].

The results from the seminal EVAR Trials have helped cement EVAR as a viable and even preferable alternative to open surgical AAA repair.

Fenestrated/branched stent-grafts (FEVAR)

The most recent aortic endograft development comprises specially made endografts, with either scallops or fully covered integrated renal artery stents (see Figure 7), for the management of both short necked and juxta-renal AAA's.

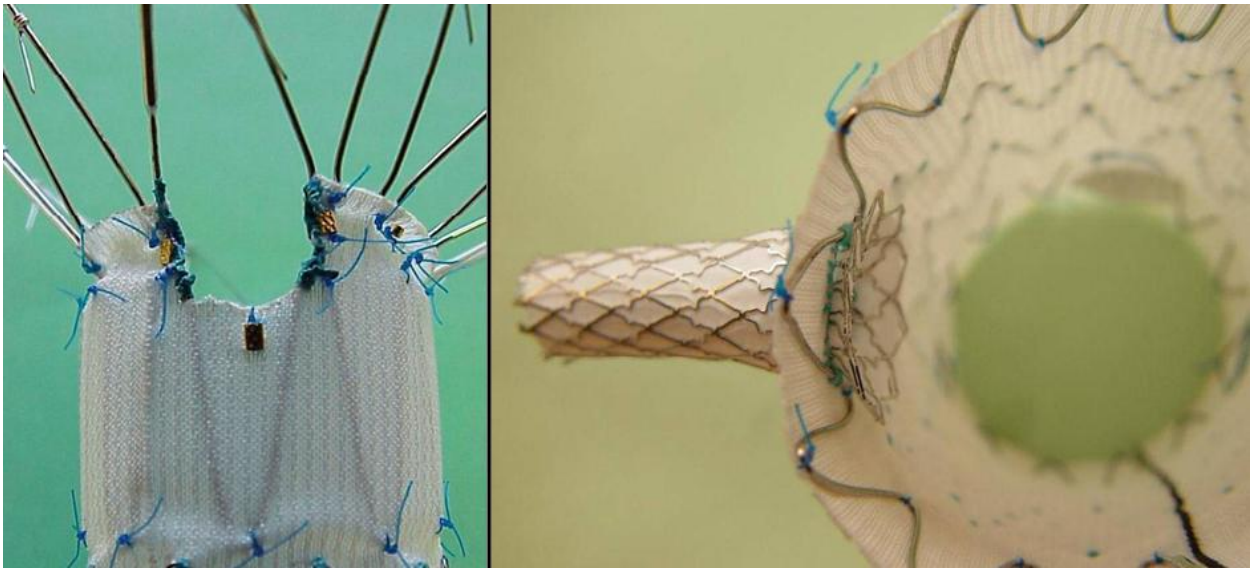


Figure 7: A scalloped endograft on the left. An endograft with a fully incorporated covered renal stent on the right.

Whilst there are no randomized controlled trials to compare their use with open repair, there are promising early results from small series of patients in specialist centres.

Anderson et al. from Australia, report on 13 patients from 1998-2000 with unsuitable infra renal necks. There was 100% deployment success, and no 30 day mortalities. Follow up ranged from

3-24 months, during which there was no endoleak and only one occlusion of a stented renal vessel[74].

Verhoeven et al. from the Netherlands, report on 18 patients with unsuitable aortic necks who are unfit for open surgery. Of the 46 targeted vessels (10 SMA, 36 renal arteries), 45 remained patent at the end of the procedure. One accessory renal artery was occluded by the stent-graft. There was one type 2 endoleak but no deaths. At mean follow up of 9.4 months, there were no additional renal complications, and all remaining targeted vessels remained patent[75].

The Cleveland Clinic in the USA have reported on 2 series of patients[76, 77]. The first included 32 patients (22 with short aortic necks and 10 with angulation or thrombus compromising neck quality). 83 visceral vessels were incorporated (most commonly renal arteries and SMA). All devices were successfully deployed. The only 30 day mortality was due to pneumonia, and endoleak rate at this time was 6.5%. There was one case of persistent type 2 endoleak, and continued aneurysmal sac growth. Mean follow up was 9.2 months, during which 6 patients had transient or permanent elevation of serum creatinine (one requiring haemodialysis), and of the 83 vessels, three late stenoses (all successfully treated), and two renal occlusions were detected. The second series focused on renal function following fenestrated EVAR (FEVAR), and involved 72 patients between 2001 and 2004 (23 patients with baseline renal insufficiency, and 49 patients without). 24 patients had deterioration in GFR >30% during the follow up period (mean 6 months, range 1-24), and 17 patients experienced 19 renal events (10 renal artery stenoses, 5 renal artery occlusions, and 4 patients required haemodialysis). Renal events and death were more common in the group with pre-operative renal dysfunction. They concluded that fenestrated endovascular repair is associated with a significant risk of adverse renal outcome

(16% in those patients with no pre-existing renal dysfunction, and 39% for those with pre-existing renal dysfunction), and that patients must be followed closely (with renal duplex ultrasound and CT), particularly in the first month post procedure.

In general the development of fenestrated and branched endografts has been slower than that of standard endografts for AAA's. This is in part due to their relative rarity of juxta-renal aneurysms compared to AAA's, and the greater complexities and costs involved in their manufacture. Recently Cook®, one of the major manufacturers of endografts have produced a fenestrated Zenith® endograft at a significantly reduced cost, making the routine endovascular treatment of juxta-renal aneurysms, or aneurysms with short necks, a viable and potentially cost effective option for the future.

EVAR for ruptured AAA's

To date the use of EVAR for the treatment of AAA rupture has involved only small series of patients or individual case reports. The lack of data and seeming indifference to open surgical repair has led to considerable controversy in this subject. It has been suggested that only 20% to 42% of AAA ruptures would be suitable for EVAR based on anatomical neck features[78] [79]. Combined with the need for the patient to be haemodynamically stable to enable pre-procedure CT scanning, it is currently unclear as to how many patients would be eligible for EVAR.

In a review of all the available literature on EVAR for ruptures, peri-operative mortality ranged from 9-45%, and of the 91 cases reported, there were 7 peri-operative endoleaks (two Type 1 and five Type 2), 15 incidents of renal failure, and hospital stay ranged from 2-70 days. The results were comparable to those for open repair[80].

Peppelenbosch et al. report similar finding from their international multicentre study using the Talent AUI stent-graft. Of the 49 treated patients, operative blood loss, ICU admission times, and duration of mechanical ventilation were all statistically significantly shorter than for open repair. However, the 30 day mortality was 35% and 39% for EVAR and open repair respectively, and the 3 month all cause mortality was 40% and 42% respectively. There were no statistically significant differences in mortality between the operative methods[81].

Inconclusive results from studies like these have lead many to question the value of EVAR for AAA ruptures.

There is still no consensus as to which stent-graft is best in EVAR for ruptures, but many advocate the use of AUI's, as they only require cannulation of one iliac system to exclude the aneurysm, enabling completion with femoral-femoral crossover once haemodynamic stability is restored. The occasional difficulties in cannulation and attaching the short limb in modular stent-grafts can lead to increased exposure to haemorrhage from rupture.

The current logistical requirements of a dedicated endovascular suite with available and appropriately trained vascular surgeons, interventional radiologists, anaesthetists, CT personnel and theatre staff all acting in co-ordination, has so far meant that EVAR for ruptured AAA's has been confined to specialist vascular centres.

Chapter 3. The assessment of renal function

3.1 Glomerular filtration rate and the clearance concept

The excretion of soluble waste products by the kidney is achieved by glomerular filtration. In reality few metabolites and exogenous compounds are secreted by the renal tubules, and regulation of the fluid composition in the body is achieved almost entirely by variations in the tubular absorption or secretion of individual components.

Renal insufficiency is defined simply as a reduction in the glomerular filtration rate (GFR). Therefore in order to assess renal function it is important to have an accurate, reproducible and reliable measure of the GFR. This is achieved in principal using the clearance concept[82]. This states that if a substance is freely filtered at the glomerulus and is not re-absorbed or secreted by the renal tubules, or modified by the kidney following filtration, then the quantity of that substance that appears in the urine per unit time, equals the quantity of substance that is filtered at the glomerulus. This is represented mathematically as:

$$C \times Pi = Ui \times V$$

Where C is the volume of plasma filtered at the glomeruli per unit time (or the volume of plasma that is completely cleared of the indicator/substance per unit time), Pi the concentration of the substance in the plasma, Ui the urinary concentration of the substance, and V the urinary flow rate.

For an ideal substance C = GFR, and therefore:

$$GFR = \frac{Ui \times V}{Pi}$$

There are two non toxic substances which fulfil these ideal criteria. They are both fructose polymers extracted from plants, called inulin and polyfructosan. Neither substance is endogenous in humans, and must therefore be continuously infused throughout the GFR measurement. In practice this involves administration of a bolus (adjusted to patient weight), followed by infusion at a constant rate to achieve stable plasma concentration (about 1 hour). The patients are also supplemented with an oral water load and periodic water to ensure adequate urine flow rate (ideally > 2ml/min). Once a stable plasma concentration of indicator/substance has been achieved, the patients empty their bladder completely, and urine samples are then taken at regular intervals (typically 30-60 minutes). The plasma concentration of the indicator/substance is measured at the beginning and end of each period of urine collection. To minimise error, typically three to five determinations are made.

3.1.1 Problems with the clearance concept

Plasma concentration

Administration of exogenous substances (inulin/polyfructosan) requires an accurate infusion pump to maintain constant plasma concentrations, and waiting for the infusion to reach a steady concentration is time consuming.

This can be countered with the use of endogenous substances, such as creatinine. This is a metabolic product of creatine and phosphocreatine, both of which are found almost exclusively in muscle[83]. However, whilst the plasma concentration of creatinine is relatively constant, and

displays little variation throughout the day, it is directly related to patient muscle mass and dietary protein intake[84], and its production can be reduced in patients with hepatic disease[85].

Urine collection

The most significant disadvantage of the clearance concept is the need for a measurement of the urinary flow rate, and subsequently a timed urine collection must be made. In practice the easiest way to achieve this is by passing a urinary catheter. Due to the general reluctance to catheterise patients with no direct clinical need, timed urine collections following induced dieresis are typically used.

When performed on an unsupervised basis (such as in the outpatient setting), achieving complete and accurately timed urine collections is paramount. Typical difficulties encountered include: lost specimens, inaccurate timing such that the sample supplied does not correspond to a 24 hour collection period, and inclusion of urine already in the bladder at the start of the monitoring period. In addition, patients with urinary tract abnormalities or reflux may not be able to provide sufficient samples. The collection of urine samples in children poses its own difficulties and restrictions.

Glomerular filtration rate and relationship to patient size

One further significant problem with GFR estimations, is the physiological variation of GFR in healthy individuals of different ages and sizes[86]. It is widely accepted that renal data should be corrected for body surface area, using tables of height and weight, with an adult male surface area of 1.73 m^2 used as standard. This assumes that GFR increases as a linear function of body surface area. Obesity, oedema or anorexia can result in either under- or over-estimation of GRF

due to variation in weight, and subsequently ideal weight for height is used instead. Thus GFR is in essence expressed in terms of height only.

When creatinine is used as the indicator, there are additional concerns as creatinine excretion, varies widely with body composition, in particular muscle mass, resulting in potentially incorrect estimations of GFR.

3.1.2 Creatinine clearance and GFR

Since the suggestion that endogenous creatinine clearance can be used instead of inulin or polyfructosan clearance, and that it equates to the GFR, this test has been popular in clinical practice. However, several inconsistencies in its use compared to the exogenous substances arise. They are due to variations in the production rate of creatinine, the accurate plasma analysis of creatinine and collection of urine samples, and the secretion of creatinine by the renal tubules[87].

Creatinine production

Creatinine is produced by the non-enzymatic degradation of muscle creatine, which is synthesised in the liver and transported to muscle[88]. The main determinant of an individual's creatine level is their muscle mass, with only a small proportion derived from dietary products (ie. meat). The production and consequent excretion of creatinine is therefore directly influenced by muscle wasting conditions, paralysis and of course dietary intake.

Plasma creatinine measurement

Due to the routine use of creatinine in the assessment of renal function, and in particular the estimation of GFR, it is important to understand the principal of the creatinine assay.

Creatinine is usually measured using the Jaffé reaction (see Figure 8). This involves reacting creatinine with alkaline picrate to form an orange-red coloured Janovsky complex[89].

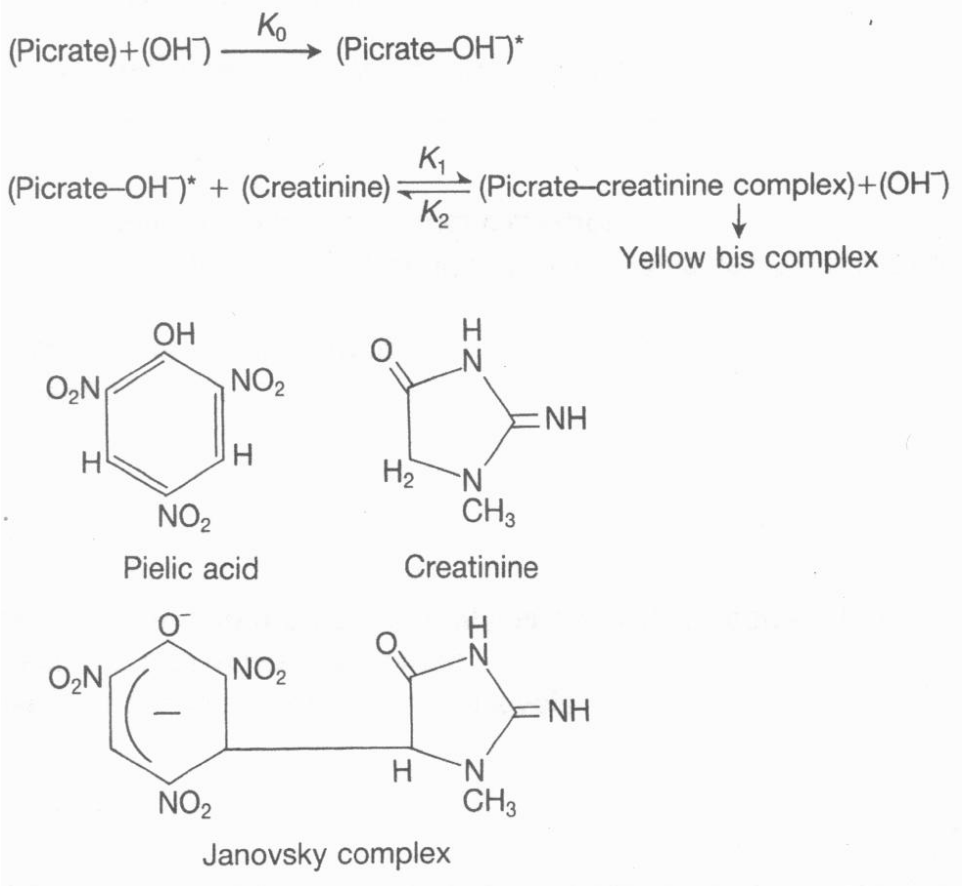


Figure 8: The reaction of creatinine and picrate under alkaline conditions to form a Janovsky complex; the basis of the Jaffé reaction.

Unfortunately the creatinine concentration is generally overestimated in plasma, with consequent underestimation of creatinine clearance. This is because other chromogens which react with alkaline picrate, are present in plasma, and produce a similar colour to the Janovsky complex[89].

This is particularly pronounced at low creatinine concentrations, and so the greatest effect is seen around normal creatinine values. To overcome this effect, the unwanted chromogens can be absorbed using Fuller's earth or resins[89], or more commonly dialysed off. Alternatively rate-dependent reactions can be used, based on the fact that the reaction of creatinine with picrate occurs faster than that of non-creatinine chromogens.

Factors affecting creatinine plasma concentration and clearance

When infused, creatinine is secreted by the renal tubule and usually the creatinine clearance equals or exceed the GFR (when accurately measure with inulin clearance techniques)[90]. More importantly is that this concept of increasing creatinine clearance to GFR steadily increases as the GFR falls and the plasma creatine rises, to the point that creatinine clearance may be more than twice the inulin clearance[90]. Thus overestimation of the GFR by creatinine clearance increases proportionally as the GFR declines.

Creatinine re-absorption is not usual in humans, but can occur in states of low urine flow, such as congestive heart failure[91]. Further, it has been suggested that in the presence of significant proteinuria, the creatinine clearance can be significantly elevated[91]. Additionally, following the ingestion of meat subjected to prolonged stewing, it has been shown that the plasma concentration of creatinine can suddenly double[92]. The stewing of the meat converts the creatine to creatinine, and so in effect a creatinine meal is ingested. The effect is not reproduced by other methods of cooking meat, or with non-meat proteins.

Creatinine clearance is directly affected by muscle mass changes, resulting in observed changes in estimated GFR. It has been demonstrated that urinary creatinine equilibrates three weeks

following a change in muscle mass[93], making urinary creatinine unreliable for patients on different diets or when taking alternating levels of proteins.

All of these factors combine to make creatinine clearance estimation through plasma and urine analysis unreliable in clinical practice.

3.1.3 Plasma creatinine levels as an indicator of GFR (Cockroft and Gault formulation)

Due to the difficulties of measuring inulin/polyfructosan clearances and obtaining accurately timed urine collections for creatinine clearances, the use of plasma creatinine to derive GFR has gained widespread clinical use.

Unfortunately the relationship of plasma creatinine and GFR is non linear, such that for small reductions in GFR, plasma creatinine is a poor index of GFR, just where precision is needed most. Additionally, whilst GFR and creatinine clearance fall steadily with age, there is no corresponding rise in plasma creatinine, with levels substantially unchanged throughout adult life[94]. Due to these relative imprecisions, the estimation of GFR from plasma creatinine has limitations.

Plasma creatinine also tends to overestimate the GFR at all levels of renal function, even in the presence of enhanced creatinine secretion with reduced GFR. Due to creatinine losses in the gastrointestinal system, and secretion of creatinine in the renal tubules, plasma creatinine will tend to overestimate the GFR in patients with reduced renal function[90]. Despite these limitations, plasma creatinine remains a popular test of renal function, principally due to its simplicity and wide availability.

Instead of using graphs to derive creatinine clearance and consequently GFR from plasma creatinine, several formulae have been developed to enable immediate and easy estimation of GFR. These are typically in the form of creatinine clearance, derived from plasma creatinine levels.

The most widely used and most validated is the Cockroft and Gault formula[95]:

$$\text{CrC (ml/min)} = 1.2 \times \frac{[140 - \text{Age (years)}] \times \text{Weight (Kg)}}{\text{sCr (umol/L)}}$$

Ideally plasma creatinine should be analysed by an automated process, and a correction factor of 0.85 should be applied for women due to smaller creatinine production.

However it should not be forgotten that estimation of GFR for plasma creatinine has multiple limitations, with estimation particularly unreliable in the old and the very obese, for reason discussed previously.

3.2 Other markers for the estimation of GFR

ß2-microglobulin

The kidney plays an important role in the disposal of peptides and small molecular weight proteins. This is principally by unrestricted filtration at the glomerulus, with pinocytic re-absorption in the tubule and catabolism to the constituent amino acids. Therefore a large number of peptides accumulate in the plasma when renal function falls. ß2-microglobulin is a small molecular weight protein that is freely filtered at the glomerulus, meaning the plasma concentration in health is low[96]. This plasma concentration rises as the GFR falls in a linear relationship throughout the whole range of values, making it an excellent marker in renal dysfunction[97]. The plasma concentration of ß2-microglobulin is not affected by muscle mass, sex or age as occurs with creatinine[97].

The principal reason for its lack of widespread clinical adoption has to date been the relative expense of the radioimmunoassay needed to measure its levels. Secondly, whilst the turnover of ß2-microglobulin is relatively constant in most patients, in those with lymphoid tissue tumours and some inflammatory conditions such as rheumatoid arthritis, there may be increased plasma concentrations due to increased production rather than reduced clearance[98].

Radionuclides

Several radiolabelled chelates have been used to assess GFR in humans. Chief amongst them is $^{99}Tc^{m}$-DTPA (diethylene thiamine penta-acetic acid)[99]. They can be used as inulin substitutes in conventional infustion assessments of GFR. However most use avoids urine collections and infusions, and centres on boluses being given, followed by analysis of the disappearance curve

from the plasma measured using gamma cameras. However, the need for bolus infusion, access to expensive equipment, and exposure to ionising radiation, limits these studies from widespread clinical use.

More recently, Cystatin C has gained popularity as an alternative endogenous marker of GFR

3.3 Cystatin C

Clinically, plasma creatinine and the calculated creatinine clearance are widely used as markers for GFR. The primary benefit is that they are cheap, and there is widespread availability to creatinine analysis on a routine basis. However, the accuracy of estimation of GFR with these methods is decreased by alterations in the metabolism and renal handling of creatinine, and the laboratory analysis of creatinine[100]. As previously stated, the ideal marker for GFR calculation should be endogenous, appear in the plasma at a constant rate, be freely filtered at the glomerulus, be neither secreted or absorbed by the renal tubule, and undergo no extra-renal elimination. A fast, reliable, and safe method of estimating the GFR is of significant value in clinical and research practice. Previous methods as previously discussed have many disadvantages. The low molecular weight protein Cystatin C meets many of these criteria, and in recent years developments have enabled Cysyatin C to be measured in a routine, accurate and reproducible method for clinical use[101].

3.3.1 Cystatin C structure

Cystatin C is one non-glycosylated polypeptide chain containing two disulphide bridges with 120 amino acid residues (see Figure 9), and a molecular weight of 13.359 kDa[102]. The entire nucleotide sequence of the Cystatin C gene has been mapped and localised to chromosome 20, and has a stable production rate by most nucleated cells[103, 104]. Due to the low molecular weight Cystatin C is freely filtered at the glomerulus and reabsorbed and catabolised in the proximal tubule[105]. The urinary concentration of Cystatin C is therefore typically low.

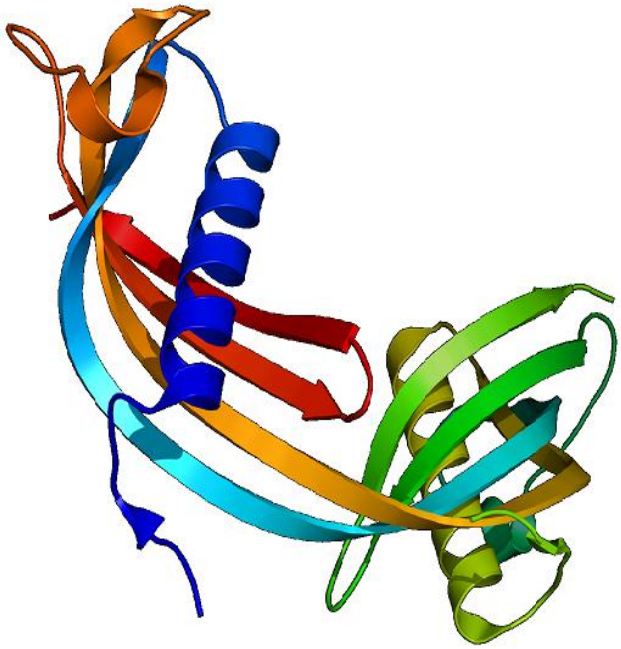


Figure 9: A Protein Data Bank (PDB) 3-D rendering of a molecule of Cystatin C

3.3.2 Role of Cystatin C

Cystatin C is a proteinase inhibitor from the Family 2 of the cystatin superfamily[106]. It is present in all human biological fluids, with particularly high concentrations in seminal plasma and cerebrospinal fluid[106, 107]. The primary function appears to be protective, with prevention of degradation of connective tissue by intracellular enzymes leaking from dying cells[108].

Additionally Cystatin C has been demonstrated to play a role in the defence against both microbial and viral infections[109, 110].

3.3.3 Stability and storage of Cystatin C

Plasma samples can be stored without degradation for up to seven days at room temperature, in a fridge, a freezer (-20°c), or up to six months in a freezer (-80°c)[111]. It is possible to prevent further degradation with the addition of proteinase inhibitors and preservatives.

3.3.4 Factors influencing Cystatin C

Cystatin C does not appear to be an acute phase reactant, with no discernible change in the rate of production of Cystatin C in patients with acute inflammatory conditions[112].

Although it was originally felt that Cystatin C levels were not affected by malignancy, recent evidence had shown raised serum levels in the presence of melanoma[113].

There is currently no evidence to suggest that drugs used in clinical practice affect the plasma levels of Cystatin C, although in vitro studies have demonstrated a dose dependent increase in Cystatin C production following dexamethasone administration[114].

The principal benefits of Cystatin C over creatinine, is that its concentration in plasma can be interpreted in the absence of correction for age, height, weight and gender. Its serum concentration is also unaffected by dietary intake, and analysis is not affected in general by interfering factors in plasma.

Cystatin C levels in plasma are therefore more reliable than sCr, due to fewer influencing factors.

3.3.5 Cystatin C assays

For accurate clinical use, Cystatin C assays must be automated for ease and free from interfering factors, which as previously discussed can compromise accurate creatinine estimation.

The first estimation of Cystatin C occurred in 1979, and utilised immune-electrophoresis[107]. This was a complicated procedure using enzyme amplified single radial-immuno-diffusion, and took approximately two days to complete. Whilst accurate, there were too slow for realistic clinical use.

It was not until 1994 that a suitably accurate, easy to perform, and quick automated assay for Cystatin C was introduced. This was the development of the latex-particle enhanced immune-turbidimetric assay (PETIA)[101]. This was quickly followed by the latex-particle enhanced nephelometric immunoassay (PENIA)[115].

These assays are precise, rapid and easy to perform for routine clinical practice. No interferences with other plasma factors have been reported, although there is a suggestion that bilirubin levels may affect the accuracy of PETIA[101].

3.3.6 Cystatin C and renal function

Serum Cystatin C was first suggested as a marker of GFR in 1985, where serum Cystatin C levels were found to be as closely correlated to GFR as serum creatinine[116]. More recently, using immunoassay techniques the degree of correlation between a reference GFR procedure and reciprocal Cystatin C concentration in plasma, has been shown repeatedly to be superior to that of creatinine concentration[117-119]. Additionally, several studies suggest that Cystatin C may in fact detect subtle early renal injury before developing clinical significance, or detection by sCr assays, with a reduction in GFR of only 30% needed to produce a doubling of Cystatin C[120, 121].

For these reasons, Cystatin C is being used increasingly instead of creatinine as an accurate marker of GFR in a variety of clinical studies.

Although Cystatin C is an accurate marker of established and evolving renal failure, there has been considerable interest recently in acute phase biochemical renal function markers, in particular neutrophil gelatinase-associated lipocalin (NGAL). Its ability to detect early renal dysfunction prior to overt clinical features, or rise in conventional biochemical markers has gathered most interest.

3.4 Neutrophil Gelatinase-Associated Lipocalin

NGAL is a member of the lipocalin family of proteins. The lipocalins are typically small secreted proteins, with an ability to bind small hydrophobic molecules in a structurally conserved pocket formed by B-pleated sheet, to bind to specific cell surface receptors and form macromolecular complexes. NGAL is also commonly known as lipocalin 2, oncogene protein 24p3, NL (neutrophil lipocalin), and HNL (human NL).

Human NGAL consists of a single disulphide bridged polypeptide chain of 178 amino-acid residues (see Figure 10), with a calculated molecular mass of 22 kDa, but glycosylation increased its apparent mass to 25 kDa[122].

In neutrophils and urine it occurs as a monomer, with a small percentage of dimer and trimer, and also in complex with 92-kDa human neutrophil type IV collagenase [matrix metalloproteinase-9 (MMP-9)][123].

NGAL was originally isolated from activated human neutrophils[122], but it is also expressed at low levels in other human tissues, including the kidney, prostate, respiratory and alimentary tract epithelia[124, 125]. It is strongly expressed in adenomas and inflammatory bowel epithelia[126], adenocarcinomas of the breast[127] and urothelial carcinomas[128].

Because of its small molecular size, and ability to resist degradation, NGAL is readily excreted and detected in the urine. Urinary levels correlate directly with plasma /serum levels whatever the cause for increased NGAL production.

Whilst the functions of NGAL are not fully understood, it appears to be upregulated in cells under stress, such as from infection, inflammation, ischaemic change or neoplastic transformation.

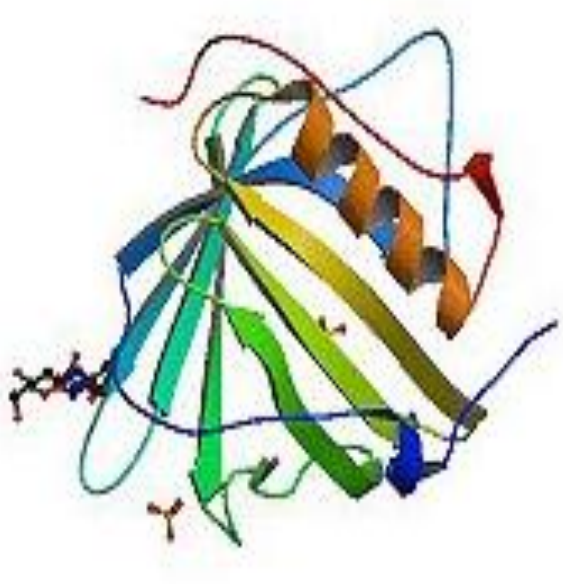


Figure 10: A Protein Data Bank (PDB) 3-D rendering of a molecule of NGAL

3.4.1 NGAL and the kidney

Dramatic upregulation of NGAL was first observed in rat proximal tubule cells after ischaemia re-perfusion injury, indicating that NGAL may be a marker of acute renal injury. Subsequently raised plasma levels were found to strongly correlate with decreased renal function in patients with vasculitis[129] and renal injury following nephrotoxic agents[130]. Further studies observed that urinary NGAL levels may serve as an early marker for ischaemia related renal injury in children following cardiopulmonary bypass[131], and raised urinary and serum NGAL levels have also been

observed in patients with established renal failure, and in patients with acute renal failure following renal transplantation[132].

Consequently a variety of renal disorders have been shown to be associated with raised plasma and urinary NGAL levels, with plasma and urinary levels closely correlated in acute conditions. It is speculated that renal expression of NGAL, and thus urinary and plasma levels, will be dramatically increased following renal injury sufficient enough to result in acute renal failure, acute tubular necrosis or acute tubule-interstitial nephropathy.

NGAL levels typically rise within two hours of the renal insult, peaking up to 48 hours, before gradually returning to baseline levels, making NGAL an early and sensitive biochemical marker for acute renal injury.

3.4.2 Collection of NGAL and assay procedure

Determination of NGAL requires 10 μL of plasma, serum or urine. Blood samples are collected into EDTA tubes, and then spun in a centrifuge to component parts. Specimens can be stored indefinitely at -80°c.

A 96 well pot and ELISA reader are required for assay, and all component parts are supplied in a pre packed AntibodyShop NGAL rapid ELISA test kit® (see Figure 11). The assay can be performed in less than 1 hour (see Figure 12).

Figure 11: NGAL Rapid Elisa Kit®, Antibody Shop, USA

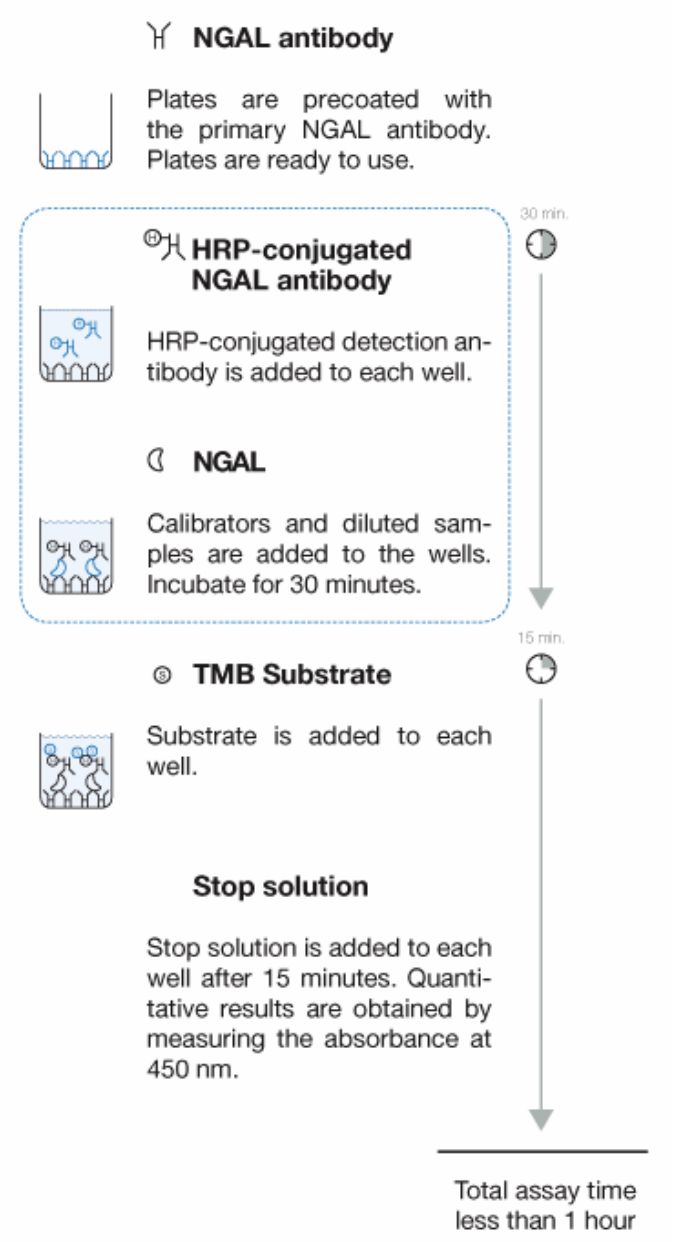


Figure 12: The NGAL assay protocol

3.4.3 Interpreting NGAL results

For calculation of results the exact values of the calibrators printed on the quality control certificate should be used. The finding of a raised NGAL level cannot be independently diagnostic of any single pathology, since a variety of independent pathologies are associated with raised levels of NGAL, although it is highly suggestive of renal dysfunction.

Raised NGAL levels are associated with renal failure as demonstrated (see Table 5). Therefore an NGAL concentration >400 ng/ml in plasma is highly likely to be due to renal injury, that may result in acute renal failure. NGAL levels lower than this may indicate either no or slight renal injury. A sudden rise in NGAL levels above previous values may indicate renal injury, even when the cut-off value is not exceeded, and close surveillance of renal function is recommended.

Sample	**Plasma**
Cutoff value	400 ng/ml
Diagnostic specificity	96.3%
Diagnostic sensitivity	84.8%
Positive predictive value	93.1%
Negative predictive value	83.9%

Table 5: Interpreting NGAL results

Chapter 4. Long term renal function following EVAR (Study 1 & 2)

4.1 Introduction

Endografts have evolved considerably in the 20 years since Parodi and colleagues described the endovascular repair of an AAA[15]. Some first generation endografts were prone to stent fracture and subsequent device migration, resulting in failure to exclude the AAA[32, 33, 35]. This has led to several technical modifications in endografts with an aim to improve overall outcome.

Perhaps the most significant technical modification to the current generation endografts has been the addition of uncovered bare metal stent struts that extend beyond the fabric covered graft proximally and cross the renal ostia. This allows the fabric covered graft to sit just below the renal arteries, covering the full length of the aneurysm neck, and the stent struts to utilise the non-aneurysmal proximal aorta. Both these factors enable a more secure proximal fixation, preventing device migration[46]. By utilising the non-aneurysmal proximal aorta they also allow treatment of patients with short aneurysm necks[58].

The impact of crossing the renal ostia has led to considerable concern regarding renal blood flow, and subsequent possible renal damage, with many early studies suggesting high levels of renal infarction and renal failure in the immediate post operative period[50, 133]. This has resulted in much controversy and ongoing research to assess renal safety, especially with regard to long term renal safety.

Current research suggests that short to medium term renal function is not significantly altered following trans-renal endograft deployment[43, 44, 50-56, 134], however further work is need to determine long term renal safety.

Although these studies demonstrate no clear evidence of adverse renal events to date, the biochemical assessment has relied almost exclusively on sCr and the Cockroft-Gault derived CrC (see Chapter 3).

Several studies have demonstrated the weaknesses of sCr and the Cockroft-Gault derived CrC in the assessment of renal function, and that renal function (GFR) may in fact have to decrease by up to 50% prior to any detectable change in sCr[117, 120].

Recently the low molecular weight protein Cystatin C has been validated as a superior endogenous renal marker to sCr. Several studies suggest that Cystatin C may in fact detect subtle early renal injury before developing clinical significance, or detection by sCr assays, with a reduction in GFR of only 30% needed to produce a doubling of Cystatin C[120, 121].

Cystatin C may therefore demonstrate previously undetected subtle renal dysfunction in the mid to long term for patients who have had SR-EVAR, but for whom the standard measurements of sCr and CrC are unchanged.

These studies aim to directly compare delayed renal function following SR EVAR with IR placement, using the conventional measurements of sCr and CrC, and to assess renal function following EVAR using Cystatin C as a more sensitive marker of renal function. Additionally they aim to confirm Cystatin C as a valid marker of renal function (GFR) in the aneurysm population.

4.2 Patients and methods

Study 1

One hundred and eighty patients consecutively undergoing EVAR for AAA at this centre over a six year period (1995-2001), were identified from a prospectively maintained EVAR database detailing basic information such as patient identifier details, date of operation, and type of EVAR device used. Patients were grouped according to the level of proximal fixation of the EVAR, either infra-renal (IR) or supra-renal (SR). The type of proximal fixation used was primarily due to availability of endografts at the time of the procedure, and not secondary to patient co-morbidities or aneurysm morphology. Most of the earlier deployments consisted of IR grafts, with later deployments comprising SR grafts, which gained favour as the endograft modality of choice at the Northern Vascular Centre. Those patients unsuitable for IR EVAR prior to the introduction of SR endografts had simply been offered open AAA repair. Therefore the groups were in essence deployed in chronology, with SR deployment tending to follow IR.

The case notes for every patient were retrieved, and reviewed exhaustively. A separate database was constructed containing full data with respect to each patient. Patient demographics such as age, sex, ASA grade, co-morbidities, tobacco use, initial AAA size, renal function pre-operatively, and operative factors such as operation length, blood loss and contrast load were recorded, as well as any interventions or complications in the post-operative period. All patients had been recalled on at least a yearly basis following their procedure, and had undergone blood sampling for renal function analysis, allowing annual assessment of renal function up to 10 years to be included in the constructed database. If the biochemical renal markers were not clearly documented in the notes, then a review of the Northern Vascular Centre's computerised

pathology results programme, allowed their determination at the appropriately documented follow up collection time point. The data was collected in this manner (from a single source), to ensure validity and minimise the potential for error. As a historical record of a patient's treatment, created at the time of treatment by physicians, the case notes are the most reliable form of documentation for each aspect of treatment and follow up care. All renal markers sourced from the computerised pathology results programme had been produced in a validated and accredited NHS Hospital pathology laboratory, and were matched to the specific follow up time points.

Between 2006-2007 (the period of the study), all patients still attending their yearly follow up were approached, provided with an information sheet (see Appendix B & C), and invited to enrol in the study. Consent was obtained (see Appendix E) for the purpose of blood analysis of renal function, and case note review for the purpose of publication. Those patients who failed to attend their yearly appointment, were contacted where possible, and arrangements were made for them to attend the out-patients for review at a time of their convenience. A single blood test was taken for the purpose of sCr measurement and CrC calculation to assess renal function up to 10 years following EVAR.

All patients having undergone successful EVAR between 1995-2001, were considered eligible for inclusion into this study. The only exclusion criteria were complete absence of paired renal data at any time point (such as lost to follow up), conversion to open AAA repair at time of original operation, and if there was less than 12 months renal follow up post-procedure.

Full ethical approval for the study was granted by the Northumberland Local Research Ethics Committee, reference 06/Q0902/40.

Study 2

This study was a continuation of a previous prospective controlled trial performed at the Northern Vascular Centre (Freeman Hospital, Newcastle, UK) during a twelve month period commencing 2002 (Newcastle & North Tyneside JEC ethics approval 2002/150)[135].

During the initial study period, all patients had been participants in the EVAR-1 Trial[17], and as such had been randomised to either Open AAA repair (OR) or EVAR as per the EVAR- 1 trial protocol. This simply meant that any patient medically fit enough for an open AAA repair had a 50: 50 chance of either EVAR or OR, with randomisation occurring centrally at the EVAR Trial headquarters, and not at the Northern Vascular centre. All consecutive patients undergoing AAA repair during this twelve month period were approached for inclusion into the study, with only pre-operative renal failure requiring replacement therapy precluding enrolment. Patients were followed for a twelve month period during which serial blood tests for analysis of sCr, CrC and CC were taken at 3,6 and 12 months. At enrolment to the study, patient factors recorded included sex, age, weight, smoking habit, AAA size and significant co-morbidities. EVAR related procedural variables included device type, deployment success and contrast load. During the initial study no significant difference was found between groups with respect to Cystatin C and renal function[135].

All patients enrolled in the initial study were subsequently followed up on a yearly basis following surgery, as per EVAR-1 Trial protocol[17]. Between 2006-2007 all original patients still attending follow up were approached (corresponding to their fourth year of follow up), provided with an information sheet (see Appendix A), and consented (see Appendix E) for blood analysis of renal function and CC, and case note review for the purpose of publication. Following case

note review a database was created containing general patient demographics (age, sex, co-morbidities, tobacco use and aneurysm size), as well as contrast load used intra-operatively. Those patients who failed to attend their yearly appointment, were contacted where possible, and arrangements were made for them to attend the out-patients for review at a time of their convenience.

A single blood test was performed allowing analysis for sCr, CrC and CC for the purpose of renal function assessment.

Renal function was recorded using sCr was analysed on an Olympus 2700 multi channel analyser (Jaffé reaction based) using the manufacturers supplied reagents, providing a between batch imprecision of less than 2% for each analyte. Considered a routine blood test, analysis of sCr was performed by the Pathology Laboratory staff at the Northern Vascular Centre.

Creatinine clearance (CrC, ml/min) was calculated using using the validated Cockroft-Gault formula[95]:

$$\text{CrC (ml/min)} = 1.2 \times \frac{[140 - \text{Age (years)}] \times \text{Weight (Kg)}}{\text{sCr (umol/L)}}$$

A gender correction factor (multiplication by 0.85) was applied for female patients.

Cystatin C was analysed with PETIA (latex particle enhanced immunoturbidimetric assay). A clotted blood sample was collected, then spun for 10 minutes at 3000 rpm. Serum was withdrawn and stored at -80°C for later batch analysis. CC was determined by PETIA using the Cobas MIRA Plus automated analyser®. The DAKO Cystatin C PETIA kit® contains polystyrene

particles chemically coupled with rabbit antibody against human CC. When these immunoparticles and CC react, agglutinates form with a concomitant change in the absorbance signal at 340 nm. The CC concentration can then be determined via a calibration curve with a typical coefficient of variance of less than 8%. The assay is rated with a specificity of 96.3%, positive predictive value of 93.1%, and a negative predictive value of 83.9%. Determination of CC was performed by the principal investigator under the direct guidance of Dr. R. Peaston, Senior Biochemist (Northern Vascular Centre, Newcastle, UK), and was performed in the pathology laboratories of The Northern Vascular Centre. There was no blinding to the assay.

Full ethical approval for the study was granted by Northumberland Local Research Ethics Committee (reference 06/Q0902/40).

4.3 Data analysis

All data was anonymised and initially stored within a Microsoft Excel® Spreadsheet on a password protected NHS Trust computer, with access granted only to the primary investigator and research supervisor. Relevant data was transferred as necessary to Minitab 14® (Minitab Inc., PA, USA) statistical software for statistical and graphical analysis.

Median values were used for continuous variables, and means for non-continuous variables. Renal data is represented by box and whisker plots, with boxes representing inter-quartile ranges, the intervening bar representing the median value, and whiskers representing the 90% range.

For serial comparison of renal function two statistical methods were employed. The 1- sample Wilcoxon Test compared non-parametric continuous variables (such as within groups), and the Mann-Whitney U-Test compared 2 sample non-parametric variables (such as between groups). A Bonferroni correction factor was used for both when repeated analysis was made.

The 2-sample t-test was employed for comparison of continuous variables. Observational comparisons with non-continuous data were made using the chi-square test.

Change in CrC over time between the two groups (change in renal function over time), was compared using the technique of summary measures (co-efficients of the change in CrC over time), and data was compared at each time point using the 2-sample t-test.

Linear regression was used when appropriate to assess the association between variables, with the relationship strength given by the Pearson correlation co-efficient, r.

Results were considered statistically significant if $p<0.05$, with NS meaning not statistically significant.

Population sizes needed were calculated based on a difference between groups of one standard deviation (20 umol/L and 0.18 mg/L for sCr and CC respectively), being clinically significant. This would equate to a difference in the biochemical renal markers of approximately 20% between groups, or 20% increase above baseline values, a level which most studies consider clinically significant. When powered to 80%, the required numbers for each group in both study 1 & 2 to gain significance are 17 patients.

Data set completeness was achieved for missing data (ie. those patients lost to follow up), by comparison of the pre-operative demographic data (see Chapter 4.2), and rates of re-intervention following surgery at each specific time point for the remaining patients. If there were more than 17 patients in each group and the above data was comparable, with no statistically significant differences between the groups at that time point, then comparison of renal function was made between the groups.

All statistical methods employed were discussed with and approved by with Professor Matthews (Department of Mathematics and Statistics, University of Newcastle upon Tyne, Newcastle, UK) as part of the application and enrollment procedure for entry to the M.D. programme.

4.4 Results

Study 1

During the 6 year study period one hundred and eighty EVAR's were performed. There were 88 IR endografts, and 92 SR endografts deployed. Paired renal data was available for one hundred and thirty patients in total, with the number of patients with paired renal data decreasing on an annual basis from time of EVAR (see Table 6).

Time interval since EVAR (months)	IR(n)	SR (n)
0	88	92
12	58	46
24	50	38
36	24	26
48	24	23
60	22	21
72	21	20
84	20	20
96	13	5
108	11	1
120	6	0

Table 6: Group specific number of patients (n) with paired renal data at annual review following EVAR

IR endografts were from a variety of manufacturers, but the majority were Boston Scientific Vanguard® devices, whereas SR devices were exclusively Cook Zenith® devices (see Table 7).

Group specific demographics as well as aneurysm size, ASA grade, operation length, blood loss, contrast load, follow up length, and pre-operative sCr and CrC are reported (see Table 8). Both groups were comparable in respect of demographics, and operative factors, although there was a statistically significant longer follow up period with the IR group ($p<0.05$, 2-sample t-test), reflecting the earlier availability of these endografts compared to SR. There were no statistically significant differences between the groups with respect to renal risk factors (age, co-morbidities, pre-existing CRF), or operative factors predisposing to long term renal failure (operation length, contrast load, blood loss) (all p=NS, chi-square test).

Device type	IR Group	SR Group
Vanguard (Boston Scientific)	49	-
Talent (Medtronic)	12	-
Excluder (Gore)	8	-
Mintec	6	-
Endologix (Powerlink)	5	-
EVT	4	-
Zenith (Cook)	-	92
Totals	88	92

Table 7: Group specific endograft device types

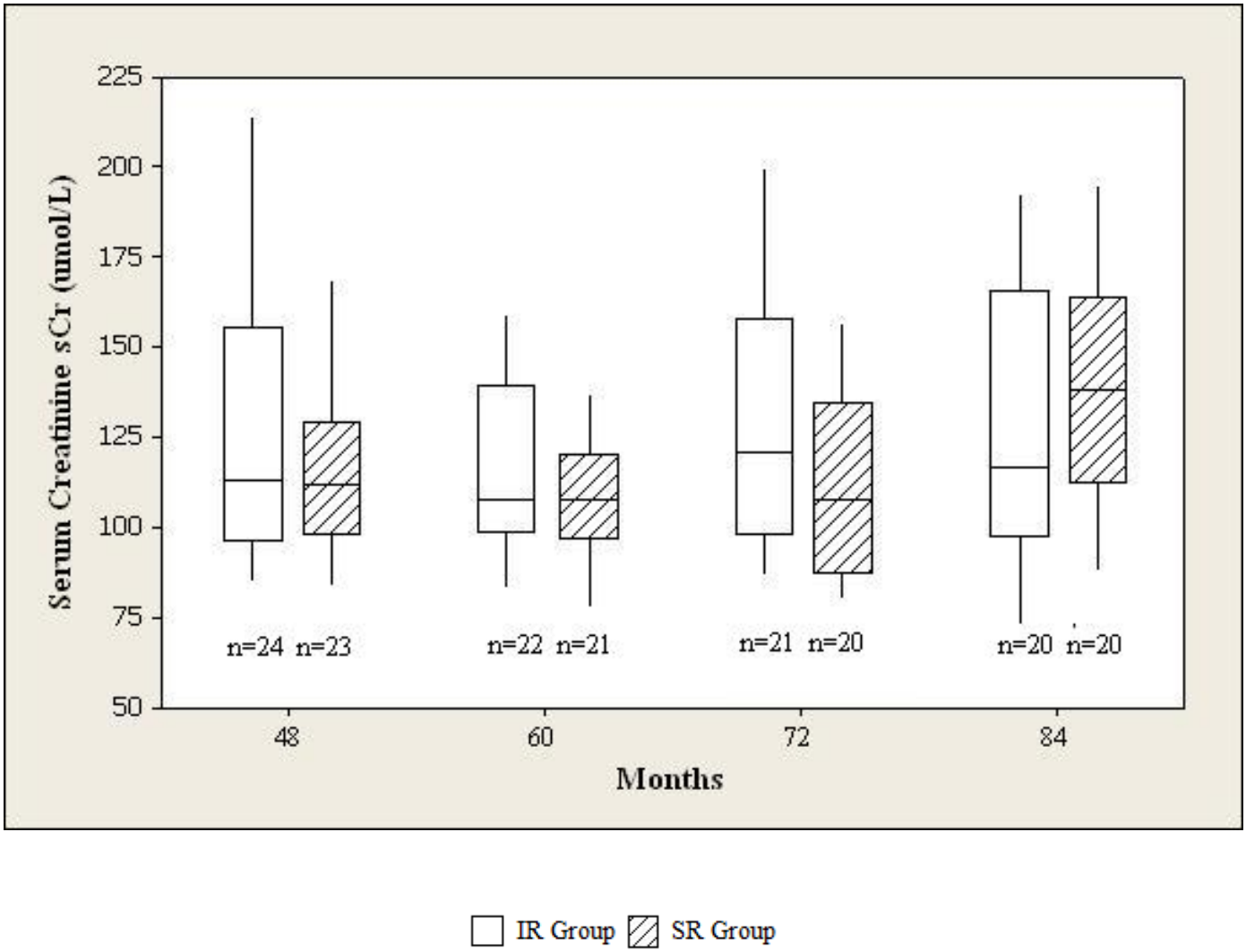
	IR Group (n=88)	SR Group (n=92)
Median age (years) Range	73 56-87	74 56-90
Sex; M: F	78: 10	83: 9
Co-morbidity: IHD Diabetes CRF	 40 19 11	 46 20 9
Tobacco use	26	25
Median AAA diam. (mm) Range	60 45-145	65 41-100
ASA Grade; Median	3	3
Op length (mins); Median Range	130 60-380	125 70-330
Blood loss (mls); Median Range	170 0-1350	155 0-545
Contrast load (ml); Median Range	193 105-405	185 95-370
F/U length (months); Mean	43.9	31.4
sCr (μmol/L); Median Range	113 72-243	108 75-307
CrC (ml/min); Median Range	57 22-102	58 22-139

Table 8: Group specific demographics

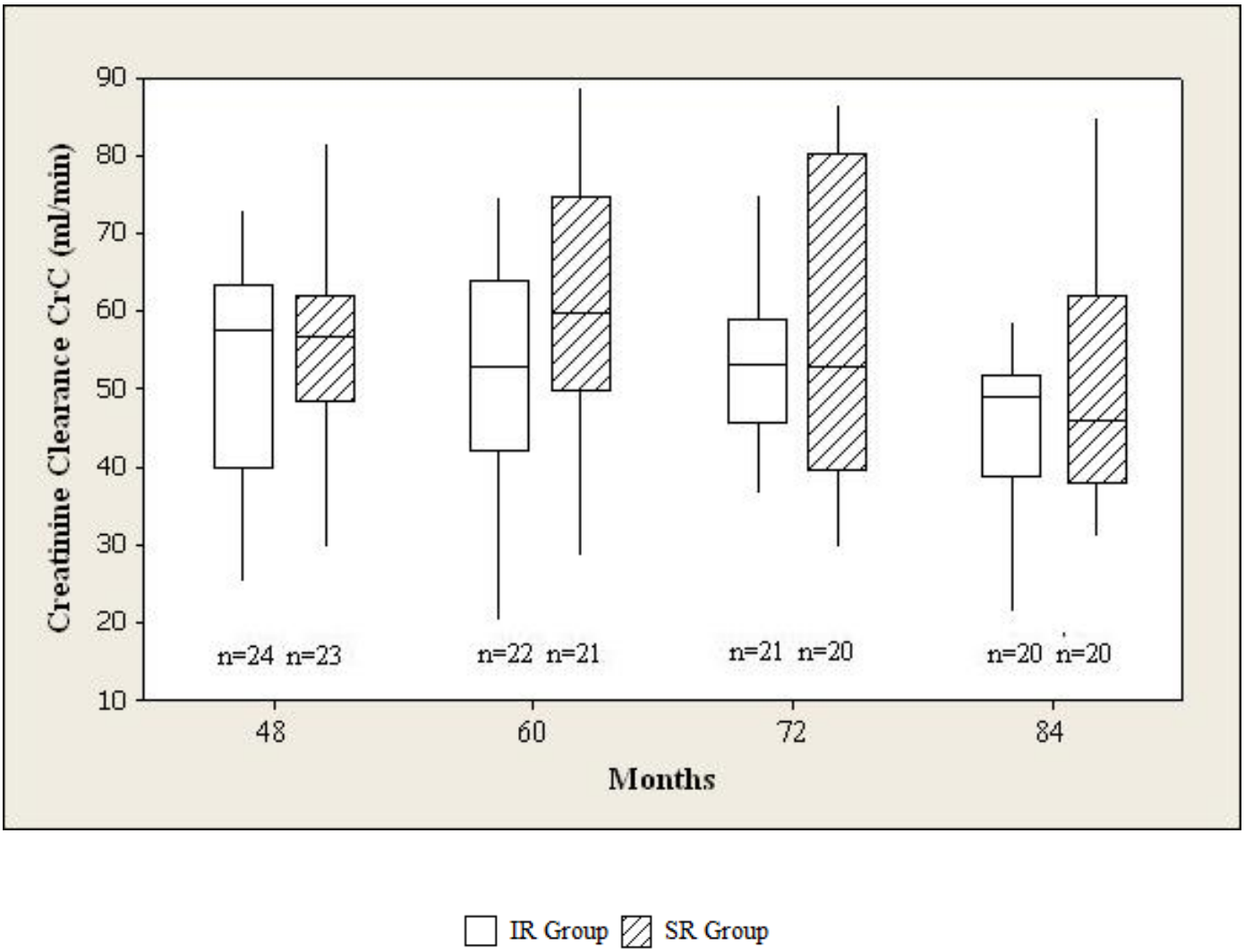
Between 48 and 84 months there was no statistically significant elevation in sCr compared to pre-operative levels (p=NS, 1-sample Wilcoxon) for either group. Similarly there was no statistical difference between each group at any specific time interval (p=NS, Mann Whitney U-Test) (see Graph 1).

CrC has apparently remained stable in long term follow up. Statistical analysis of CrC at each time interval both within and between the two groups has shown no significant change in CrC over time following EVAR irrespective of proximal fixation type (see Graph 2).

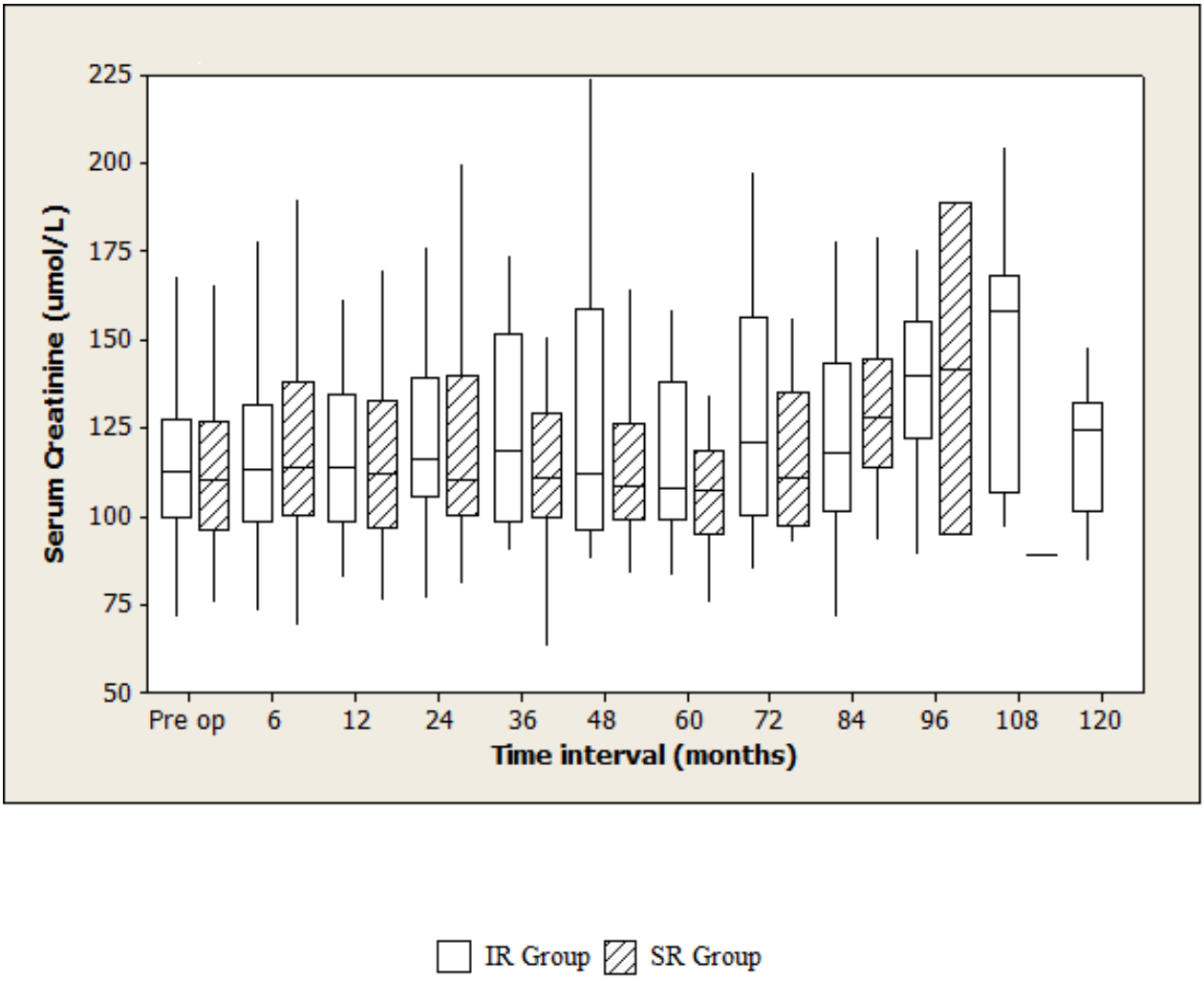
Renal function up to 10 years post endograft deployment for both SR and IR groups was also assessed. There was no apparent deterioration in renal function up to 120 months following IR deployment, and 96 months following SR deployment, as measured by either sCr (μmol/L) or CrC (ml/min) (see Graphs 3 & 4). Statistical analysis was not possible in either group beyond 84 months due to insufficient patient numbers [less than 17 per group and per time period (see Table 6)].



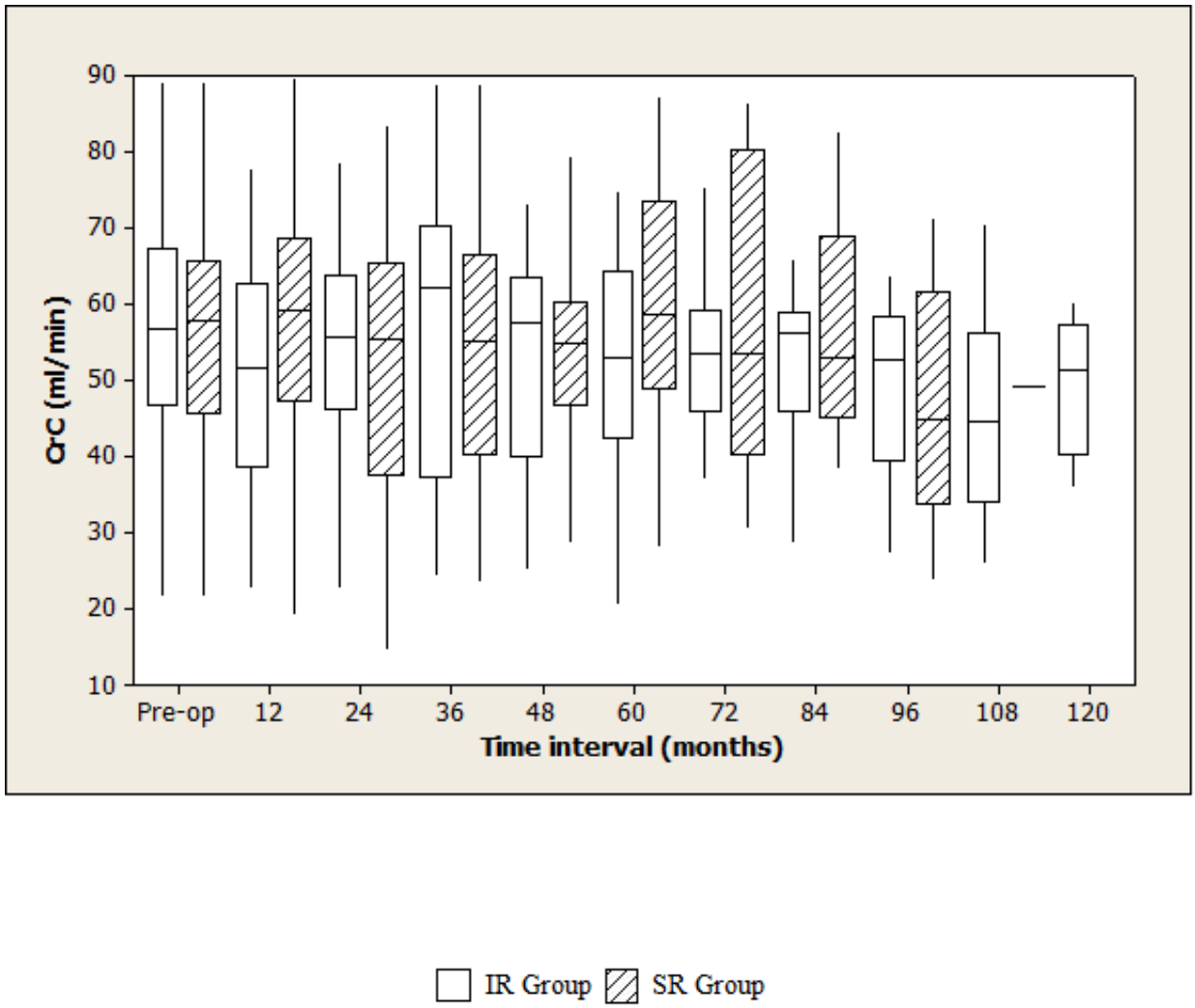
Graph 1: Fixation specific late sCr (all p=NS, Mann-Whitney U test/1-Sample Wilcoxon)



Graph 2: Fixation specific late CrC (all p=NS, Mann-Whitney U test/1-Sample Wilcoxon)



Graph 3: Fixation specific sCr to 10 years (all p=NS, Mann-Whitney U test/1-sample Wilcoxon)



Graph 4: Fixation specific CrC to 10 years (all p=NS, Mann-Whitney U test/1-sample Wilcoxon)

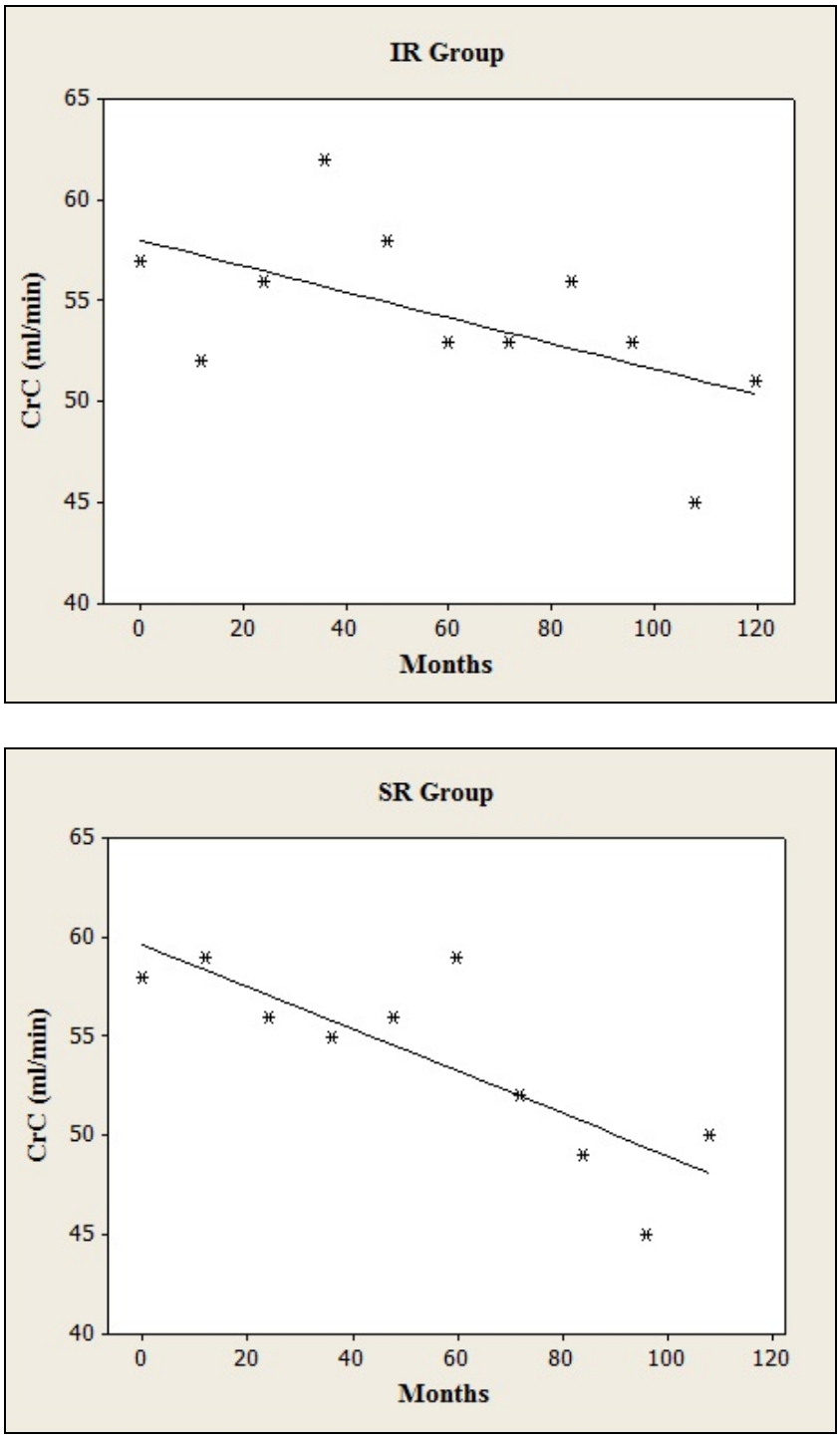
Comparitive change in renal function over time

As CrC decreases over time in any population, it is more valuable to compare the comparative change in renal function (ΔCrC) over time between the two groups.

Whilst the previous analysis compares renal function with sCr and CrC at specific time points, using the Pearson Correlation Co-efficient (change CrC/year), it is possible to compare both groups over the whole time period (see graph 5).

The Pearson Correlation Co-efficient was -0.76 and -1.28 (ml/min per year) for the IR group and SR group respectively (p=NS, 2-sample t-test).

Although the SR group appeared to have a greater decline in renal function over time, this was not found to be statistically significant in our study population.



Graph 5: Comparative change in CrC over time, Pearson Correlation Co-efficient r = -0.76 and -1.28 (ml/min per year) for IR and SR respectively (p=NS, 2-sample t-test)

Group specific complications and re-interventions

When considering the long term renal function following EVAR, it is important to consider EVAR specific complications, which may affect renal function post endograft deployment. Most of these complications are treated with a further endovascular procedure, often requiring re-cannulation of the aorta, and the administration of intravenous contrast agents for the purpose of radiological imaging. The typical EVAR specific complications include endoleaks, graft migration, endograft limb disconnect, and endograft thrombosis, and these may occur at varying times post endograft deployment (see Table 9). During the study and follow up period, 40% (35/88) of the patients in the IR group underwent at least one post EVAR re-intervention with a mean interval to intervention of 47.7 months. There were less re-interventions in the SR group, with only 9% (8/92) undergoing at least one re-intervention, with a mean interval to intervention of 31.0 months. This certainly corroborates recent evidence that endografts with trans-renal fixation (SR group), are less prone to device failures, and consequently the need for re-intervention, however it must be remembered that since the IR and SR group were essentially deployed chronologically, then this discrepancy can also be explained by the more recent technological advancements of the SR endografts.

Although there are differences in complication and re-intervention rates between the groups, these are not born out in long term differences in renal function.

	IR Group		SR Group	
Re-intervention type & order of intervention	No. Patients (n)	Mean interval to intervention (months)	No. Patients (n)	Mean interval to intervention (months)
Endograft limb extension:				
1st intervention	19	47.7	1	31.0
2nd intervention	5	81.6	1	39.0
3rd intervention	1	58.0	-	-
Conversion to AUI:				
1st intervention	1	60.0	-	-
2nd intervention	3	71.3	-	-
3rd intervention	-	-	-	-
Proximal aortic cuff insertion:				
1st intervention	8	55.3	1	75.0
2nd intervention	1	33.0	-	-
3rd intervention	1	48.0	-	-
Limb thrombolysis:				
1st intervention	-	-	1	1.0
2nd intervention	1	14.0	-	-
3rd intervention	1	20.0	-	-
Conversion to open AAA repair (rupture/infection):	4	53.5	2	19.0
1st intervention	-	-	-	-
2nd intervention	-	-	1	33.0
3rd intervention				
Embolisation of endoleak:				
1st intervention	3	10.0	3	39.0
2nd intervention	2	15.0	2	52.5
3rd intervention	1	70.0	-	-

Table 9: Group specific late complications following EVAR

Study 2

52 consecutive patients with AAA's were recruited into the original phase of this study (24 EVAR and 28 OR) in 2002, with no statistically significant differences between main patient demographics for each group, and both study groups analogous with respect to existing co-morbidities and tobacco use (see Table 10). Whilst no patient required pre-operative renal replacement therapy (dialysis), those with renal impairment, simply defined as sCr beyond the normal reference range, but not requiring dialysis, were not excluded.

There were no detectable differences biochemically between the study and control group prior to surgical intervention, with pre-operative renal function comparable between groups and no statistically significant difference detected (see Table 11).

	EVAR (n=24)	OR (n=28)
Age (years)		
Median	74	75
Range	64-83	52-87
Sex (M:F)	21:3	23:5
Co-morbidity		
IHD	12	11
HTN	11	15
Diabetes	6	4
CRF	4	5
Tobacco use	6	8
Aneurysm size (mm)		
Median	62	63.5
Range	55-85	44-103
Contrast Load (ml)		
Median	163	-
Range	110-350	-

Table 10: Group specific demographics.

	EVAR (n=24)	OR (n=28)
Renal function pre-operatively		
sCr (umol/L)	110.5	110.5
CrC (ml/min)	61.8	54.9
Cystatin C (mg/L)	1.04	0.96

Table 11: Mean pre-operative renal assessment values. All p=NS, 2-sample t-test

Stent deployment was successful in all but one case in the study series. Post EVAR deployment the Zenith® stent slipped proximally and partially covered the left renal artery with the covered portion of the endograft. The patient subsequently became oliguric, which did not respond to aggressive fluid resuscitation, and the patient became anuric. By day three post EVAR they were permanently dependent on dialysis. There were no renal complications observed in the open repair group following surgery. Although temporary supra-renal clamping was required in two cases to gain proximal control, there were no adverse sequelae.

There was one death in the early post-operative period for both groups, which was not specifically aneurysm related. The patient appeared to recover well following EVAR and was discharged on day 6 post-operatively. Within days they were readmitted to hospital with severe pneumonia, and ultimately succumbed to multi organ failure following a short stay on the Intensive Care Unit.

At 4 years following AAA repair, and during the current study period, it was possible to re-recruit 34 patients (17 EVAR and 17 Open repair), for analysis of long term renal function

following AAA repair. Of the 18 missing patients from the original cohort, 8 were dead, and 10 were lost to follow up, at this time point. None of the deaths were attributed to renal dysfunction, or aneurysm specific complications, and the most common reason for patients lost to follow up was a geographical change of domicile. There were no instances of re-intervention for complications in any of the patients.

CC and long term renal function

At 4 years post AAA repair, renal function was comparable between the two study groups (see Table 12, Graph 6), with no statistically significant difference in either CrC or CC between the EVAR group and the control OR group detected (p=NS, Mann-Whitney U-test), or between earlier time points (p=NS, 1-sample Wilcoxon test)

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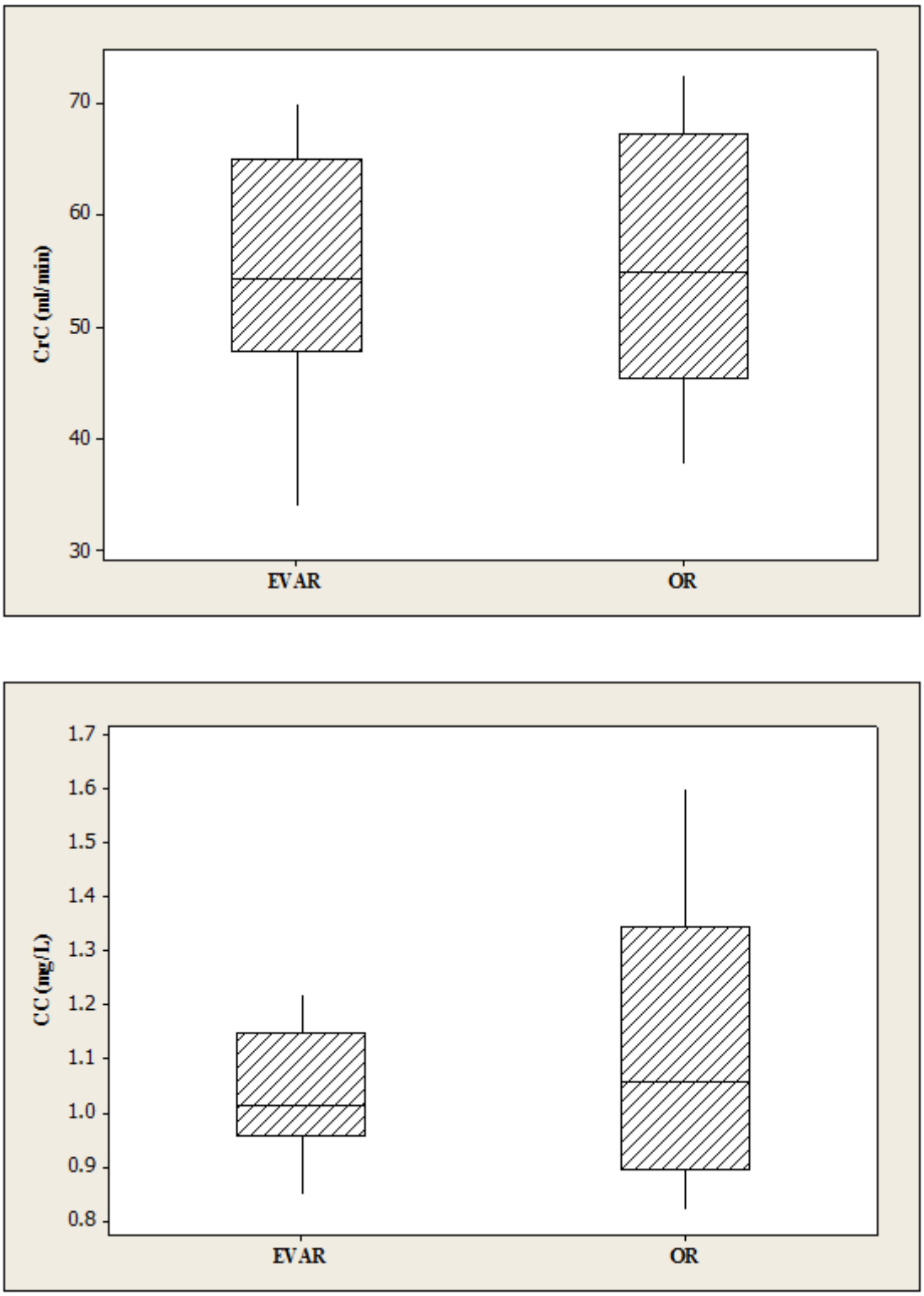
	EVAR (n=17)	OR (n=17)
Renal function at 4 years		
sCr (umol/L)	112.75	112.94
CrC (ml/min)	55.4	55.5
Cystatin C (mg/L)	1.06	1.12

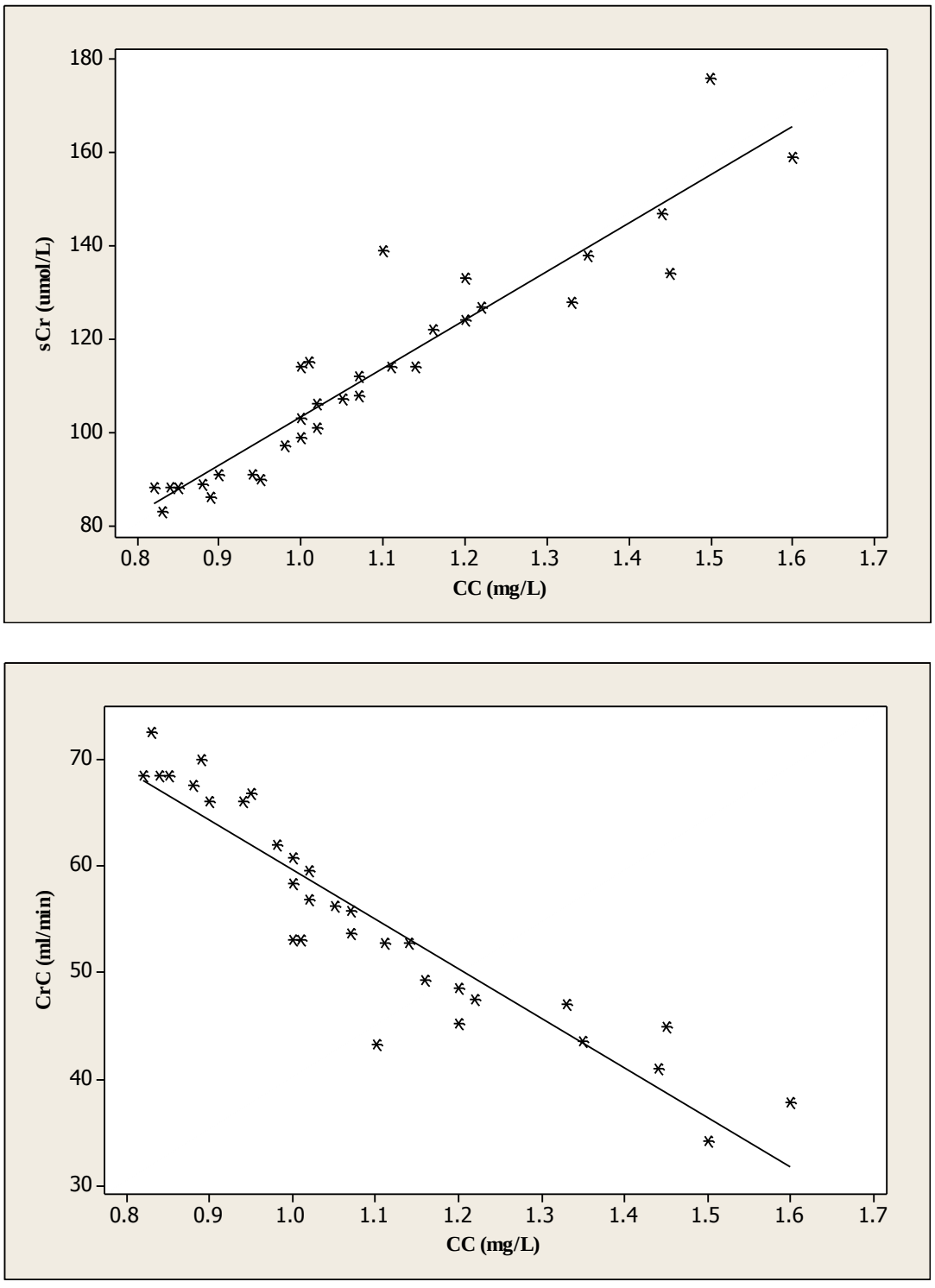
Table 12: Mean post-operative renal assessment values (all p=NS, Mann Whitney U-Test)



Graph 6: Group specific renal function 4 years post treatment, all p=NS (Mann Whitney U- test)

Validation of CC as a renal marker in long term aneurysm follow up

Although previously well described as a marker of renal function (GFR), it is important to assess the relationship between CC and estimated GFR in the AAA population, in case this population in particular possess confounding factors which could affect its accuracy. Using the estimated GFR for each patient (Cockroft-Gault derived CrC), and the routine biochemical marker sCr, the observed relationship between CC and renal function in the AAA population is demonstrated (see Graph 7). This study demonstrates a statistically significant relationship between sCr and CC (r=+0.9), and CrC and CC (r= -0.9), for both $p<0.05$ (Pearson correlation co-efficient), suggesting that CC is a valid index of excretory renal function (GFR) in the AAA population.



Graph 7: Variation of sCr and CrC with CC ($p<0.05$, Pearson Correlation co-efficient)

4.5 Discussion

Since the advent of proximal bare metal stent struts crossing the renal ostia (to improve endograft durability and reduce migration rates), concern has arisen regarding the potential adverse effects on renal function. Initial concern centred on the metal struts partially covering the renal ostia, altering the renal blood flow, and causing renal dysfunction. Although partial coverage of a unilateral renal ostia occurs in up to 40% of cases, and 9% bilaterally[37], early laboratory studies using animal models suggested that the placement of bare metal stents across the renal ostia (SR-EVAR) was at least safe in the short term[40, 41].

These early studies were soon followed by reports from several centres, which assessed mid-term renal function following SR-EVAR[49, 51, 134]. Unfortunately these early reports invariably involved study groups of only SR-EVAR patients, with no control groups for comparison, leaving a need for further evaluation of fixation specific renal outcome

The first report of fixation specific renal outcome (comparing SR and IR fixation), was published by Kramer et al. in 2002 [50]. In this study post-operative CT images of 99 patients having undergone either SR or IR-EVAR were reviewed up to 12 months following endograft deployment. They found no increased risk of adverse renal events (infarcts), with the SR-fixation group.

In the studies that followed, there was a common reliance on the use of insensitive sCr and CrC (Cockroft-Gault derived), to assess renal function. As previously discussed there are several limitations with the use of sCr as an indicator of renal function. Principally sCr is formed by the conversion of muscle creatine and phosphocreatine, and therefore its production is variable, and dependent on many external factors, such as diet, sex of patient, muscularity and surgical

intervention. Whilst the calculation of creatinine clearance (CrC) using the Cockroft-Gault formula[95] has gone some way to correct these variables, it has been shown that GFR may have to fall by up to 50% prior to any associated rise in sCr and subsequent decrease in CrC[136, 137]. Hence sCr and CrC may remain within normal limits even in the presence of considerable renal dysfunction. Additionally the estimation of sCr itself, performed using the Jaffé reaction and colorimetric assay, may be altered by the presence of other chromogens in plasma, such as plasma proteins, resulting in falsely high estimations of sCr, and inaccurate CrC calculations.

To overcome these limitations this study utilised both sCr and CrC, as well as cystatin C to assess long term renal function following fixation specific EVAR. Cystatin C is a low molecular weight protein produced by all nucleated cells. It is unaffected by patient sex or muscle mass, is freely excreted and metabolised by the kidney, and has been proposed as a more accurate estimate of GFR. The biochemical level of CC has been shown to double with even modest decreases in GFR of up to 30%[121], and as such CC should be able to detect mild renal dysfunction, previously missed by sCr and CrC.

In Study 1, analysis of sCr and CrC values up to 8 years following EVAR, suggests no significant deterioration in renal function over time irrespective of proximal fixation type for the endograft. Additionally, both groups demonstrated a comparative change in renal function over time equivalent to the generally accepted deterioration of 1 ml/min per year (for the general population over the age of sixty five)[95], suggesting no accelerated decrease in estimated GFR following EVAR, regardless of proximal fixation type. Although this would seem at first glance to contradict the previous findings (of stable sCr and CrC in long term follow up), graphical analysis of long term renal function for both groups did show a trend towards decreasing renal

function over time, although never reaching statistical significance. While there were insufficient patients to statistically assess renal function up to 10 years following EVAR, there did not appear to be any obvious difference in long term renal function between groups. In Study 2 it was possible to re-recruit 34 patients 4 years following original surgery. Of those deaths in the period between studies, none were from renal dysfunction or aneurysm related complications, and no patient required re-intervention for post operative complications. Up to 4 years following surgery, there were no clinical or statistically significant differences in renal function detectable between either group, and CC correlated well with renal function in the aneurysm population.

Although relatively small numbers of patients were analysed in Study 1 from 48 months onwards, it is important to remember that there were sufficient numbers for statistical analysis up to 84 months, with a mean follow up of 40.5 months, longer than most similar studies at the time of writing (see Table 2). Since the AAA population are elderly, with significant co-morbidities, this should be considered long term renal follow up, as life expectancy longer than 10 years following AAA repair is likely to be low.

The decision regarding proximal fixation type in Study 1 was independent of aneurysm morphology (determined by contrast enhanced CT scanning), and decided by the commercial availability of devices at the time on implantation [SR devices were not employed until nearly 3 years (60 IR endografts) after the commencement of EVAR procedures]. Patients were not randomised to any particular group, rather the one providing the most clinically appropriate and cost effective solution. Subsequently most of the earlier EVAR's performed by this centre were of IR type. Therefore the IR patients were theoretically exposed to the 'learning curve' of a new procedure, and the earlier generation, less advanced endografts. Renal dysfunction risk factors,

such as patient demographics (age, co-morbidities and pre-existence of CRF), and operative factors (blood loss, operation length and contrast load), were comparable and analogous between groups, with no statistically significant difference detected, other than mean follow up periods. These similarities were despite the earlier generation endografts (IR group) theoretically having an increased risk, in particular to operative risk factors, due to this 'learning curve'. Although there were significantly more re-interventions in the IR group, a finding not unsurprising in early generation less advanced endografts, this did not appear to significantly affect long term renal function. All endografts deployed in Study 2 were of SR design, consistent with the preference of The Northern Vascular Centre for a specific make of endograft during the study period.

Recent publication of the UK EVAR Trial results confirms our findings from Study 1 & 2. The UK EVAR Trial participants have reported no statistically significant difference in decrease in eGFR up to a mean follow up of 3.6 years, between either EVAR or open repair (OR) groups (-1.13 vs. -1.00 mL/min/1.73 m per year respectively), suggesting no long term difference in renal function following EVAR[138]. Although their data compared EVAR with open AAA repair, as in Study 2 (which found no significant difference in eGFR between groups), their deterioration in renal function over time was comparable to that demonstrated Study 1, and came from over 1000 patients having had a variety of IR and SR devices implanted.

Follow up of patient groups over long periods of time presents its own problems and complications. AAA patients tend to be aged with multiple co-morbidities. It is inevitable that significant numbers of patients will succumb to these over long periods of time. To ensure adequate numbers for long term follow up, there must be considerable sized groups from the outset. From the very first year following treatment, patient numbers decreased in the follow up

period, although it was still possible to recruit sufficient numbers in each study, to allow meaningful statistical analysis. If the patient did not attend follow up, then attempts were made to contact them, and arrange a more suitable time. If it was not possible to get data at that specific time point, then comparison of the demographics and renal confounding variables for all patients with data at each individual time point was performed. This was undertaken to prevent bias from high loss to follow up, and was felt that if the groups were still comparable, with no statistically significant difference between them (especially with respect to renal confounding variables), then comparison and analysis of renal function could occur.

Unfortunately the only routine renal biochemical markers used in the follow up of EVAR patients in this centre since 1996 was sCr. This therefore limited Study 1 to the continuing use of sCr, and the Cockroft-Gault derived CrC to assess long term renal function. Continued and long term analysis of Cystatin C in the EVAR population seems unlikely beyond the 4 year mark, as there will be insufficient numbers for accurate statistical analysis beyond this point.

One of the weaknesses of both studies was the absence of control groups. Study 1 would have benefitted from a control group of open AAA repairs over the same time periods. This would have allowed long term analysis of renal function following EVAR, and direct comparison to an AAA population who don't have the potential renal risks of EVAR (operative risk factors, contrast loads at follow up, re-intervention for complications). Study 2 would have benefitted from a control group of non AAA patients, such as those undergoing major abdominal surgery, to allow comparison with a population who have no AAA associated risk factors.

Whilst there was no formal renal protection policy within the Northern Vascular Centre during the period of the studies, every effort was made to avoid renal hazards. All patients had urinary

catheters and central venous pressure monitoring to enable accurate fluid management peri and post-operatively. Maximum effort was used intra-operatively to reduce the contrast load applied, and associated blood loss, both of which can affect renal function. Although available in the ITU/HDU setting, ‘reno-protective’ agents such as steroids, dopexamine and mannitol, were only given to a very small selection of patients, at the discretion of the attending Physician.

In conclusion, this study adds further supporting biochemical evidence that EVAR in the treatment of AAA is safe from a renal perspective in mid to long term follow up. Furthermore, this preservation of renal function is independent of proximal fixation design. Although there would be insufficient patients to allow longer follow up periods, it seems likely that this trend of renal safety would continue.

Chapter 5. Serum NGAL and the management of AAA's (Study 3)

5.1 Introduction

As life expectancy within the population rises and increasing numbers of AAA's are detected via screening programmes, or incidentally through scans for other pathology, the number of AAA's referred for treatment seems set to rise. Traditionally these would have been repaired through an open approach with major abdominal surgery. Most vascular centres within the UK now follow an 'EVAR first' policy, meaning that all patients are considered primarily for EVAR over open surgery, unless there are specific contra-indications to EVAR. The endografts currently commercially available allow up to 66% of patients to be treated with EVAR[58], although with further technological advancements, and the advent of widespread fenestrated EVAR (FEVAR) this is destined to increase.

Acute renal failure following AAA repair is a serious complication, and has been observed in up to 10% of patients undergoing open AAA repair[139] and EVAR[44], and up to 39% in those having FEVAR[76, 140]. Acute renal failure is independently associated with significantly increased mortality and prolonged hospital stay following AAA repair, and up to 2% of these patients will require dialysis, with an associated mortality of up to 66%[141]. It is therefore vitally important to recognise renal failure promptly, to allow effective management, and hopefully reduce morbidity and mortality.

Patients undergoing EVAR typically have a shorter hospital stay than that for open repair, and are sometimes discharged within 48 hours. Additionally in those vascular centres still learning EVAR, commencing a FEVAR service, or undertaking complex EVAR cases, there is a tendency to use greater quantities of radiological contrast agents peri-operatively, exposing the patients to increased nephrotoxic risk.

Whilst serum creatinine (sCr) is a cheap and readily available marker of renal function for use in day to day clinical activities, it is widely recognised as a poor marker of renal function, with a marked reduction in GFR (up to 50%), and a stabilisation period of up to 72 hours needed, prior to biochemically detectable changes in sCr[136, 137].

As an acute phase marker of renal function, NGAL has been demonstrated to dramatically increase following renal injury from a variety of causes, particularly hypo-perfusion states and nephrotoxic insult. NGAL levels start to rise within two hours of the renal insult, rapidly peaking, and typically remain elevated for up to 48 hours, making NGAL an early and sensitive biochemical marker and predictor for acute renal injury[132, 142]. Due to the high risks associated with renal failure in the AAA population, it is hoped that NGAL may serve as a useful adjunct in the management and detection of renal failure.

Never previously assessed in the AAA population, the aims of this study are to test NGAL as a valid biochemical marker of renal function following AAA repair, and to investigate the relationship between NGAL and other variables (such as age, operation length, BMI), in the aneurysm population.

5.2 Patient and methods

All patients consecutively listed for AAA repair in the Northern Vascular Centre (Newcastle, UK), for a 12 month period between August 2006 to 2007, were approached, given a full information sheet regarding the study (see Appendix D), and asked to sign a consent form (see Appendix F) for participation. The decision to treat individual patients was at the discretion of the Consultant in charge of that patient, and required an AAA diameter of greater than 5.5 cm, as well as a patient medically fit enough for surgery. The decision as to which method of AAA repair to use (EVAR or open repair), was decided at a multi-disciplinary meeting comprising several Vascular Surgeons and Consultant Radiologists, and was based on an 'EVAR first policy', whereby EVAR was the preferred method of treatment, assuming no specific contra-indications.

All patients were considered eligible for inclusion in the study, unless they suffered from chronic renal failure requiring dialysis, malignancy of any cause, acute or chronic inflammatory conditions (such as rheumatoid arthritis, inflammatory bowel disease), or infective AAA's (mycotic aneurysms). These exclusion criteria were specifically chosen, since NGAL has been independently shown to be elevated in each of these conditions[126-128], which could skew the results, making interpretation difficult.

Once participation is the study was confirmed, patients were grouped according to repair type (EVAR or open repair), and then general demographic data (age, BMI, co-morbidity), as well as operative data (contrast load, operation length, type of operation), was collected for each patient. Patients were asked to provide blood samples for sCr and NGAL estimation pre-operatively, and then within 4, 24 and 48 hours of the procedure, with a final blood sample taken at standard

follow up, which was six weeks post procedure. All blood samples were collected by the primary investigator for the study. The timing of the blood samples was chosen specifically to correspond with any potential increases in NGAL following the procedure. All baseline sCr and NGAL levels were taken pre-operatively. The next blood test was taken at 4 hours following the start of the procedure, which was a convenient time for blood collection as all patients still had central access lines for blood collection, and any rise in NGAL due to renal insult (which would normally start after 2 hours), should have been readily detectable at that point. Bloods were then collected at 24 and 48 hours post-procedure to correspond to the routine blood tests that all patients underwent, so as to minimise invasive procedures on patients. Additionally, if there was any significant rise in NGAL, it would plateau at 24 hours, and start to decrease by 48 hours. Bloods were finally collected at 6 weeks follow up to confirm that all biochemical markers had returned to normal (pre-operative levels). At each specific time point, any general or procedure related complications were recorded, and stored within a Microsoft Excel® database, constructed to store all the above information.

Renal function was recorded using sCr was analysed on an Olympus 2700 multi channel analyser (Jaffé reaction based) using the manufacturers supplied reagents, providing a between batch imprecision of less than 2% for each analyte. Considered a routine blood test, analysis of sCr was performed by the Pathology Laboratory staff at the Northern Vascular Centre.

NGAL levels were determined using the AntibodyShop NGAL Rapid ELISA test kit®. This involved a clotted blood sample being spun in a centrifuge for 10 minutes at 3000 rpm, and the resulting serum withdrawn and stored in a patient specific labelled well, at -80°C for later batch analysis. When analysis was to take place, the serum samples were diluted to 1/100, and a 50 µL

sample collected. This was then combined with 50 µL of HRP (horseradish peroxidise)-conjugated monoclonal NGAL antibody (provided in the test kit), to produce a 100 µL substrate, which could be placed in the coated microwells of the 96 well ELISA test plates. These were incubated at room temperature on a shaking platform set at 200/minute for 30 minutes. The microwells were then emptied, washed with a pre-supplied diluted wash solution, before 100 µL of TMB (tetramethylbenzidine) substrate was added to each microwell, and the plates once again left to incubate at room temperature for 15 minutes. 100 µL of a supplied 'stop solution' was then added to each well to stop the reaction, and the 96 well plates were read at 450 nm in an ELISA microplate reader, using calibrated ELISA reader software incorporating curve fitting procedures to estimate NGAL. NGAL Rapid Calibrators were pre-supplied in the test kit, and used to form a calibration curve for the ELISA plate reader. Determination of NGAL was performed by the principal investigator under the direct guidance of Dr. R. Peaston, Senior Biochemist (Northern Vascular Centre, Newcastle, UK).

Full ethical approval was sought and approved by Gateshead and South Tyneside Local Research Ethics Committee (reference: 07/H0901/42).

5.3 Data analysis

All study information was anonymised and stored within a Microsoft Excel® (Microsoft Ltd.) spreadsheet. Relevant data was exported to Minitab 14® (Minitab Inc., PA, USA) for statistical analysis.

Median values were used for continuous variables, and means for non-continuous variables. Renal data is represented by box and whisker plots, with boxes representing inter-quartile ranges, the intervening bar representing the median value, and whiskers representing the 90% range.

For serial comparison of renal function two statistical methods were employed. The 1-sample Wilcoxon Test compared non-parametric continuous variables (such as within groups), and the Mann-Whitney U-Test compared 2 sample non-parametric variables (such as between groups). A Bonferroni correction factor was used for both when repeated analysis was made.

The 2-sample t-test was employed for comparison of continuous variables.

Linear regression was used when appropriate to assess the association between variables, with the relationship strength given by the Pearson correlation co-efficient, r.

Results were statistically significant if $p<0.05$, with NS meaning not statistically significant.

There is no clear consensus on the mean level of NGAL in a healthy population, as ranges vary widely, however most studies have reported mean levels of approximately 200ng/mL, with a standard deviation in the range of 100-150ng/mL. In those patients developing renal failure, the NGAL level would have to raise 200ng/mL to exceed the NGAL cut-off level of 400ng/mL, and

if powered to 80%, there would have to be between 6 or 10 patients within the renal failure group (for a SD of 100 or 150 ng/mL respectively), to achieve significance.

All statistical methods employed were discussed with and approved by with Professor Matthews (Department of Mathematics and Statistics, University of Newcastle upon Tyne, Newcastle, UK) as part of the application and enrollment procedure for entry to the M.D. programme.

5.4 Results

44 patients were enrolled in the study (23 EVAR, 21 open repair), with paired renal data at all time points, up to 48 hours available for all patients. Data was missing for 2 patients at six weeks because one had moved from the geographical area, and one patient died following EVAR due to myocardial infarction and subsequent left ventricular failure.

Both groups were comparable and analogous with respect to demographics and co-morbidities (see Table 13), with the only statistically significant difference between the groups being the shorter operation length of EVAR vs open repair (210 vs 240 minutes respectively; $p<0.05$, 2-sample t-test).

All endografts were successfully deployed with no conversions to open repair during the study period. One EVAR patient re-presented to hospital within the first few weeks with bilateral buttock claudication, but patent internal iliac arteries, and is being kept under surveillance, with no current plans for re-intervention. A further EVAR patient presented with an occluded endograft limb, requiring femoral-femoral cross over grafting, and has subsequently made a full recovery with no further complications. There were no further cases of re-intervention needed in either study group.

Within both study groups there were 3 cases of biochemically proven (raised Troponin-T), none of which needed emergency intervention (cardiac vessel stenting or thrombolysis). There were 4 cases of post-operative acute renal dysfunction (sCr raised above baseline levels), in the open repair group, with no intra-operative precipitating factors identified. 3 of these patients responded to aggressive fluid replacement and management, and subsequently made a full recovery, with biochemical markers of renal function returning to pre-operative levels. One

patient required a short period of haemodialysis on the ITU for an acute renal failure developing at day 3, but made a full recovery, and return to normal renal function by the time of discharge from the hospital. There were two patients within the EVAR group who had a mild renal dysfunction (sCr >20% above baseline levels), persisting at 6 weeks, with unknown aetiology, and normal renal artery radiological imaging, which is being kept under surveillance.

Demographic	EVAR (n=23)	Open repair (n=21)
Age (years)		
Median	71	71
Range	57-85	28-82
Co-morbidity:		
HTN	14	12
MI/IHD	8	8
Diabetes	4	2
CVA	1	1
CRF	2	2
Smoking		
Ex smoker	9	5
Current smoker	2	6
Aneurysm size (mm)		
Median	59	63
Range	55-80	55-93
Operation length (mins)		
Median	210	240
Range	120-330	150-660
Contrast load (mls)		
Median	180	N/A
Range	85-310	
Pre-operative sCr (μmol/L)		
Median	104	104
Range	72-154	58-211
Pre-operative NGAL (ng/ml)		
Median	129	150
Range	53-339	61-719

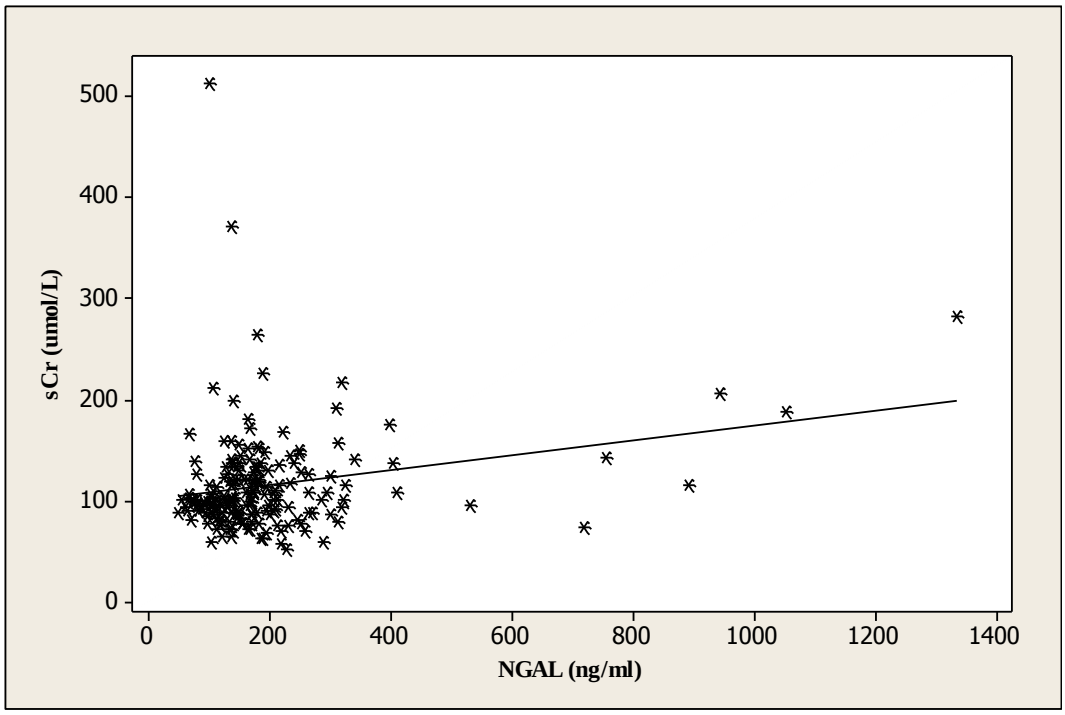
Table 13: Group specific demographics

Correlation of NGAL with patient specific variables

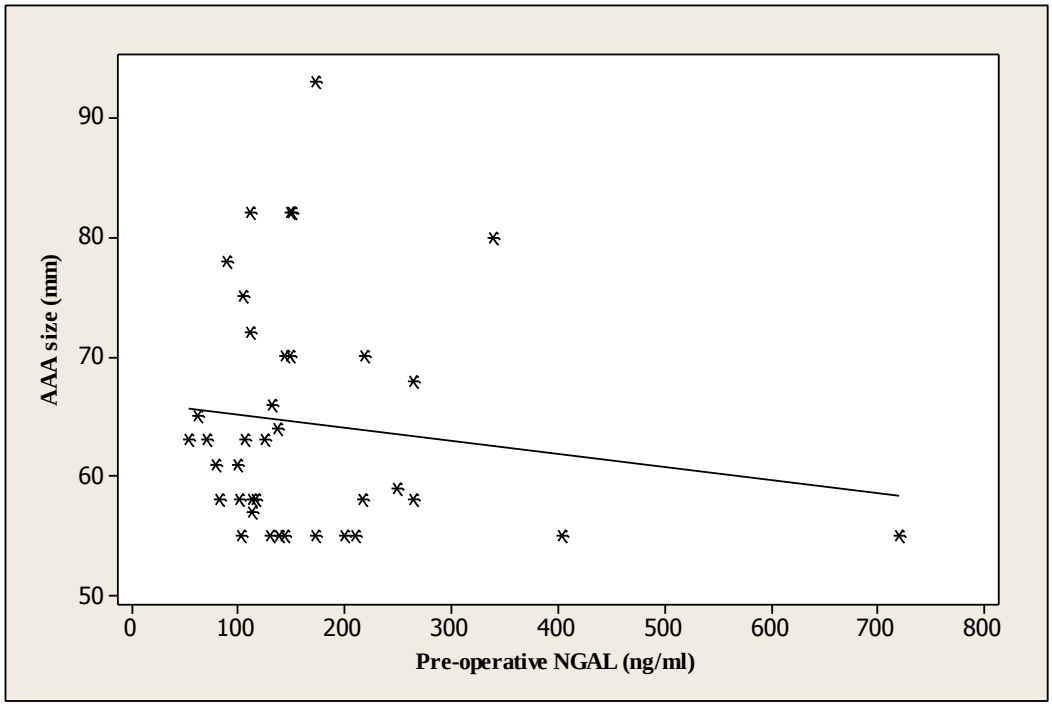
NGAL has previously been validated as a marker of renal function in patients undergoing cardiac and transplant surgery[132, 142], but to date there is no understanding of its relationship to renal function in patients with AAA's, or its relationship to potential confounding variables in patients having surgery for AAA's.

This study demonstrated a weak but statistically significant relationship between NGAL and sCr ($r = +0.24$, Pearson Correlation Co-efficient, $p<0.05$)(see Graph 8), and statistically significant relationships between operation length and NGAL at 4, 24 and 48 hours ($r = +0.58, +0.33, -0.31$ respectively, Pearson Correlation Co-efficient, all $p<0.05$)(see Graph 11-13).

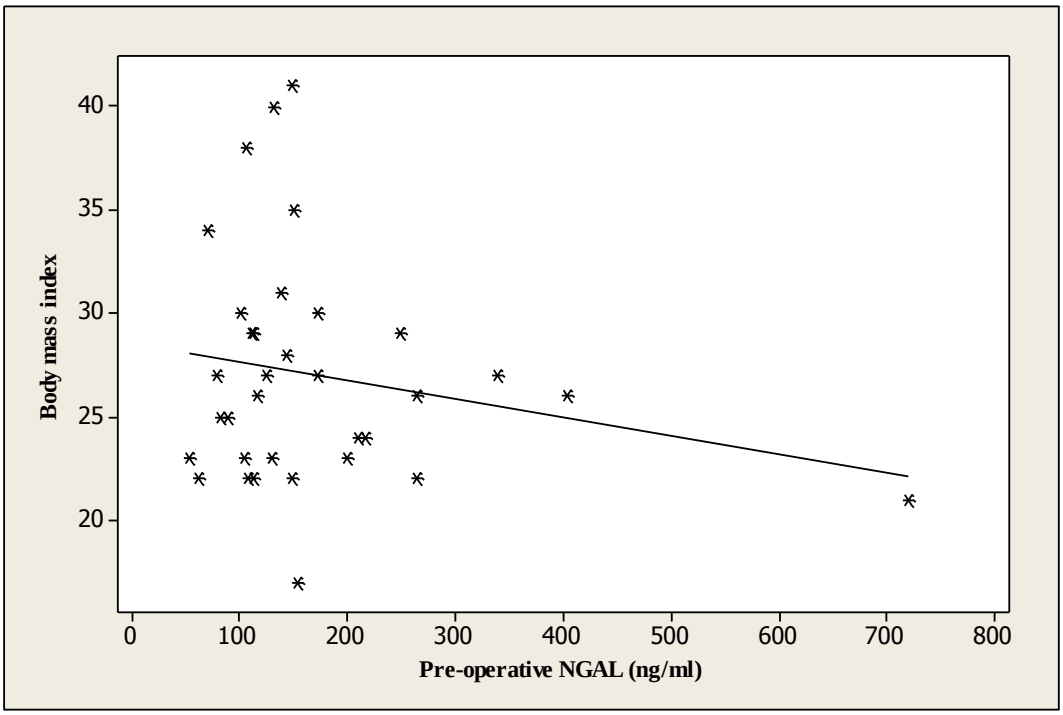
There was no statistically significant relationship demonstrated between NGAL and AAA size or patient body mass index in the study (see Graph 9 & 10).



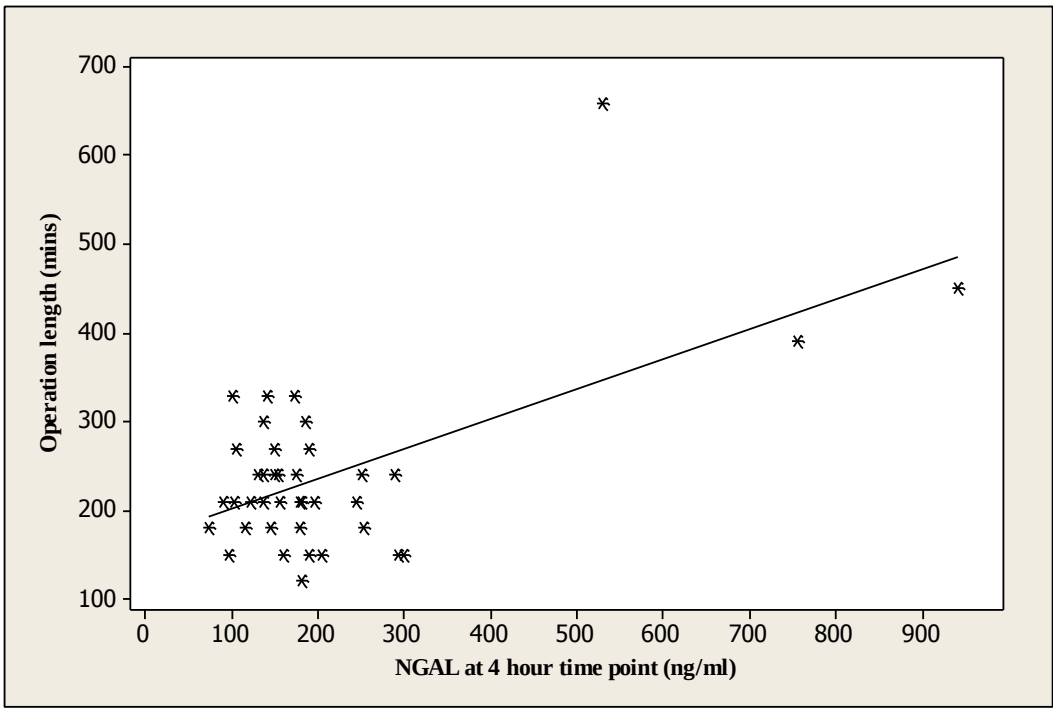
Graph 8: Correlation between NGAL and sCr (r= +0.24, p<0.05)



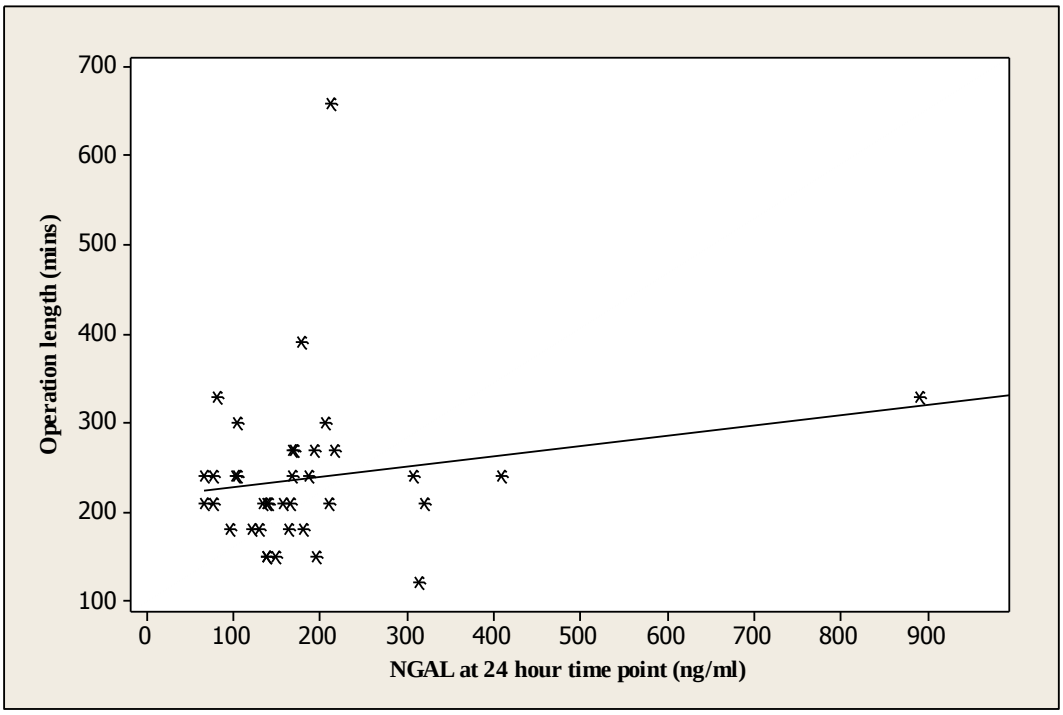
Graph 9: Correlation between pre-operative NGAL and AAA size (r= -0.13, p=NS)



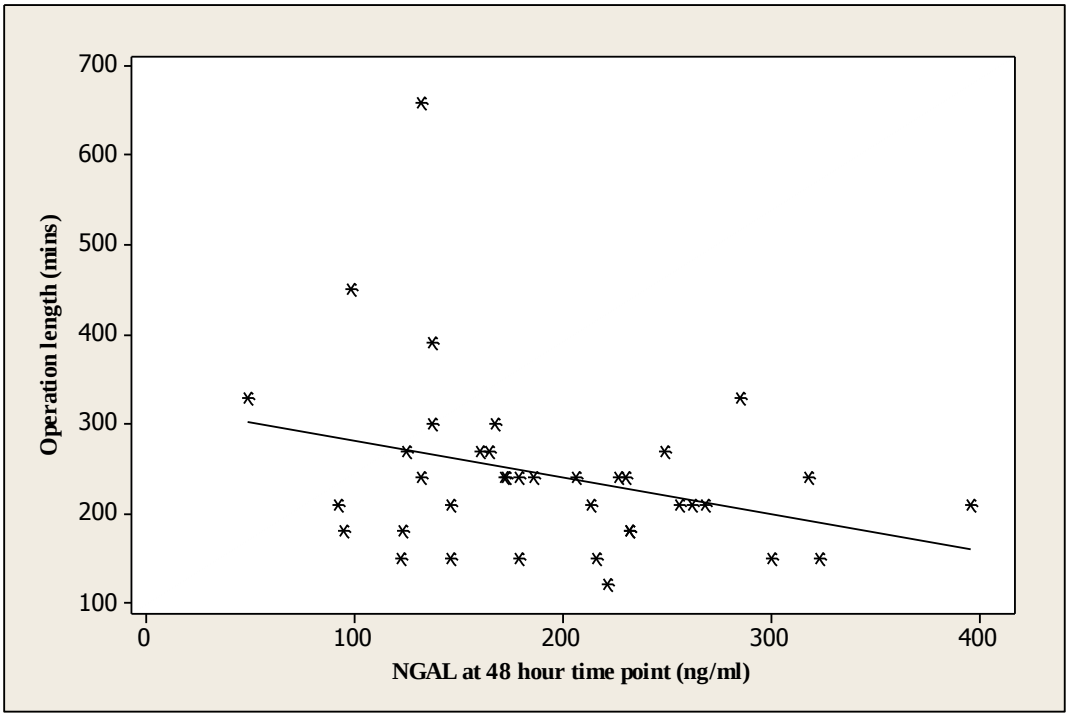
Graph 10: Correlation between pre-operative NGAL and BMI (r= -0.20, p=NS)



Graph 11: Correlation between operation length and NGAL at 4 hours (r= +0.58, p<0.05)



Graph 12: Correlation between operation length and NGAL at 24 hours (r= +0.33, p<0.05)



Graph 13: Correlation between operation length and NGAL at 48 hours (r= -0.31, p<0.05)

NGAL and renal function

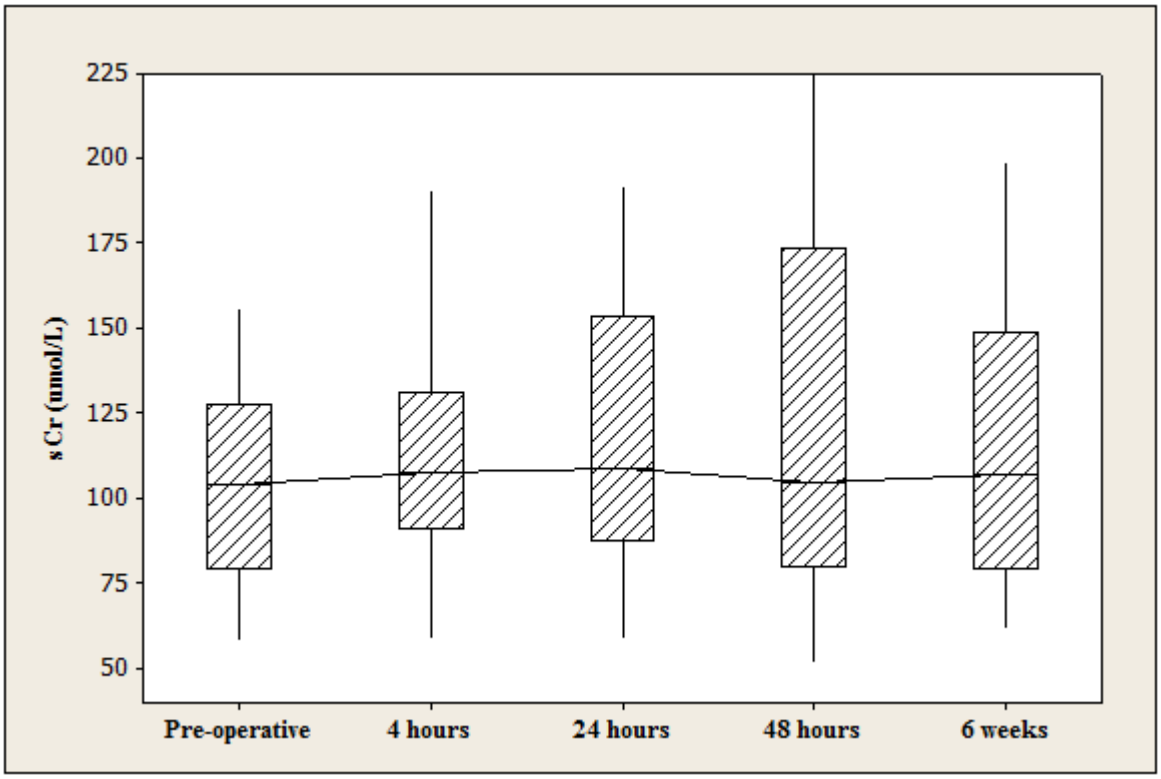
Throughout the study period, median sCr was comparable at each individual time point for the OR group (see Graph 14), with no statistically significant difference at any time point measured (p=NS,1-sample Wilcoxon test). There was however an increase of NGAL at both 4 and 24 hours post procedure (see Graph 14), which showed statistical significance in comparison with other assay points in this group ($p<0.05$, 1-sample Wilcoxon test), and when compared to the corresponding 4 and 24 hour time points for the EVAR group ($p<0.05$, Mann Whitney U-Test). Within the OR group there were 3 instances of NGAL rising above the renal dysfunction predictor level (>400 ng/ml) at 4 hours. In one patient with NGAL at 942 ng/ml at 4 hours, the sCr rose from 144 μmol/L pre-operatively to 512 μmol/L at 48 hours. In another with NGAL at 755 ng/ml at 4 hours, the sCr rose from 111 μmol/L pre-operatively to 371 μmol/L at 48 hours. In the third patient, NGAL rose to 530 ng/ml at 4 hours, but there was no significant rise in sCr, and NGAL levels subsequently fell. There was one instance of renal dysfunction, where pre-operative sCr rose from 126 μmol/L to 217 μmol/L at 48 hours, and NGAL did not rise significantly until 24 hours post-operative, at which point it rose to 1051 ng/ml. There was one case of renal dysfunction, with sCr rising from 95 μmol/L to 176μmol/L at 48 hours, with no associated change in NGAL level.

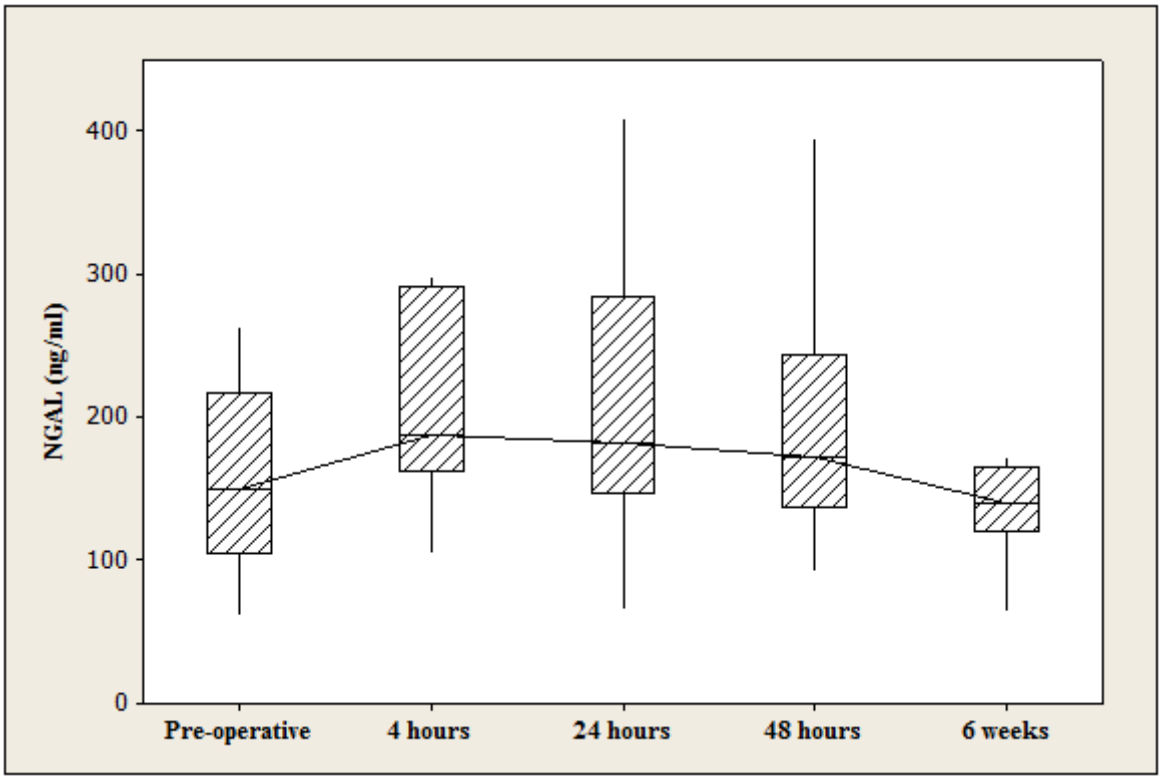
The EVAR group demonstrated a small rise in both sCr and NGAL at the 48 hour time point post procedure (see Graph 15), but this failed to gain statistical significance both within the EVAR group (p=NS, 1-sample Wilcoxon test) and when compared to the OR group (p=NS, Mann-Whitney U-Test).

There were no instances of NGAL rising above the renal dysfunction predictor cut off level (>400 ng/ml) in the EVAR group at the 4 hour time point. Only two EVAR patients developed a mild renal dysfunction. For one their sCr rose from 120 umol/L pre-operatively to 157 umol/L at 6 weeks, and for the other 150 umol/L to 181 umol/L respectively. Neither patient demonstrated an elevation in NGAL at 4 hours. At follow up CT angiography (6 weeks post operatively), both patients had patent renal arteries with good endograft position, and no evidence of renal infarcts. They are being managed conservatively with surveillance at present, and the aetiology of the renal dysfunction is not clear.

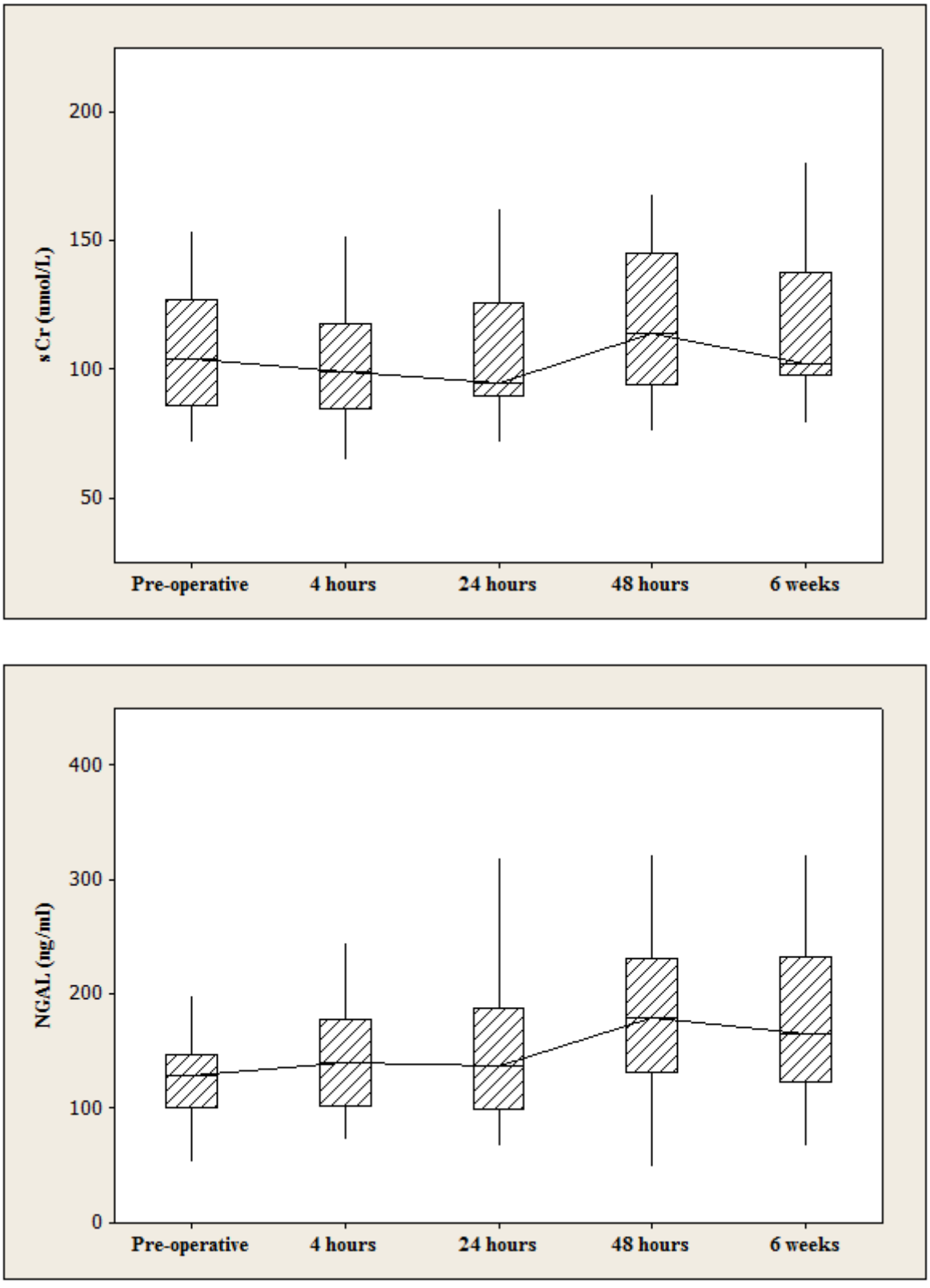
Predictive value of NGAL in renal dysfunction

When assessing the value of NGAL in predicting renal dysfunction in the AAA population, it is best to directly compare NGAL levels at all time points between those patients with and without renal dysfunction (see Graph 16). In this study, a total of 6 (13%) patients developed renal dysfunction (sCr rise >20% from baseline), following AAA repair. At the 4, 24 and 48 hour time point they have a much greater range of NGAL values compared to the normal renal function group (as demonstrated by the larger inter-quartile ranges on the box and whisker plots), indicating a possible trend towards renal dysfunction prediction. However median values were comparable between the two groups, with no statistically significant difference within groups (1-sample Wilcoxon) or between groups (Mann-Whitney U-Test), at any time point.

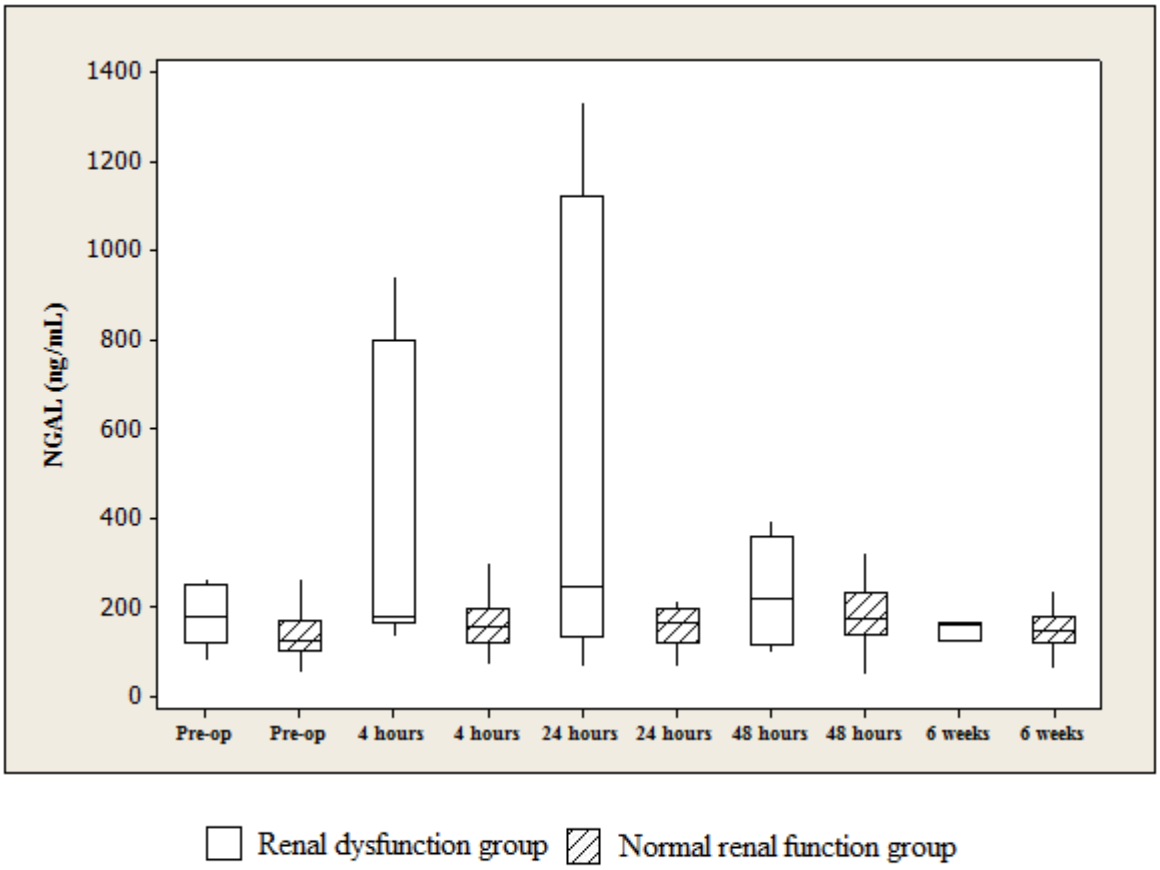




Graph 14: NGAL and sCr at specific time points (OR group)



Graph 15: NGAL and sCr at specific time points (EVAR group)



Graph 16: Predictive value of NGAL in renal dysfunction, p=NS (1-sample Wilcoxon, Mann-Whitney U-Test)

5.5 Discussion

Renal failure following AAA repair of any type is an important entity, occurring in up to 10% of patients[44], and is independently associated with significant morbidity and mortality[141]. Prompt recognition of renal failure is therefore necessary to allow treatment, and prevent adverse outcomes.

Following renal injury from ischaemia or nephrotoxic agents, NGAL has been shown to up-regulate in the kidney, and has emerged as a novel biochemical marker of acute renal failure[131]. It has been successfully used in both cardiac and transplant surgery, and as a predictor for contrast nephropathy in patients undergoing percutaneous coronary intervention [132, 142]. To date it has not been assessed in the AAA population, and it is unknown if AAA specific factors will affect its use.

Since NGAL occurs naturally in complex with matrix metalloproteinase-9 (MMP-9), a proteinase associated with AAA development and rupture[143], there was concern that the AAA population may have naturally occurring higher levels, making NGAL less useful as a marker of renal function. This study assessed the relationship of NGAL to AAA size, and patient BMI, and found no statistically significant correlation. This was most likely because the majority of NGAL occurs as a monomer in neutrophils, with only a small percentage in complex with MMP-9, resulting in no significantly elevated levels in the AAA population, and because NGAL, unlike sCr, is not directly influenced by body muscle mass or size.

NGAL correlated positively and significantly with operation length at 4 and 24 hours post procedure, indicating a positive relationship between renal confounding factors and NGAL in the AAA population. Additionally, when assessing the relationship between NGAL and sCr in the

AAA population, there was a statistically significant, albeit weak correlation found. We suggest that this correlation was weak, because unlike other biochemical renal function markers, which correlate linearly with sCr, NGAL rises exponentially with renal dysfunction, making individual predictions of NGAL levels from sCr difficult. Additionally, since sCr is a relatively poor marker of renal function, requiring significant changes in GFR prior to alteration in levels, it may be that any subtle change in GFR, detected by small but not clinically significant rises in NGAL, is just not represented by the associated sCr levels, resulting in a weak correlation.

This study demonstrated a small but statistically significant rise in NGAL at 4 and 24 hours following open AAA repair, with no corresponding similar change in the EVAR group. It was not entirely clear why there was no similar rise in the EVAR group, but it was felt that this difference occurred due to the greater physical stresses placed on the body and kidneys during the open AAA repair. Of particular note, no patients in the EVAR group suffered inadvertent cannulation of the renal arteries, or developed contrast nephropathy, whereas all open AAA patients underwent dissection of the aortic neck and manipulation of the tissues surrounding the renal arteries to enable safe clamp application. This could potentially have exposed the open AAA patients to small, but clinically insignificant changes in renal function, accounting for the change in NGAL. It is believed that the median sCr did not subsequently rise in the open AAA group because the rise in median NGAL observed was below the renal dysfunction cut off level (>400ng/L), and thus represents only a mild or sub clinical renal dysfunction, unable to be detected by sCr. Of the 4 patients that developed renal dysfunction in the OR group, demonstrated by a rise in sCr at 48 hours, 2 were predicted by a rise in NGAL at 4 hours well above the cut off level. Of the remaining two, one never experienced an NGAL rise, and for the other the rise occurred at 24 hours post-procedure.

In the EVAR group there was a small but statistically insignificant rise in NGAL at 48 hours post-procedure, and this was not associated with any significant rises in sCr. It is possible this occurred because EVAR patients were all managed in the high dependency unit (HDU) post-procedure for at least 24 hours, enabling accurate control of hydration. They were generally moved to standard surgical wards between 24 and 48 hours, with cessation of intravenous fluids and commencement of oral intake. It is possible that this change in fluid intake prompted a mild dehydration and renal insult, detected by NGAL, although not sufficient to cause a frank renal failure and rise in sCr. The open AAA group generally stayed for at least 48 hours in the intensive care unit (ITU), avoiding this potential complication. Another possible explanation is the use of CT angiography to check the endograft (correct position, absence of endoleaks), prior to discharge. This typically occurred at 48 hours post-procedure, and involved a further bolus of contrast agent. It is suggested that since this second renal insult was insufficient to precipitate renal failure, that this is the reason the rise in NGAL was small and not statistically significant. Of the two patients that developed mild renal dysfunction (not requiring renal replacement therapy) in the EVAR group, there was no rise in NGAL at any time point. Their renal dysfunction is unchanged and persists at 6 weeks post procedure, with aetiology unknown (no renal infarcts or stent migration proximally detected on follow up CT).

When those patients with renal dysfunction are compared directly to those without renal dysfunction (see Graph 16), a clear trend is demonstrated. Those patients who develop renal dysfunction have a much greater range of NGAL values at the 4 and 24 hour time point, indicating a potential trend towards the prediction of renal dysfunction in the AAA population. Although median values were comparable between groups and time points, with no statistically significant differences detected, the numbers of patients with real dysfunction were too small for

accurate analysis. This demonstrates one of the limitations of this study. When used in other clinical scenarios, such as renal transplantation and percutaneous coronary intervention, there are generally much higher rates of clinically significant renal dysfunction recorded (up to 40% of patients), making any correlation of NGAL with renal function easier. In this study only 13% (6/44) of all patients developed renal dysfunction. These findings do however highlight a potential for prediction which should be assessed with greater patient numbers. To fully assess the predictive value of NGAL in the AAA population would require greater patient numbers (from several study years), or the use of a multi-centre collaboration.

The addition of a control group may have been of value to this study. A group with no history of AAA disease, but undergoing either major abdominal surgery or angiography with contrast agents would have added validity to the use of NGAL in AAA patients, by removing the potential confounding factor of AAA disease.

Additionally it would be of value in any future studies to use a more accurate measurement or estimation of GFR to confer greater validity on any change in NGAL found. This study used sCr as it was cheap, readily available and was simple to analyse. The most obvious and simple marker to use in its place for greater accuracy would be Cystatin C to allow more accurate GFR estimation.

Sampling of blood for NGAL analysis was taken as close as possible to the defined time points both peri and post-operatively, but it is acknowledged that there will be some sampling error here. The commencement of renal insult was defined as the introduction of the first guide wire intra-vascularly through the AAA for EVAR patients, and the commencement of retro-peritoneal dissection of the AAA neck for OR patients.

Whilst there is no formal renal protection policy within this centre for patients undergoing AAA repair, much was done to prevent renal dysfunction. All patients underwent urinary catheterisation and central venous pressure monitoring to enable optimisation of fluid management peri-deployment of the endograft, and in the immediate post care setting of HDU or ITU. If clinically indicated, then 'reno-protective' agents, steroids, mannitol, dopexamine were administered, but were not done so on a routine basis, and were at the discretion of the Consultant Physician in charge of ITU/HDU. No participants in this study required 'reno-protective' agents as part of their treatment.

Instead of predicting renal failure, several recent studies have investigated the prevention of renal dysfunction. The Department of Vascular Surgery at the University of Cologne, has investigated the use of statins given pre-operatively in the protection of SR-EVAR patients from renal dysfunction. They demonstrated a post-operative reduction in CrC from 74.1 ml/min to 68.0 ml/min ($p<0.001$), in patients undergoing SR-EVAR without statin cover, and no clinical or statistically significant deterioration in those that were on statins[144]. Since all patients with vascular disease in the UK are routinely prescribed statins (unless contra-indicated), their findings appear to be limited, other than to emphasise the importance of statins in vascular patients. Perhaps of more importance to UK Vascular Centres is the reduction in the use of contrast agents used during EVAR. The Munich Department of Vascular Surgery report on the use of real time contrast enhanced ultra-sound in the deployment of EVAR, as an alternative to angiography or CT. They successfully visualised the proximal landing zone in 82.4% of patients, and the distal landing zone in 89.3%. They report a statistically significantly lower volume of contrast used, compared to conventional angiography[145]. Although a novel suggestion, this would require significant re-training of surgeons, investment in expensive equipment, and access

to traditional angiography if visualisation of the deployment was not possible. As an evolving technology, it may yet be of value.

Although essentially a study of negative findings, there are still important conclusions to be made. If NGAL had been inappropriately elevated at all study points (because NGAL is a modulator of MMP-9), then it would have demonstrated the failure of NGAL as a renal function marker in the AAA population; and this was not the case. Due to insufficient numbers of patients with renal dysfunction following AAA repair, it was not possible to fully assess the role of NGAL in this clinical scenario, although a weak (but statistically significant) relationship between NGAL and renal function in the AAA population was demonstrated.

It is still believed that further research into the role of NGAL in the management of AAA's is of value. There is a relatively high rate of renal failure following AAA repair of all types, and decrease in renal function post operatively is independently associated with decreased 5 year survival following surgery[146] and increased morbidity[141]. There is only limited benefit that can be achieved by manipulation of intra-operative renal confounding factors, and only so much pre-operative patient optimisation to reduce this risk of renal failure (aggressive pre-hydration). An early renal marker, which could be sampled peri-operatively with no added hassle, potentially detecting renal failure within hours of the renal insult would be of great benefit. It would allow the use of 'reno-protective' agents pre-emptively, and on a targeted basis to reduce these risks.

Perhaps the most obvious direction for further research involving NGAL and AAA's would be in the management of FEVAR. With much higher rates of acute renal dysfunction reported (up to 39%)[76, 140, 147], the importance of early detection through a simple to use biochemical marker could not be more paramount.

Chapter 6: Summary & Conclusion

As life expectancy improves and screening for AAA's becomes commonplace, there will be increasing numbers of patients referred for the treatment of their AAA's. Traditionally this was performed by open surgical endo-aneurysmorrhaphy, and placed considerable stresses on the patient, with considerable morbidity and mortality risks. As such only patients deemed 'medically fit' for surgery were considered. The need for a treatment option with lower associated risks, and suitable for 'medically unfit' patients, was great.

Since Parodi first described EVAR some 20 years ago[15], there have been considerable developments. Endografts have evolved from simple tube stents with single point fixation, to complex modular devices with trans-renal (SR) fixation. This has improved eligibility of AAA's to over 60% of the AAA population[58], and this figure seems set to rise with further endograft development, and the advent of cheap and accessible fenestrated endografts (FEVAR).

A key concern with SR EVAR was the impact on renal function. Several studies reported comparable rates of renal infarction following SR-EVAR compared to IR-EVAR [50, 133], and similar rates of renal dysfunction following both methods in the immediate to mid-term follow up[44, 51-56, 134]. To date evidence for renal safety following SR-EVAR in the long term is lacking, but needed to determine SR EVAR safety.

Renal function is typically measured in the clinical setting using sCr and the Cockroft-Gault derived CrC to estimate GFR. This is easy to perform, cheap and readily available in most centres. sCr metabolism however can be directly influenced by muscle mass, sex and dietary intake of proteins. Additionally, sCr and CrC are poor renal markers, requiring significant changes in GFR prior to any detectable alteration in their levels.

Cystatin C, a low molecular weight protein and proteinase inhibitor, has been validated as an effective and accurate measurement of renal function, compared to gold standard clearance methods[120]. Unlike sCr it is not affected by sex, muscle mass or dietary intake, and can be readily and economically quantified with a commercially available PETIA kit. Whilst it has demonstrated the renal safety of SR EVAR in the short term[135], it has not been used in mid to long term follow up of SR EVAR patients, and is hoped that it will confirm the findings already shown by sCr and CrC.

Additionally there has been considerable interest recently in NGAL as a novel marker of acute renal dysfunction. NGAL is a member of the lipocalin family of proteins, and although its role is not fully understood, it is believed to play a role in stress response. Studies have demonstrated considerable rises in NGAL shortly following renal insult during cardiac and transplant surgery, and following nephrotoxic injury[132, 142]. With the increasing use of EVAR and future potential for FEVAR, it is of vital importance to have a reliable indicator and predictor of potential renal dysfunction. This would enable rapid treatment of any predicted renal failure, reducing associated morbidity and mortality.

The aims of this thesis include:

- To assess long term renal safety following EVAR, in particular SR-EVAR (Study 1)
- To assess mid to long term renal function following EVAR using Cystatin C (Study 2)
- To evaluate the role of NGAL in the management of AAA's (Study 3)

Study 1 was a retrospective and prospective analysis of all patients having undergone EVAR (either IR or SR) at the Northern Vascular Centre between 1996 and 2001.

Using sCr and the calculated CrC, the study confirmed there was no statistically significant deterioration in renal function in either group up to 84 months post deployment. Paired renal data was available up to 120 months, and demonstrated a lack of difference in renal function to this time point, however there were insufficient patient numbers for statistical analysis.

Other recent studies have confirmed these findings, demonstrating the renal safety of EVAR in the mid to long term. The recently reported long term follow up from the EVAR trials found no statistically significant difference in rate of change in eGFR between OR and EVAR with a mean follow up of 3.6 years, and 1194 patients[138]. Additionally, this study confirms the findings of and adds to the body of work already performed demonstrating long term renal safety following EVAR (utilising sCr and CrC)[35, 44, 49, 50, 54-57].

The strengths of this study were long follow up periods, with a mean of 40.5 months, and paired renal data with sufficient numbers for statistical analysis up to 84 months. Further, all procedures were performed in a single centre, by a select group of surgeons/radiologists, using only one type of SR device, in contrast to other studies.

Principal weaknesses of the study include the use of outdated IR devices (the Vanguard® device is no longer commercially available), and the lack of long term renal data following OR (as a potential control group) from the same time period, patients having OR are not routinely followed in clinics long term (unless enrolled in specific trials). Additionally, due to the relatively small number of patients during the study period, longer follow up will be difficult to

perform. AAA patients have co-morbidities which generally preclude long term survival following AAA repair.

Study 2 was a prospective analysis of a previously selected group of patients from a previous study, having undergone EVAR or OR, using Cystatin C as a marker of renal function. Cystatin C was used to ensure that there was no renal dysfunction mid to long term following EVAR, that sCr was unable to detect due to lack of sensitivity. Paired renal data was available up to 4 years post AAA treatment, and confirmed the renal safety of SR-EVAR compared to open AAA repair. Validation of Cystatin C as an effective renal marker in AAA patients was confirmed at midterm follow up.

This study validated the recently published finding from the EVAR trial[138] midterm data. Using estimated GFR the EVAR Trial found no significant difference in renal function between OR and EVAR with a mean follow up of 3.6 years. Using Cystatin C, an acknowledged and accurate marker of renal dysfunction and GFR, this study demonstrated no significant difference in renal function up to 4 years between OR and EVAR, confirming the mid to long term renal safety of EVAR (SR EVAR in this respect as all endografts were SR type).

The strength of this study include long follow up periods using Cystatin C as a marker of renal function in AAA patients, and the use of a more sensitive renal function marker (GFR marker), to truly determine the renal safety of EVAR.

The principal weaknesses are the small number of patients enrolled in the initial trial period. This has enabled follow up to 4 years, however at this point there were only 17 patients in each arm of

the study, the minimum required for successful statistical analysis, and as such further long term follow up seems unlikely. Further work could involve taking a sample of IR, SR and OR patients from any time point following surgery, and analysing renal function using Cystatin C. There would be no paired renal data, but if demographics between the groups were similar, comparison of renal function could be made. Additionally, it would have been more accurate to have an IR control group as part of the original study, since SR EVAR and OR are two different technologies. For true comparison it would be necessary to compare different endograft types directly, ie. those with SR and IR fixation using Cystatin C.

Study 3 was a prospective analysis of patients undergoing EVAR or open AAA repair using NGAL as a marker and predictor of acute renal dysfunction post-operatively. Whilst there was a small but significant rise in the first few hours following open AAA repair, this did not result in a subsequent rise in sCr and renal dysfunction. There was no statistically significant rise of NGAL in the EVAR group, and no subsequent statistically significant rise in sCr. These results were primarily felt to reflect the greater stresses and impact of open surgery on the kidneys, and the resultant rise in sCr lacking since the NGAL level did not rise above 400 ng/L (previously shown as the renal dysfunction cut off value). The EVAR group had relatively short operation durations, small contrast loads, and were well hydrated, and no EVAR patients developed overt contrast nephropathy as a result.

Whilst NGAL has been validated for use in other procedures (coronary catheterisation, transplant), its role as a modulator of MMP-9 (associated with the development of AAA's) has clouded its use in the aneurysm population. NGAL was demonstrated to correlate weakly, but

significantly with sCr as a marker of renal function in AAA patients. It did not significantly correlate with AAA size, or patient BMI, confirming that it may yet have a role in AAA management.

In 3 of the 6 patients who developed renal dysfunction , NGAL levels rose within the first 24 hours, indicating a potential predictive role for NGAL. In 2 patients there was no rise in NGAL, and in the last patient there was a delayed rise in NGAL. The number of patients within the study developing renal dysfunction following AAA repair 13% (6/44), was insufficient to make accurate statistical analysis for the role of NGAL as a predictor of potential renal dysfunction, although there was a trend identified of wider ranges of NGAL levels in the renal dysfunction patients at the 4, 24 and 48 hour time points post-surgery.

To achieve appropriate numbers of AAA patients developing renal failure and to allow the assessment of NGAL as a predictor of renal function, the study would have to be a longer duration, or potentially multi-centre. In any further analysis of NGAL it would be helpful to include a control group, of patients undergoing major abdominal surgery, to allow direct comparison with OR, without vascular disease as a potential confounding factor.

In conclusion, this research has demonstrated the continued renal safety of EVAR in the mid to long term follow up, regardless of proximal fixation type.

Despite correlating with routine biochemical renal function markers in AAA patients, the role of NGAL in the management of AAA patients needs further exploration and assessment.

Appendices

Appendix A: Cystatin C patient information sheet

Patient Information sheet

The long term impact of trans-renal aortic endograft fixation for abdominal aortic aneurysm repair on renal function

(Cystatin C Cohort)

The study

You are invited to take part in a research study to evaluate the long term effect of placing an aortic implant (artificial blood vessel), for the treatment of abdominal aortic aneurysms (dilated aortic blood vessel), across the blood supply of the kidneys. Before you decide it is important to understand why the research is being done, and what it will involve. Please take time to read the information sheet carefully, and talk to others about the study if you wish. If the information sheet is not clear, or if you require more information, please feel free to ask questions. Take time to decide whether to participate.

Thankyou for reading this.

Background

Over the last fifteen years medical advances have enabled some patients to undergo key-hole repair of abdominal aortic aneurysms (dilated aortic blood vessel). This means faster recovery and less invasive surgery for eligible patients compared to traditional surgical repair (requiring a large abdominal operation). Whilst usually performed in specialist vascular surgery centres, this procedure is gaining popularity nationwide. The manufacturers have constantly developed the implants, so that the latest implants have a portion that covers the blood supply of the kidneys. This is in contrast to the earlier devices which were fixed in place below this blood supply. The reason for this change is to allow the implant better attachment, and to prevent it slipping after the operation.

A lot is now known about the benefits and disadvantages that can occur with both types of implants. Research studies from around the world have shown no disadvantage to covering the

blood supply of the kidneys in the first few years after the operation, but we do not know the long term effect, if any, of covering the blood supply.

There is a theoretical risk of reducing the blood supply to the kidneys by covering the blood vessels, thus preventing their normal function.

You will have had either the implant covering the kidneys' blood supply or the traditional surgical repair (large abdominal operation).

Purpose of the study

This study will allow us to compare the effect of the different surgical options on the long term function of the kidneys. It will allow us to compare the effect of covering the blood supply with an implant versus not covering the blood supply as happens in the traditional surgical repair.

It will allow us to create more accurate guidelines for monitoring patients with these implants after the operation, and help confirm the safe use of such implants.

Do I have to take part?

When you had the operation you consented to enrolment in the Cystatin C trail, which was an earlier version of this trial, and were followed closely for the first two years after the operation with routine and experimental blood tests for renal function. The analysis of this data to date has helped to confirm the safety of this type of operation.

We hope to re-recruit each of the 60 patients that were part of the Cystatin C trial so that we can take a single blood test in the out-patients department, and compare this to the previous blood test results from yourself and other patients that are held on our database.

It is your decision to take part or not.

If you are happy to participate, you will be given a copy of this information sheet, and asked to sign a consent form.

You are free to withdraw from the study at any point, and doing so will not affect your continuing standard of care.

What will I have to do?

Once you agree to participate we will need to take a sample of blood. This is in addition to the routine blood tests that you have on a yearly basis. This will take place in the out-patient clinic, when you will be attending for your yearly follow up. From this sample of blood we will be able to estimate how well the kidneys are working, and compare this to previous samples from yourself and other patients (following the operation), that are held within the database. This is the only participation we require of you, and so does not require further attendance at the hospital. The only difference to your routine clinical follow-up is the need for an extra blood test.

If an unexpected abnormal result is detected in the blood test then the Consultant in charge of your care will be informed, and appropriate action taken.

The next time you are seen will be in one years time for your routine follow up.

Confidentiality

Patients enrolled in this study will be treated confidentially to the same level as standard NHS practice. All data received will be stored in a database on a password controlled hospital computer, and only those doctors contributing to the study will have access.

All data collected will be fully anonymised prior to any presentations at medical conferences or publication in medical journals. All data held within the database will be anonymised at the first available opportunity.

Results of the study

The results will be presented at medical conferences, and in medical journals.

The research will also contribute to the completion of an MD for Mr. Tim Parkinson (principal researcher).

Funding

The research is funded by the Northern Vascular Research Trust.

Appendix B: Eurostar Cohort patient information sheet

Patient Information sheet

The long term impact of trans-renal aortic endograft fixation for abdominal aortic aneurysm repair on renal function

(EUROSTAR Cohort)

The study

You are invited to take part in a research study to evaluate the long term effect of placing an aortic implant (artificial blood vessel), for the treatment of abdominal aortic aneurysms (dilated aortic blood vessel), across the blood supply of the kidneys. Before you decide it is important to understand why the research is being done, and what it will involve. Please take time to read the information sheet carefully, and talk to others about the study if you wish. If the information sheet is not clear, or if you require more information, please feel free to ask questions. Take time to decide whether to participate.

Thankyou for reading this.

Background

Over the last fifteen years medical advances have enabled some patients to undergo key-hole repair of abdominal aortic aneurysms (dilated aortic blood vessel). This means faster recovery and less invasive surgery for eligible patients compared to traditional surgical repair (requiring a large abdominal operation). Whilst usually performed in specialist vascular surgery centres, this procedure is gaining popularity nationwide. The manufacturers have constantly developed the implants, so that the latest implants have a portion that covers the blood supply of the kidneys. This is in contrast to the earlier devices which were fixed in place below this blood supply. The reason for this change is to allow the implant better attachment, and to prevent it slipping after the operation.

A lot is now known about the benefits and disadvantages that can occur with both types of implants. Research studies from around the world have shown no disadvantage to covering the

blood supply of the kidneys in the first few years after the operation, but we do not know the long term effect, if any, of covering the blood supply.

There is a theoretical risk of reducing the blood supply to the kidneys by covering the blood vessels, thus preventing their normal function.

You will have had either of the implant types mentioned above in your original operation.

Purpose of the study

This study will allow us to compare the effect of the different surgical options on the long term function of the kidneys. It will allow us to compare the effect of covering the blood supply versus not covering it when using the different types of implant.

It will allow us to create more accurate guidelines for monitoring patients with these implants after the operation, and help confirm the safe use of such implants.

Do I have to take part?

When you had the operation you consented to enrolment in the EUROSTAR database, and were followed closely for the first two years after the operation with blood tests and scans, and then yearly thereafter with scans. This analysis of this data to date has helped to confirm the safety of this type of operation.

We hope to re-recruit each of the 240 patients that are part of the EUROSTAR database so that we can take a single blood test in the out-patients department, and compare this to the previous blood test results that are held on the database.

It is your decision to take part or not.

If you are happy to participate, you will be given a copy of this information sheet, and asked to sign a consent form.

You are free to withdraw from the study at any point, and doing so will not affect your continuing standard of care.

What will I have to do?

Once you agree to participate we will need to take a sample of blood. This will take place in the out-patient clinic, when you will be attending for your yearly follow up. From this sample of blood we will be able to estimate how well the kidneys are working, and compare this to previous samples from yourself and other patients (following the operation), that are held within the database. This is the only participation we require of you, and so does not require further attendance at the hospital. The only difference to your routine follow-up is the need for a blood test.

If an unexpected abnormal result is detected in the blood test then the Consultant in charge of your care will be informed, and appropriate action taken.

The next time you are seen will be in one years time for your routine follow up.

The process of taking blood will add approximately 10 minutes to your clinic attendance.

Confidentiality

Patients enrolled in this study will be treated confidentially to the same level as standard NHS practice. All data received will be stored in a database on a password controlled hospital computer, and only those doctors contributing to the study will have access.

All data collected will be fully anonymised prior to any presentations at medical conferences or publication in medical journals. All data held within the database will be anonymised at the first available opportunity.

Results of the study

The results will be presented at medical conferences, and in medical journals.

The research will also contribute to the completion of an MD for Mr. Tim Parkinson (principal researcher).

Funding

The research is funded by the Northern Vascular Research Trust.

Appendix C: EVAR Trial Cohort patient information sheet

Patient Information sheet

The long term impact of trans-renal aortic endograft fixation for abdominal aortic aneurysm repair on renal function

(EVAR Cohort)

The study

You are invited to take part in a research study to evaluate the long term effect of placing an aortic implant (artificial blood vessel), for the treatment of abdominal aortic aneurysms (dilated aortic blood vessel), across the blood supply of the kidneys. Before you decide it is important to understand why the research is being done, and what it will involve. Please take time to read the information sheet carefully, and talk to others about the study if you wish. If the information sheet is not clear, or if you require more information, please feel free to ask questions. Take time to decide whether to participate.

Thankyou for reading this.

Background

Over the last fifteen years medical advances have enabled some patients to undergo key-hole repair of abdominal aortic aneurysms (dilated aortic blood vessel). This means faster recovery and less invasive surgery for eligible patients compared to traditional surgical repair (requiring a large abdominal operation). Whilst usually performed in specialist vascular surgery centres, this procedure is gaining popularity nationwide. The manufacturers have constantly developed the implants, so that the latest implants have a portion that covers the blood supply of the kidneys. This is in contrast to the earlier devices which were fixed in place below this blood supply. The reason for this change is to allow the implant better attachment, and to prevent it slipping after the operation.

A lot is now known about the benefits and disadvantages that can occur with both types of implants. Research studies from around the world have shown no disadvantage to covering the

blood supply of the kidneys in the first few years after the operation, but we do not know the long term effect, if any, of covering the blood supply.

There is a theoretical risk of reducing the blood supply to the kidneys by covering the blood vessels, thus preventing their normal function.

As part of the EVAR trial you will have had either the key-hole or traditional surgical repair (requiring a large abdominal operation).

Purpose of the study

This study will allow us to compare the effect of the different surgical options on the long term function of the kidneys. It will allow us to compare the effect of covering the blood supply with the implant in key-hole repair versus not covering it when using the traditional surgical repair.

It will allow us to create more accurate guidelines for monitoring patients with these implants after the operation, and help confirm the safe use of such implants.

Do I have to take part?

When you had either operation you consented to enrolment in the EVAR trial, and were followed closely for the first two years after the operation and then yearly thereafter with blood tests and scans held on a database. The analysis of this data to date has helped to confirm the safety of this type of operation.

We hope to re-recruit each of the 140 patients that were part of the EVAR trial so that we can obtain consent to use the results of the scans and blood tests to date to fully evaluate the different operations.

It is your decision to take part or not.

If you are happy to participate, you will be given a copy of this information sheet, and asked to sign a consent form.

You are free to withdraw from the study at any point, and doing so will not affect your continuing standard of care.

What will I have to do?

The only requirement we have is the signing of the consent form to enable us to access the previous and current scan and blood test results. There is no other difference to your routine follow-up.

If an unexpected abnormal result is detected in either the scan or blood tests then the Consultant in charge of your care will be informed, and appropriate action taken.

The next time you are seen will be in one years time for your routine follow up.

Confidentiality

Patients enrolled in this study will be treated confidentially to the same level as standard NHS practice. All data received will be stored on a database in a password controlled hospital computer, and only those doctors contributing to the study will have access.

All data collected will be fully anonymised prior to any presentations at medical conferences or publication in medical journals.

All data held within the database will be anonymised at the first available opportunity.

Results of the study

The results will be presented at medical conferences, and in medical journals.

The research will also contribute to the completion of an MD for Mr. Tim Parkinson (principal researcher).

Funding

The research is funded by the Northern Vascular Research Trust.

Appendix D: Vascular patients patient information sheet

Patient Information sheet

VASCULAR PATIENTS

Neutrophil gelatinase associated lipocalin (NGAL) and the management of renal function following abdominal aortic aneurysm (AAA) repair

The study

As a patient with an abdominal aortic aneurysm/AAA (dilated aortic blood vessel), you are invited to take part in a research study to evaluate a new type of blood test for kidney function following repair of the AAA.

This study will involve patients with AAA's, having various forms of surgery, and patients who do not have AAA's, ie. Colorectal (bowel) operations, who will be used for comparison.

Before you decide it is important to understand why the research is being done, and what it will involve. Please take time to read the information sheet carefully, and talk to others about the study if you wish. If the information sheet is not clear, or if you require more information, please feel free to ask questions. Take time to decide whether to participate.

Thank you for reading this.

Background

Over the last fifteen years medical advances have enabled some patients to undergo key-hole repair of abdominal aortic aneurysms (dilated aortic blood vessel). This means faster recovery and less invasive surgery for eligible patients compared to traditional surgical repair (requiring a large abdominal operation). Whilst usually performed in specialist vascular surgery centres, this procedure is gaining popularity nationwide. The manufacturers have constantly developed the implants, so that the latest implants have a portion that covers the blood supply of the kidneys. This is in contrast to the earlier devices which were fixed in place below this blood supply. The reason for this change is to allow the implant better attachment, and to prevent it slipping after the operation.

A lot is now known about the benefits and disadvantages that can occur with both types of implants. Research studies from around the world have shown no disadvantage to covering the blood supply of the kidneys in the first few years following implantation of the device.

However a small number of people experience a decrease in kidney function immediately following this procedure, and for the vast majority this requires no treatment other than a intravenous infusion of water (a drip), for a day or two.

It is however important to detect this decrease in kidney function, and to act on it as appropriate.

Purpose of the study

Our standard blood tests (which are used globally), can be slow to demonstrate decreases in kidney function, occasionally only altering after a few days, by which time most people having key hole repair will have gone home.

This study will allow us to analyse the efficiency of a new blood test (NGAL) at detecting kidney function following these operations, and compare it to the standard blood tests used at present.

It will also allow us to compare the effect of covering the blood supply with the implant in key-hole repair versus not covering it when using the traditional surgical repair.

It will allow us to create more accurate guidelines for monitoring patients with these implants after the operation, and help confirm the safe use of such implants.

Do I have to take part?

We hope to recruit about 50 patients into this study, some having treatment for AAA's, and some undergoing Colorectal (bowel) operations (who do not have aneurysms).

The Consultants responsible for your care are aware of the study, and happy for your participation, although it is your decision as to whether to take part.

If you are happy to participate, you will be given a copy of this information sheet, and asked to sign a consent form.

You are free to withdraw from the study at any point, and doing so will not affect your continuing standard of care.

What will I have to do?

The study requires 5 blood tests from you. One before the operation, and then at 6, 24 and 48 hours following the procedure. There will be one last blood test when you return for your routine out-patient appointment.

No additional attendance above the routine practice will be required.

Blood tests are routinely taken as part of normal care pre-procedure, and at 24 and 48 hours, during which the research sample can be taken.

This means you will only need to provide 2 blood samples above and beyond your routine care and management.

Confidentiality

Patients enrolled in this study will be treated confidentially to the same level as standard NHS practice. All data received will be stored on a database in a password controlled hospital computer, and only those doctors contributing to the study will have access.

All data collected will be fully anonymised prior to any presentations at medical conferences or publication in medical journals.

All data held within the database will be anonymised at the first available opportunity.

Results of the study

The results will be presented at medical conferences, and in medical journals.

The research will also contribute to the completion of an MD for Mr. Tim Parkinson (principal researcher).

Funding

The research is funded by the Northern Vascular Research Trust.

Appendix E: Renal function & Cystatin C consent form

CONSENT FORM

The long term impact of trans-renal aortic endograft fixation for abdominal aortic aneurysm repair on renal function

Researchers : Mr Tim Parkinson & Mr MG Wyatt

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

.

3. I agree to my GP being informed of my participation in the study. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient Date	Signature	
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

When completed, 1 for patient, 1 for researcher site file, 1 (original) to be kept in medical notes

Appendix F: NGAL study consent form

CONSENT FORM

Renal function and Neutrophil Gelatinase Associated Lipocalin (NGAL) in the management of abdominal aortic aneurysms

Researchers : Mr Tim Parkinson & Mr MG Wyatt

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

.

3. I agree to my GP being informed of my participation in the study. ☐

4. I agree to take part in the above study. ☐

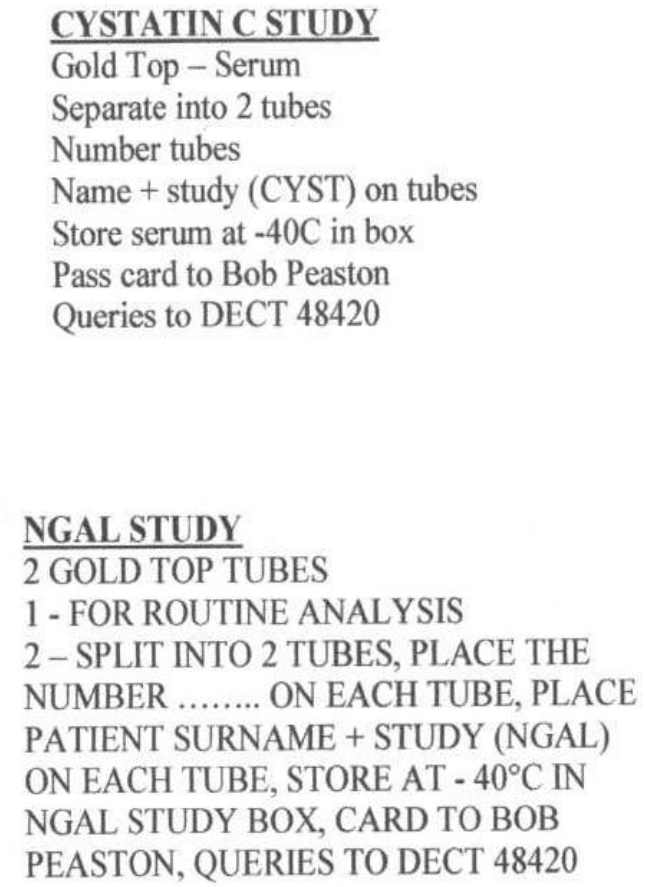
_____	_____	_____
Name of Patient Date	Signature	

_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature

_____	_____	_____
Researcher	Date	Signature

When completed, 1 for patient, 1 for researcher site file, 1 (original) to be kept in medical notes

Appendix G: Blood sample bottle labels



Labels created for the management and storage of blood samples.

Appendix H: Study 1 RAW data

IR fixation time interval specific sCr (umol/L) and CrC (ml/min) levels													
48 months		60 months		72 months		84 months		96 months		108 months		120 months	
sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC
104	64.5	*	*	*	*	114	56.3	*	*	*	*	102	60.2
84	73.2	*	*	*	*	*	*	*	*	*	*	99	56.4
*	*	138	35.4	132	36.4	128	36.8	142	32.6	*	*	*	*
110	59.1	*	*	119	53.0	*	*	*	*	*	*	125	47.4
*	*	*	*	152	57.8	177	49.0	*	*	168	50.2	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	91	57.0	90	56.8	*	*	*	*	88	55.4
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	162	48.9	142	54.9	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	121	47.9	130	46.3	155	36.0	160	34.2	149	36.0
*	*	*	*	89	65.7	70	82.4	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
95	64.2	105	53.0	*	*	125	46.7	*	*	126	44.9	133	41.8
128	48.3	*	*	*	*	*	*	*	*	*	*	*	*
92	48.4	83	52.6	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	106	52.5	*	*	*	*	*	*	*	*	*	*
*	*	104	74.7	95	80.7	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	107	69.8	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
114	39.6	108	41.2	102	43.0	105	53.0	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
163	46.4	141	53.0	139	53.0	120	60.6	124	57.8	100	70.7	*	*
138	25.5	*	*	*	*	*	*	*	*	*	*	*	*
*	*	108	48.8	107	48.4	114	44.7	*	*	107	46.1	*	*
*	*	92	63.5	*	*	100	56.6	89	62.6	97	56.6	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*

*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	198	19.0	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	119	51.9	*	*	*	*	140	42.8	158	36.8	*	*
245	25.6	*	*	*	*	*	*	*	*	*	*	*	*
163	28.0	*	*	*	*	*	*	*	*	150	27.8	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
159	31.1	153	31.7	*	*	162	28.8	168	27.2	171	26.2	*	*
*	*	148	42.4	158	39.1	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
213	26.7	276	20.3	429	12.8	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	122	57.8	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	111	67.8	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	193	58.7	175	63.9	193	57.2	*	*
111	44.3	122	39.6	*	*	*	*	*	*	*	*	*	*
160	42.4	*	*	*	*	*	*	*	*	*	*	*	*
88	65.4	83	68.2	85	65.6	*	*	103	52.4	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
113	60.0	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
121	64.8	*	*	102	74.9	114	66.1	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
97	60.1	92	62.3	*	*	*	*	103	52.8	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
96	59.9	101	56.0	98	56.7	94	58.1	96	55.9	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
142	56.5	159	49.8	155	50.3	177	43.4	*	*	*	*	*	*
88	73.4	97	65.7	107	58.7	99	62.6	104	58.7	*	*	*	*
101	60.3	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
90	62.1	99	55.6	93	58.4	94	56.9	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*

*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	161	58.8	182	51.3	176	52.3	213	42.6	*	*

SR fixation time interval specific sCr (umol/L) and CrC (ml/min) levels													
48 months		60 months		72 months		84 months		96 months		108 months		120 months	
sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC	sCr	CrC
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	89	50	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	88	79.3	96	71.6	*	*	*	*
*	*	*	*	160	34.9	169	27.6	190	24.1	*	*	*	*
95	55.4	*	*	*	*	94	52.2	94	52.3	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	70	86.1	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
124	41.6	120	42.3	132	37.7	119	41.1	106	45.2	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	102	43	*	*	*	*	*	*	*	*
*	*	*	*	*	*	90	56.6	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
126	58.1	135	53.3	135	52.4	158	44.0	155	44.0	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
105	55.5	*	*	*	*	106	56.8	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	116	51.9	114	52.8	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	121	47.9	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
105	57.3	100	62.4	102	59	156	36.9	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
130	47.5	*	*	160	37.3	194	30.3	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	106	56.8	*	*	*	*	*	*	*	*	*	*
165	41.0	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	102	43	105	42.0	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
142	60.8	*	*	*	*	138	60.0	*	*	*	*	*	*

*	*	*	*	*	*	128	54.1	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	113	59.6	*	*	106	61.6	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	125	36.2	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
164	29.1	168	27.9	157	29.4	171	26.5	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
116	47.4	111	48.7	107	49.8	98	53.4	*	*	*	*	*	*
107	57.9	*	*	133	45.0	148	39.1	*	*	*	*	*	*
91	80.0	95	75.6	83	85.3	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	105	53.0	*	*	*	*	*	*
*	*	112	77.4	108	79.2	*	*	*	*	*	*	*	*
123	48.1	161	36.1	*	*	*	*	*	*	*	*	*	*
70	100	80	86.9	81	84.6	*	*	*	*	*	*	*	*
109	44.6	96	49.8	100	47	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
101	62.5	106	58.5	92	66.3	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	92	59.1	88	60.7	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	80	63.7	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	100	62.4	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
109	54.8	108	54.5	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
131	45.1	*	*	146	39.2	*	*	*	*	*	*	*	*

*	*	90	73.2	*	*	*	*	*	*	*	*	*	*
88	79.0	105	65.3	*	*	*	*	*	*	*	*	*	*
84	79.0	76	86.0	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*	*	*	*	*
120	56.7	118	56.9	*	*	*	*	*	*	*	*	*	*
107	51.7	*	*	*	*	*	*	*	*	*	*	*	*
92	56.9	106	48.5	*	*	*	*	*	*	*	*	*	*

Appendix I: Study 2 RAW data

Group specific sCr (umol/L) and corresponding CC (mg/L) levels			
EVAR group		**OPEN group**	
sCr	**CC**	**sCr**	**CC**
90	0.95	134	1.45
114	1.00	159	1.60
115	1.01	124	1.20
139	1.10	112	1.07
176	1.50	107	1.05
91	0.90	89	0.88
97	0.98	138	1.35
86	0.89	106	1.02
133	1.20	83	0.83
127	1.22	147	1.44
122	1.16	128	1.33
101	1.02	114	1.14
103	1.00	91	0.94
114	1.11	88	0.82
108	1.07	88	0.84
88	0.85	99	1.00
103	1.07	110	1.05

Appendix J: Study 3 RAW data

EVAR group sCr (μmol/L) and corresponding NGAL levels (ng/ml) at specific time points									
Pre-operative		4 hours post-op		24 hours post-op		48 hours post-op		6 weeks post-op	
sCr	NGAL	sCr	NGAL	sCr	NGAL	sCr	NGAL	sCr	NGAL
120	132	116	136	122	157	145	*	157	*
81	116	85	97	88	148	96	122	94	231
101	138	99	73	88	121	99	95	103	67
86	199	86	104	93	210	134	146	*	*
93	88	90	146	94	130	101	123	99	107
72	112	65	121	72	137	76	213	*	*
138	136	120	178	121	180	145	232	134	178
154	*	140	74	137	184	152	164	160	137
85	*	82	245	80	133	89	268	101	*
95	82	88	101	90	81	88	49	97	90
127	129	108	204	116	*	115	216	138	239
123	124	130	149	107	67	102	206	133	128
138	149	118	140	163	*	152	*	145	*
121	143	103	136	126	77	154	179	*	*
101	53	85	*	95	102	97	132	100	137
106	101	99	91	102	77	113	*	95	167
104	102	78	154	95	103	117	173	98	*
101	73	88	179	90	193	87	170	100	168
84	110	79	115	78	96	*	*	79	312
86	144	77	155	94	319	88	262	102	322
142	339	128	*	141	167	146	249	*	*
150	248	152	182	157	313	168	221	181	163
121	172	107	189	131	195	116	323	129	*

OPEN group sCr (μmol/L) and corresponding NGAL levels (ng/ml) at specific time points									
Pre-operative		4 hours post-op		24 hours post-op		48 hours post-op		6 weeks post-op	
sCr	NGAL	sCr	NGAL	sCr	NGAL	sCr	NGAL	sCr	NGAL
138	403	129	252	122	164	118	232	132	*
108	264	96	160	88	*	87	300	*	*
156	149	148	190	135	216	172	165	164	*
104	107	95	196	104	141	88	92	*	*
58	217	59	288	63	186	52	227	*	*
126	264	134	175	188	1051	217	318	119	*
115	99	96	105	87	169	108	160	98	*
114	112	95	130	109	409	109	172	*	*
94	110	108	293	102	137	84	146	91	64
144	150	207	942	282	1335	512	98	160	123
95	79	120	180	167	66	176	396	107	166
211	106	191	*	192	308	227	186	199	140
81	70	88	137	90	205	99	167	110	173
69	194	78	251	80	168	76	230	72	*
78	154	63	185	59	103	65	137	62	*
71	218	95	530	101	212	73	132	72	164
111	210	143	755	265	178	371	137	328	*
129	172	124	299	141	137	130	179	138	140
75	719	78	181	73	166	71	256	76	119
96	104	121	149	114	192	105	125	83	152
94	61	109	172	116	890	102	285	87	*

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The Mid-Term Effect of Bare Metal Suprarenal Fixation on Renal Function Following Endovascular Abdominal Aortic Aneurysm.

Davey P, Rose J, **Parkinson T**, Wyatt M

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Presentations

Endovascular Aneurysm Repair and Long Term Renal Function: Posters of Distinction

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Measurement of Serum Cystatin C to Assess the Safety of Uncovered Bare Metal Supra-Renal Fixation in Endovascular Aneurysm Repair (SR-EVR).

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